STATISTICAL ANALYSIS PLAN

OPALINE

Novartis pharma S.A.S and Pfizer S.A.S

Real-life observational study of systemic treatment for progressive unresectable or well-differentiated metastatic pancreatic neuroendocrine tumours (pNET): 2-year morbidity and mortality study

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1. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations	Definitions
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
(e)CRF	(electronic) Case Report Form
HAS	French National Health Authority
LOCF	Last Observation Carried Forward
MA	Marketing Authorisation
NET	Classification of neuroendocrine tumours
PD	Progressive Disease
pNET	Pancreatic neuroendocrine tumour
PR	Partial Response
PT	Preferred Term
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TLG	Tables, Listings and Graphs
TNCD	Thésaurus National de Cancérologie Digestive (French National Gastrointestinal Oncology Thesaurus)
vs	Versus

2. INTRODUCTION

This Statistical Analysis Plan (SAP) defines the structure of the statistical analysis for the OPALINE study, consistent with the protocol version 13 dated 17 July 2018.

This document was reviewed, approved and signed by the biostatistician and sponsor no later than the time when the database was frozen.

It is the reference document for all statistical analyses in this study.

3. DESCRIPTION OF THE STUDY

3.1. Objectives of the Study

3.1.1. Primary Objective

The primary objective of this observational study is to describe the real-world outcome of treated patients (targeted therapies and other treatments) for progressive unresectable or well-differentiated metastatic pancreatic neuroendocrine tumour in adults, in terms of 2-year morbidity and mortality.

3.1.2. Secondary Objectives

Setting up this study will also help to meet the following secondary objectives:

- To describe the characteristics of the population of patients treated for a progressive or well-differentiated metastatic pancreatic neuroendocrine tumour in adults.

- To describe the management of patients suffering from a progressive unresectable or well-differentiated metastatic pancreatic neuroendocrine tumour treated with targeted therapies and other treatments (type of treatment, treatment regimens and prescribing details).

3.2. Design of the Study

This is a prospective (partially retrospective) national observational descriptive multicentre study conducted in France in adult patients treated for a progressive unresectable or well-differentiated metastatic pancreatic neuroendocrine tumour.

In order to provide the answers to the requests from the HAS, two major treatment groups will be formed:

- “targeted therapies” group consisting of two subgroups:

    - Everolimus;

    - Sunitinib.

- "other treatments" group made up of the most commonly prescribed treatment subgroups:
    - Chemotherapy;
    - Somatostatin analogs;
    - Interferon alpha;
    - Metabolic radiotherapy.

3.3. Study Design

The eligibility criteria for patients in the study are shown below:

Inclusion criteria

1. Patients over 18 years old.
2. Patients treated with a targeted therapy (sunitinib, everolimus) or with other treatments (interferon, metabolic radiotherapy, chemotherapy or somatostatin analog)* for:
    - an unresectable or metastatic histologically confirmed pancreatic neuroendocrine tumour;
    - well differentiated;
    - in progression before treatment is started in the opinion of the investigator (clinical or radiological progression).

*patients whose treatment line (targeted therapy or other treatment) is started 1st, 2nd, 3rd or 4th line at the time of inclusion ('incident' patients) or patients during their 1st, 2nd, 3rd or 4th line of treatment provided that treatment was started in the centre in which the patient was included in the study ('prevalent' patients): a change in treatment line is defined as a change in molecule or combination treatment.

3. Patients who have been informed of the details of the study and have given their signed consent.

Patients participating in any another observational study may be included. It is important to include patients from clinical studies because the follow-up bias (potentially due to the follow-up frequency and conditions imposed for the study) will have less impact than the selection bias which may result only in inclusion of patients ineligible for studies. Nevertheless, in order to be able to identify and classify patients in the different groups of interest, patients who are participating in a clinical study may be included if they are participating in a clinical study, in an arm involving treatment approved by the MA (Marketing Authorisation) and the TNCD (French National Gastrointestinal Oncology Thesaurus) according to the versions dated December 2013 if the trial is not double-blind and if the patients are not included in the placebo arm in a placebo-controlled study.

Non-inclusion criteria

The following patients may not be included in the study:

1. Patients with a diagnosis of poorly differentiated neuroendocrine carcinoma or neuroendocrine adenocarcinoma.

2. Patients receiving a targeted therapy (everolimus or sunitinib) already received during a previous treatment line (re-challenge patient).

3. Patients who refuse to give their consent.

4. Patients treatment fifth line of systemic treatment or higher.

5. Patients participating in a clinical study in a treatment arm not approved by the MA and TNCD, versions dated December 2013.

6. Patients randomised into the placebo arm of a placebo-controlled study or into a double-blind study.

It is important to limit the number of lines of systemic treatment to four, as some pNET tumours on fifth line treatment may have a history of up to 12 years. It would not be either feasible or reliable (information bias) to collect these findings. It is also important to make the patient sample as consistent as possible. In addition, the targeted therapies are rarely prescribed beyond the first 4 treatment lines.

The study will be proposed to specialist oncology, gastroenterology or endocrinology doctors in centres which manage pNET tumours. After agreeing to the study protocol, the participating doctor will have two years to recruit the intended number of patients. In view of the small target population, the prevalence of the treatments studied and the study eligibility criteria, 70 patients per year may be included in the study, ie, approximately 150 patients over a total of 2 years.

Within the limits of the inclusion period, a maximum of 75 patients treated with “other treatments” regardless of treatment line and a minimum of 75 patients treated with “targeted therapies” regardless of treatment line will be followed ie, a minimum of 35 patients treated with sunitinib and a minimum of 35 patients treated with everolimus.

The patient inclusion period for the study will allow patients seen in a consultation or hospitalisation to be included during the inclusion period and treated with a targeted therapy or other treatments (as defined for the study) of which:

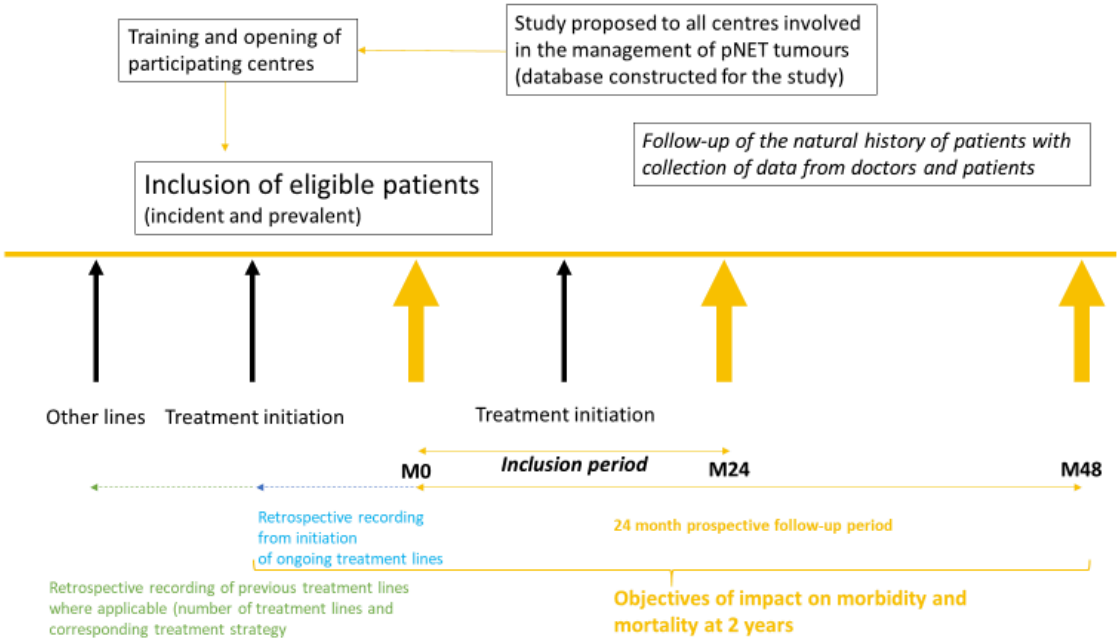
- The treatment is started first, second, third or fourth line at the time of inclusion into the study, a change in treatment line being defined as a change in molecule or combination treatment (so-called ‘incident’ patients);

- The ongoing treatment was started first, second, third or fourth line before inclusion into the study provided that the treatment was started in the centre in which the patient is included in the study (so-called 'prevalent' patients).

The patients will be followed up prospectively throughout the period of the study (24-month follow-up) from their inclusion into the study. The follow-up visits will be conducted during usual patient tumour assessment consultations at the centres (ie, approximately every 2 to 3 months) independently of interruptions, changes or discontinuations of treatment which may have occurred. No consultations will be imposed by the protocol for this observational study and the follow-up and treatment details will remain according to the judgment of the doctor.

The general plan of the study is shown in the figure below.

Figure 1. *General plan of the study*



The study will include a retrospective and/or prospective data collection period, depending on whether the patient is prevalent or incident in terms of his/her tumour treatment at the time of his/her inclusion into the study as described in the table below.

Tableau 1: *Collection of Retrospective and/or Prospective Data*

	'Prevalent' patients	**'Incident' patients**
Retrospective collection	- Initial diagnosis of the tumour - Previous cancer treatments - Patient characteristics and description of the disease when the study treatment was started - Initiation of the study treatment and reference data on starting this treatment - Safety (see paragraph 7 of the Pharmacovigilance protocol): - If the treatment is ongoing at inclusion and involves everolimus, retrospective record of adverse events: - Clearly linked to everolimus since it was started until inclusion. - Clearly linked to a Pfizer product since first line management of the disease and until the inclusion.	- Initial diagnosis of the tumour - Previous cancer treatments

	- For all other treatments ongoing at inclusion (Sunitinib, chemotherapy, somatostatin analogs, metabolic radiotherapy or interferon alpha), retrospective collection of adverse events: - Clearly linked to a Pfizer product since the first line of management of the disease until inclusion.	
Prospective collection	- Follow-up data after inclusion into the study: description if treatments and tumour assessments (2 years) - Safety (see paragraph 7 of the Pharmacovigilance protocol)	- Patient characteristics and description of the disease on initiation of the study treatment - Initiation of the study treatment and reference data on starting this treatment - Follow-up data after inclusion into the study: description of treatments and tumour assessments (2 years) - Safety (see paragraph 7 of the Pharmacovigilance protocol)

4. STATISTICAL METHODS

4.1. General Statistical Considerations

The analyses will be performed using SAS® software (version 9.1 or subsequent, SAS Institute, North Carolina USA).

The descriptive analysis of qualitative and ordinal variables will include numbers and frequency of each modality together with its 95% confidence interval and the number of missing data. Quantitative variables will be described as numbers, mean and median values, standard deviation, confidence interval and the number of missing data.

Overall survival and progression-free survival data will be described by Kaplan Meier curves. Median survival will be estimated and presented with its 95% CI.

Wherever possible, a graphical representation will be combined with results of the analyses.

Association measurements between two variables (univariate analyses excluding comparison of subgroups of interest) will use standard methods. The association between the two qualitative variables will be measured by calculating the Chi squared Pearson coefficient. If validity is not met, the continuity correction will be used (Yates Chi squared coefficient)

provided it is logically possible to group modalities together. Mean values of quantitative variables will be compared using the Student test with and without the hypothesis that variances are equivalent. Equivalence of variances will be estimated using a Levène test and the definition of a normal distribution will be assessed from the appearance of histograms and result of the Shapiro-Wilk test.

4.2. Calculation of the number of subjects

The number of subjects required is calculated based on the primary descriptive objective of morbidity and mortality assessed in particular by progression-free survival and overall survival.

The calculation is based on the expected precision of the estimate of median survival (confidence interval).

An estimation of S(t) variance (Kaplan Meier estimate) is given by the Greenwood equation:

$$\hat{Var}[\hat{S}(t)] = [\hat{S}(t)]^2 \sum_{j:t_j \leq t} \frac{d_j}{n_j(n_j - d_j)}$$

Where *tj* is the events time, *dj* is the number of events at these times and *nj* is the number of patients at risk.

Assuming no right censoring before the median and the occurrence of a single event by event time, the Greenwood equation can be simplified for median survival:

$$\hat{Var}[\hat{S}(t)] = \frac{0,5^2}{n}.$$

Different variances and the CI of S(t) can therefore be calculated depending on n and therefore on precision.

s(t)²	**n**	**Variance (s(t)²/n)**	**Lower CI**	**Upper CI**	**Precision**
0.25	75	0.0033	0.38	0.61	0.113
	100	0.0025	0.40	0.59	0.098
	125	0.0020	0.41	0.58	0.088
	150	**0.0016**	**0.42**	**0.58**	**0.080**
	200	0.0012	0.43	0.56	0.069
	225	0.0011	0.43	0.56	0.065
	250	0.0010	0.43	0.56	0.062
	360	**0.0010**	**0.44**	**0.55**	**0.052**

A total of 360 patients will need to be included to achieve a precision of 5%.

Given:

- The estimated target population of 150 to 170 cases per year,
- The prevalence of the treatment groups of interest and need to stratify the inclusions on treatment subgroups,
- The study inclusion criteria.

The number of patients to be included in the study must be calculated balancing the statistical calculations against the feasibility of the study. According to the data which are available, a number of 150 patients included over a period of 2 years would appear to be a feasible objective. Inclusion of a total of 150 patients would allow an estimate of median survival (progression-free survival, or overall survival) with a precision in the region of 8%.

It should be noted that analyses in the subgroups (targeted therapy, other treatments) enable the median value to be estimated with greater inaccuracy as the numbers in the stratification groups are smaller. Considering for example a balanced distribution of patients between the targeted therapy and other treatments groups ie, 75 patients per group, precision will be 11%.

In terms of the other descriptive objectives of the study, the estimated number of patients is based on the precision of proportion as defined by the equation below:

$$n = \frac{\varepsilon^2}{i^2} p(1 - p)$$

Depending on the proportions found and the patient numbers (overall or by treatment stratification) the following precision values may be expected:

Observed proportion	**Expected precision**		
	n=75	**n=150**	**n=200**
10 – 90	6.8	4.8	4.2
20 – 80	9.1	6.4	5.5
30 – 70	10.4	7.3	6.4
40 -60	11.1	7.8	6.8
50	11.3	8.0	6.9

4.3. Analysis Sets

4.3.1. Patient Sets

- Non-included patients: all patients who are not included in the study (as recorded in the non-inclusion register).
- Included patients: all patients included in the study.
- Safety analysis set: all patients included in the study who received at least one dose of the documented treatment (the treatment start date must be entered) in the study (targeted therapy or other treatment). If the patient is prevalent, the treatment must

still be ongoing at the time of inclusion in the study and if the patient is incident, the treatment must be started at or after inclusion in the study.

- Reference set (Full Analysis Set): patients included who meet the eligibility criteria and have received at least one dose of the treatment documented during the prospective follow-up period (the treatment start date must be completed and the treatment stop date must be after the date of inclusion if the start date is prior to the date of inclusion) in the study (targeted therapy or other treatment). Patients with no follow-up data will be excluded from this population.

Two treatment groups will be analysed: the "targeted therapy" with two subgroups, everolimus (AFINITOR®) and sunitinib (SUTENT®); and an "other treatments" group with four subgroups: chemotherapy, somatostatin analogs, interferon-alpha and metabolic radiotherapy.

4.3.2. Doctor Sets

- Active doctors: who have included at least one patient.
- Inactive doctors: doctors who have not included any patients.

4.4. Protocol Deviation

Deviations from the protocol will be defined from the CRF database. They will be defined and identified prior to the data review meeting and will be reviewed during this meeting.

In particular, deviations from the following inclusion and non-inclusion criteria will be identified for the data review:

- Breach of inclusion criteria defined below:
  - Patients over 18 years old,
  - Patients treated with a targeted therapy (Sunitinib, Everolimus) or with other treatments (interferon or metabolic radiotherapy or chemotherapy or somatostatin analog)* for:
    - an unresectable or metastatic histologically confirmed pancreatic neuroendocrine tumour,
    - well differentiated,
    - in progression before treatment is started in the opinion of the investigator (clinical or radiological progression),

*patients whose treatment line (targeted therapy or other treatment) is started 1st, 2nd, 3rd or 4th line at the time of inclusion (patient 'incidents') or patients during their 1st, 2nd, 3rd or 4th line of treatment, provided that treatment was started in the centre in which the patient was included in the study ('prevalent' patients): a change in treatment line is defined as a change in molecule or combination.

    - Patients who have been informed of the details of the study and have given their signed consent.

- Breach of non-inclusion criteria defined below:

    - Patients with a diagnosis of poorly differentiated neuroendocrine carcinoma or -neuroendocrine adenocarcinoma.

    - Patients receiving a targeted therapy (Everolimus or Sunitinib) already received during a previous treatment line (re-challenge patient).

    - Patients who refuse to give their consent.

    - Patients treatment fifth line of systemic treatment or above.

    - Patients participating in a clinical study in a treatment arm not approved by the MA and TNCD, versions dated December 2013.

    - Patients randomised into the placebo arm of a placebo-controlled study or into a double-blind study.

- No follow-up data available.

4.5. Handling of Missing Values

In general, missing values will not be used either in calculating the percentages or in computing statistical tests.

The number of missing values for each analysed variable will be shown in the summary tables. Key data will be mandatory in the electronic CRF in order to control the proportion of missing data.

<u>Dates, only used to calculate time periods:</u>

- For the data of birth, the day is not requested in the CRF and will be replaced by 15.

- For calculations involving dates:

    - If the day is missing, it will be replaced by day 15 of the month;

    - If the month and day are missing, they will be replaced by 30 June of the year;

    - If the date is completely missing, it will not be replaced.

These rules will be used if they do not create inconsistencies (negative time intervals). Otherwise the time interval will be deemed to be missing.

The other specific management requirements for missing data are described in the relevant sections of this document.

4.6. Listings

All listings will include at least the following items:

- Centre number
- Subject number
- Age/Sex
- Documented treatment in the study
- Inclusion data
- Date of first receipt of the documented treatment in the study
- Visit date (if applicable)
- Visit (if applicable)
- Safety analysis set (yes/no)
- Reference set (yes/no)

The functions will be sorted by group (targeted therapy/other treatment), centre number, subject number and visit date (if applicable). Missing data will not be replaced in the listings.

4.7. Derived Variables

- Total duration of exposure to the documented treatment in the study (months)

  (Date of last receipt of treatment – Date of first receipt of treatment + 1)/30.4375

  For patients who drop out of the study early, the date of last receipt of the treatment considered will be the date of the last visit.

  To analyse exposure times by treatment received at least once during the study, if the start date is after the date of the last visit, the treatment will not be considered.

  In terms of exposure time for treatments used in combination, the start date and end date of the combination were not recorded in the CRF. The visit prior to the report describing addition of the combination will be deemed to be the start date and the visit in which the combination is reported as being discontinued will be deemed to be the end date for the combination, unless the combination began or finished during a line of treatment (or includes the start and end date).

- In general, the time between two dates expressed in days will be obtained as follows:

  Most recent date – Least recent date

  The following conversion factors will be used to convert the times into months or years:

  - 1 month = 30.4375 days
  - 1 year = 365.25 days

- Age (in years) will be calculated as follows:

  (Inclusion date – Date of birth)/365.25

- The disease duration (in years) will be calculated as follows:

  (Inclusion date – Disease start date)/365.25

- The disease duration (in years) at start of the current treatment at inclusion will be calculated as follows:

  (Treatment start date - Diagnosis date) / 365.25

- Time until first temporary discontinuation since inclusion into the study:

  (Date of first temporary discontinuation – Date of inclusion + 1)/30.4375

- Time until permanent treatment discontinuation since inclusion into the study:

  (Date of final discontinuation – Date of inclusion + 1)/30.4375

- Lines of cancer treatment:

Treatment lines will be defined in two ways:

- Main treatment line: All new treatments will be considered as a new main treatment line.
- Main concomitant treatment line: All new treatments or new combinations will be deemed to be a new concomitant treatment line.

The reason for discontinuing treatment will not be considered in the definition of a treatment line.

The same treatment stopped for over 3 months will be deemed to be two different lines of treatment and to be one line if the discontinuation lasts for less than 3 months.

The treatment lines will be counted differently depending on whether they are a previous treatment or a treatment administered during the study and whether the date of collection is retrospective or prospective.

Prior treatment lines only include systemic treatments (chemo-embolisation will not be deemed to be a previous treatment line) whereas treatment lines during the study will be deemed to be as such whether they are systemic or locoregional treatments (chemo-embolisation will be deemed to be a treatment line in this case).

Treatment with Lutathera will be considered to be metabolic radiotherapy.

If the combination involves a somatostatin analog (as the main treatment), then the combination becomes the main treatment unless surgery is involved. The start date of the main treatment is the date of the visit recording the combination (and this same date will be considered as the discontinuation date of the previous line). The discontinuation of the main treatment also corresponds to the date when the treatment was discontinued before starting a new line.

Moreover, if Pazopanib is recorded as the previous "other" treatment it should then be reclassified as targeted therapy and presented as the 3rd targeted therapy line (in addition to Everolimus and Sunitinib).

5. STATISTICAL ANALYSES

In all of the analyses, somatostatin analogs (octreotide, lanreotide) will be grouped into one single group, except for the description of treatment at inclusion.

5.1. Dates of the Study

The following data will be described globally:

- inclusion date of the first patient,
- inclusion date of the last patient,
- duration of inclusions (months),
- date of last visit of last patient,
- duration of the study (between first inclusion and last visit).

5.2. Distribution of Doctors

The numbers and percentages of active and inactive doctors will be described.

5.3. Distribution of Patients

A summary table will show the numbers and percentages of patients (prevalent and incident patients and total number of patients) in each population in each group and globally:

- Number of non-included patients;
- Number of included patients;
- Number and percentage of patients in the safety analysis set;
- Number and percentage of patients in the reference set.

Percentages will be calculated from the population of included patients.

The following parameters will also be described:

- Reasons for non-inclusion in the reference set;
- Centre characteristics: number of centres, number of patients per centre;
- Reasons for dropping out of the study in the safety analysis set and reference set;
- Patient status at the end of the study (alive/dead/lost to follow-up) in the safety analysis set and reference set;
- Protocol deviations.

Patients excluded from the reference and safety analysis sets with their reasons for non-inclusion will be listed.

5.4. Baseline Characteristics

5.4.1. Description of Patients

Descriptive statistics will be used for the demographic data and baseline patient characteristics analysis. These parameters will be presented globally and by analysis group in the reference set and will also be described in each of the two patient subgroups treated with targeted therapy at inclusion:

- everolimus (AFINITOR®),
- sunitinib (SUTENT®).

and in the 4 subgroups of patients treated with another treatment at inclusion:

- chemotherapy,
- somatostatin analogs,
- interferon alpha,
- metabolic radiotherapy.

The demographic characteristics will include patient age and sex at inclusion into the study. They will be presented in the population of included patients and in the reference set.

The following parameters will also be described at inclusion in the reference set:

- ECOG Index.
- Past medical history and concomitant diseases (the LVEF value (%) will be presented as classes <50% vs ≥50%).
- Proportion of patients with a past history of at least one comorbidity (all comorbidities listed plus "OTHERS" category).
- Proportion of patients with a past history of at least one comorbidity of interest (only the set of comorbidities listed).
- Number of treated comorbidities of interest in the past history by patient (quantitative analysis and by classes 0, 1-3, >3).
- Proportion of patients with a past history of at least one treated comorbidity of interest (only the set of comorbidities listed).
- Number of treated comorbidities of interest per patient in the patient's past history (quantitative analysis and analysis by classes 0, 1-3, >3).
- History of the disorder: duration, type of tumour at diagnosis, previous locoregional cancer treatments, surgery, investigations performed.
- Previous lines of cancer treatments: number of lines, type of treatments and combinations, duration, reasons for discontinuation.
- Current treatment: type and details of cancer treatment, presentation of the list of chemotherapies defined according to the main treatment protocols (see Appendix 1), time between starting treatment and inclusion, time between diagnosis and starting treatment (overall analysis and by group depending on the position of the treatment line, whether ongoing or administered at inclusion), temporary discontinuations, antisecretory agent treatments, presence of metastases.

5.4.2. Description of Doctors

The participating doctors will be described using the following parameters: specialty, type of practice, type of facility, active file.

5.4.3. Representativeness of Samples of Doctors and Patients

Comparisons will be made between active doctors who took part in the study (who included at least one patient) and inactive doctors who did not include any patients, by calculating standardised differences.

These standardised differences will be calculated as follows:

Type of variable	Equation
Qualitative	$d = \frac{P_1 - P_2}{\sqrt{\frac{P_1(1-P_1) + P_2(1-P_2)}{2}}}$ P_1: proportion of individuals with the feature in group 1 P_2: proportion of individuals with the feature in group 2
Quantitative	$d = \frac{moy_1 - moy_2}{\sqrt{\frac{var_1 + var_2}{2}}}$ $mean_1$: mean in group 1 $mean_2$: mean in group 2 var_1: variance in group 1 var_2: variance in group 2

Similarly, comparisons will be made between included and non-included patients based on information collected in the non-inclusion register (age, sex), The reasons for non-inclusion will be presented. The "others" reasons for non-inclusion will be listed.

In addition, patients who are lost to follow-up and/or dropped out of the study (for a reason other than death) will be compared to patients with complete follow-up (follow-up until progression, death, end of main treatment ongoing at the time of inclusion or 2-year cutoff date) in the reference set.

We will deem the observed difference to be small if the standardised difference is between [0.2 and 0.3], average if between [0.3-0.8] and large if it is over 0.8. A value of 0.2 or less will be considered to represent no difference.

5.5. Analysis of the Primary Objective

The following parameters will be analysed in the reference set in order to meet the primary objective of the study:

- Progression-free survival at 2 years when receiving the main treatment at the time of inclusion. Progression-free survival is defined by the time between starting treatment (the sequence ongoing at the time of patient inclusion into the study) and the date of

first documented disease progression or all-cause death when receiving the main treatment at the time of inclusion.

- Overall survival rate at 2 years. Overall survival is defined by the time between starting treatment (the sequence ongoing at the time of patient inclusion into the study) and all-cause death.

- Treatment safety (targeted therapies and other treatments) during the prospective period of the study described in terms of treatment discontinuations and the reasons for these, adverse events (graded according to CTCAE version 4.0, May 2009) and any complications of these adverse events. This analysis is described in Section 5.7.

5.5.1. Analysis of Progression-free Survival and Overall Survival

Progression-free survival and overall survival will be measured using the Kaplan-Meier method. The survival function S(t) will be the likelihood of event of interest (progression or death respectively) not occurring before the date t. This function will be represented graphically with a survival curve.

These analyses will be carried out as shown in the table below:

	Progression-free survival	**Overall survival**
Start date	Date of starting (the treatment line ongoing at the time of patient inclusion) of the targeted therapy or other treatment	
Date of event	Date of progression or death when receiving the main treatment at the time of inclusion	Date of death
Right censoring	Patients without an event when receiving the main treatment at the time of inclusion or lost to follow-up will be censored at the last recorded time to progression or the last tumour assessment, last disease assessment in the early study completion form, when receiving the main treatment at the time of inclusion. For patients without a tumour assessment but with a clinical assessment, the date of the tumour assessment visit will be used in the PFS analysis. If patients have both a	Patients with no event or lost to follow-up or alive at the end of the study will be censored at their last follow-up date (last follow-up date or last news).

	Progression-free survival	**Overall survival**
	tumour and clinical assessment, the maximum time between the date of the visit and the assessment date will be used in patients with no disease progression. When there is no tumour or clinical assessment date, patients will be censored using the treatment discontinuation date.	

Progression: information obtained from the "tumour assessment" section, tumour assessment visit or the "disease progression" section in the early study completion form or in the "treatment discontinuation" section if the main treatment is discontinued for disease progression.

Death: information obtained from the "patient status" section in the early study completion form or in the "outcome" section of the adverse event record page.

In the progression-free survival analysis, the first progression when receiving the main treatment at the time of inclusion will be used, either radiological progression or clinical progression if this occurs first.

The following details will be presented in summary tables:

- Number of patients;
- Number of events (with details of progression/death);
- Number of right censors (with details of patients who are lost to follow-up, no disease progression/death);
- Survival (in months): median (+95% CI), Q1 (+95% CI), Q3 (+95% CI), minimum, maximum;
- Estimated survival rate at a specific time (for example 6 months, 1 year and 2 years): number of subjects at risk, survival rate at each time.

These survival rates will be estimated and described in each of the following groups and subgroups:

- Targeted therapies group (with an estimate in the Everolimus and Sunitinib subgroups);
- Other treatments group (with an estimate in the chemotherapy, somatostatin analogs, interferon alpha and metabolic radiotherapy subgroups).

Handling of truncation/left censoring:

The study includes a retrospective and/or prospective data collection period depending on whether the patient is prevalent or incident in terms of his/her tumour treatment at the time of inclusion into the study.

The time to event of interest ("survival" time) or censoring if no event occurs (right censoring) will be based on the treatment line start date at the time the patient was included into the study.

As a result, when patients are recruited into the study, those patients who have already died on treatment could not be included, whereas patients who were still alive on treatment were included. This is left truncation.

In addition, the prevalent patients included could progress before inclusion into the study and not stop the treatment started or ongoing at the time of inclusion. This progression could not be identified and is a left censoring.

In practice, after disease progression on a given treatment, the treatment is changed. As a result, prevalent patients we observed on a given treatment at inclusion could not by definition experience disease progression.

As a result, we also do not see patients on a given treatment at inclusion who progressed on the same treatment prior to entering the study and we therefore deem these cases to be left truncations.

The distribution of an estimator which is both left-truncated and right censored can be estimated using the estimator of Kaplan and Meier (Klein and Moeschberger, 1997).[1] The likelihood of conditional survival will be estimated as $S_a(t) = Pr [X > t \mid X \geq a]$. Occurrence of an event will be studied over time t (the time since the start date) conditional on being free of this event at study entry where a represents the time between the start date and inclusion into the study. This is estimated as follows:

$$\widehat{S_a}(t) = \prod_{a \leq t_i \leq t} \left\{1 - \frac{d_i}{Y_i}\right\}, t \geq a$$

where d represents the number of events and Y represents the risk set

In addition, the Kaplan-Meier estimator does not work well when the size of the risk set is extremely small. This may occur at the end of the curve when right censorings are present and also at the start of the curve if left truncation of data occurs. This latter situation confers early instability in the point estimator of the survival function which may propagate throughout the entire curve. Lai and Ying (1991)[3] suggested a solution to this problem by a slight modification of the Kaplan-Meier estimator where events are ignored when the risk set is small:

$$\widehat{S_a}(t) = \prod_{a \leq t_i \leq t} \left\{1 - \frac{d_i}{Y_i} I[Y_i \geq cn^{\alpha}]\right\}, t \geq a$$

where I represents an indicator, n represents the population size and c and α represent constant values. These constant values are used to define a minimum risk set size below which the events are not counted. This minimum risk set size is defined in terms of the size n of the study population. As the sizes of the subgroups we wish to compare in the OPALINE study are variable, the constants will be set arbitrarily to ensure that the minimum risk set size is equal to 5 for all subgroups. The method proposed by Lai and Ying therefore will only be effective for portions of the Kaplan-Meier curve in which the risk set does not exceed 5 patients for all the subgroup analyses.

The following analyses will be performed:

- Survival analyses (OS/PFS) for all patients with a Kaplan-Meier estimator using right censoring and left truncation (main analysis) by the PROC PHREG SAS® procedure.
- Subgroup survival analyses (OS/PFS) with a modified Kaplan-Meier estimator using right censoring and left truncation, stabilising the estimates when small samples are present (Lai and Ying method).
    - Targeted therapy vs other treatments;
    - Everolimus vs sunitinib;
    - Chemotherapy vs somatostatin analogs vs metabolic radiotherapy.

    This analysis will be performed using the SAS® PROC HPSEVERITY procedure.
- Supportive survival analyses (OS/PFS) overall and by targeted therapy vs Other treatments subgroups in incident patients by the Kaplan-Meier estimate using right censoring (conventional analysis using PROC LIFETEST).

<u>Planned visits:</u>

The primary endpoint analysed is the overall survival rate and the progression-free survival rate at 24 months after starting treatment. A follow-up of at least the 24 month is therefore expected for all patients. Eight visits are possible in the eCRF. If the eighth study visit was carried out before 24 months, a further visit must be recorded in the eCRF to reduce the right censoring.

All of the visits (including those after follow-up for 2 years) will be taken into account in the statistical analyses.

Handling of missing data:

For survival analyses, missing data due to study drop outs may give rise to bias in the results. In order to reduce this bias, particular attention will be paid to collecting data on disease progression in the study patients.

Patients lost to follow-up without a declared event at last news in these analyses will be censored at their last follow-up time.

5.5.2. Best Response to the Treatment at Inclusion and During Follow-up

The best response to the main treatment at inclusion with targeted therapy or other treatment (ongoing at the time of patient inclusion into the study) will be described by analysis group (targeted therapy or other treatment) then according to targeted therapy, chemotherapy and somatostatin-analogs groups.

In addition, the best response during follow-up will also be described overall.

The following ranking will be used in order to define this variable:

complete response>partial response>clinical response>stable disease>disease progression

Data will be deemed to be missing if they have not been completed, or if the "un-assessable" box is checked.

The criterion used in this analysis will be the RECIST criterion if available or the clinician's assessment if it is not.

5.6. Analysis of Secondary Objectives

The analysis of patient characteristics is shown in Section 5.4.1.

The following analysis will also be carried out in order to meet the secondary objectives of the study:

- Patient management: frequency of visits, tumour assessment methods, therapeutic management.

5.6.1. Management of Patients

The following parameters will be analysed in order to describe management of the study patients:

- Number and frequency of tumour assessment visits;
- Investigations used for the tumour assessment;
- Treatment management: changes to treatment, dose steps, concomitant treatments, number and type of treatment lines received during follow-up.

The different main treatment lines and main concomitant treatment line received by patients during the follow-up period will be listed.

The numbers and percentages of patients who received a treatment at least once during the study will be described by analysis group (targeted therapy or other treatment) and for each type of study treatment (everolimus, sunitinib, somatostatin analogs, chemotherapy, metabolic radiotherapy or interferon-alpha) in the reference and safety analysis sets. The numbers and percentages of patients receiving a combination at least once during the study will also be described, with details of the combinations. An "other treatments" category will be created for combinations other than the study treatment.

5.7. Safety

Safety assessment criteria will be used to:

- Treatment discontinuations and reasons for this,
- Adverse events and any complications recorded prospectively (graded according to the 'Common Terminology Criteria for Adverse Events' (CTCAE) version 4.0, dated May 2009).

These criteria will be shown descriptively in the safety analysis set.

The analyses of adverse events will be performed twice on the safety analysis set:

- by treatment group at inclusion;
- by group in which treatment was received at least once during the study. In this analysis, the AE will be attributed to ongoing treatment at the start of the AE. An AE beginning after a treatment was discontinued could be attributed to the treatment depending on the rules shown in the table below.

Prior to the safety analysis, the number of patients who received the treatment at least once in the group (targeted therapy/other treatments) and in the treatment subgroups will also be presented. Exposure for each treatment group and subgroup will be calculated.

5.7.1. Treatment Drop-outs and Documented Reasons for Dropping Out of the Study

The following parameters will be presented for each of the analysis groups (targeted therapy or other treatment) and for each treatment:

- Total duration of exposure since starting treatment (also shown for the reference set).
- Numbers and percentages of patients who had at least one documented discontinuation of treatment in the study. The results will be shown for incident patients, prevalent patients and then for all patients.
- Number of documented temporary discontinuations by patient in the study.

- Time to the first temporary discontinuation from inclusion into the study. The results will be shown for incident patients, prevalent patients and then for all patients.
- Reasons for temporary discontinuations.
- Durations of temporary discontinuations.
- Numbers and percentages of patients who discontinued treatment permanently.
- Time until permanent discontinuation from inclusion into the study. The results will be shown for incident patients, prevalent patients and then for all patients.
- Time until permanent discontinuation from inclusion. Results will be shown for incident patients, prevalent patients and then for all patients.
- Reason for permanent discontinuation.

The analyses of exposure to treatment will be described by treatment received at inclusion but also by treatment received at least once during the study (main treatment or as a combination). If the patient takes the same treatment on several occasions over different periods, the sum of the exposure periods will be calculated.

The analyses of temporary discontinuations will be described by main treatment received at inclusion but also by main treatment ongoing at the time of temporary discontinuation.

In addition, the total duration of exposure of the treatment at inclusion since it was started will be analysed by the ECOG index value at inclusion.

5.7.2. Adverse Events

The numbers and percentages of patients with the following characteristics will be shown overall, and by group at inclusion during the study (targeted therapy/other treatments). We will also show the results by treatment being received at the time of inclusion and during the study: everolimus/sunitinib/chemotherapy/somatostatin analogs etc.

- at least one adverse event,
- at least one serious adverse event,
- at least one adverse event with a suspected relationship with the study treatment,
- an adverse event which was fatal,
- at least one adverse event resulting in permanent discontinuation of treatment,
- at least one adverse event resulting in dosage adjustment/temporary discontinuation of treatment,

- at least one adverse event with a suspected relationship with the study treatment leading to permanent discontinuation of the treatment,
- at least one adverse event with a suspected relationship with the study treatment leading to a dosage adjustment/temporary discontinuation of treatment,
- at least one serious adverse event with a suspected relationship with the study treatment leading to permanent discontinuation of the treatment,
- at least one serious adverse event with a suspected relationship with the study treatment leading to a dosage adjustment/temporary discontinuation of treatment.

The same information will be produced for grade ≥3 adverse events.

The following information will also be shown:

- at least one grade 3 adverse event,
- at least one grade 3 serious adverse event,
- at least one grade 3 adverse event with a suspected relationship with the study treatment,
- at least serious grade 3 adverse event with a suspected relationship with the study treatment,
- at least one grade 4 or higher adverse event,
- at least one grade 4 or higher adverse event with a suspected relationship with the study treatment.

The adverse events will also be described by treatment group, in patients who received treatment at least once during the study (targeted therapies/other treatments; the other treatments will also be described depending on whether these involved chemotherapy/somatostatin analogs/others) by System Organ Class (SOC) and Preferred Term (PT). The same analysis will be presented for adverse events with a suspected relationship with the study treatment, grade 3 adverse events with a suspected relationship with the study treatment, serious grade 3 adverse events with a suspected relationship with the study treatment, adverse events grade =3, adverse events ≥4, for serious adverse events, non-serious adverse events, serious grade =3 adverse events, adverse events which resulted in temporary discontinuation of treatment, adverse events which resulted in permanent discontinuation of treatment and adverse events which resulted in the death of patient.

In terms of the analysis by treatment received during the study, several rules have been defined:

The denominator will be the number of patients who received the ongoing treatment during the prospective period at least once. In the case of combination treatments, the treatments will be separated and the patient will be counted several times.

The AE will be deemed to be on treatment until 28 days after the treatment is stopped. Similarly, if the investigator links an AE to a treatment, this will also be counted on this related treatment (regardless of the dates the treatment is taken).

If the treatment is still ongoing at the time of last news, the AE will be deemed to be on treatment for up to 28 days after the date of last news.

Amongst the "other" treatments, Lutathera treatment will be deemed to be metabolic radiotherapy.

If the date of onset of the adverse event is missing:

- If the day of the event is missing, the event will be attributed to all treatments received during the month when the AE was declared.

- if the day and month of the event are missing, the event will be attributed to all treatments during the year in which the AE is declared unless the treatment was received after the end of the AE.

For combination treatments, the start and end date of the combination were not recorded in the CRF. The visit immediately before the report of the additional combination will therefore be deemed to be the start date and the visit corresponding to discontinuation of the combination will be deemed to be the end date of the combination, unless the combination began or finished during a treatment line (where start and end dates are reported). The 28-day rule also applies to combination treatments.

The AEs will be analysed as follows:

	Actual exposure	Actual exposure +28 days	Treatment reported in the "Causality with the study treatment" column
At least one adverse event		X	
At least one serious adverse event		X	
At least one adverse event with a suspected relationship with the study treatment			X
At least one adverse event resulting in death		X	
At least one adverse event leading to permanent discontinuation of treatment	X		
At least one adverse event leading to change in dosage/temporary discontinuation of treatment	X		
At least one adverse event with a suspected relationship with the study treatment leading to permanent discontinuation of treatment	X		X
At least one adverse event with a suspected relationship with the study treatment leading to adjustment of dosage/temporary discontinuation of treatment	X		X
At least one adverse event with a suspected relationship with the study treatment leading to temporary discontinuation of treatment	X		X
At least one serious adverse event with a suspected relationship with the study treatment leading to permanent discontinuation of treatment	X		X
At least one serious adverse event grave with a suspected relationship with the study treatment leading to adjustment of dosage/temporary discontinuation of treatment	X		X
At least one serious adverse event with a suspected relationship with the study treatment leading to temporary discontinuation of treatment	X		X

***** AEs on treatment analysed as reported in the actual exposure and in the "causality with the study treatment" column.

Adverse events will be listed overall, together with the grade ≥3 adverse events, serious adverse events, adverse events with a suspected relationship to the study treatment leading to permanent discontinuation of the treatment and adverse events with a suspected relationship to the study treatment leading to temporary discontinuation of the treatment.

NB: the listings will show the retrospective adverse events and the prospective adverse events, whereas the summary tables will only include the prospective adverse events.

The listing of adverse events reported in patients excluded from the safety analysis set will be provided where applicable.

Handling of missing data:

If the seriousness (serious/non-serious) and/or causality with the treatment are missing, the most adverse situation for treatment is assumed in the summary tables, i.e. a serious case and/or one related to the study treatment.

5.7.3. Deaths

A listing of deaths describing the cause of death will be presented. All patients who died will be shown in this listing (including cases in which death is reported in the AEs after the end of the study).

5.8. Amendments from the Statistical Part of the Protocol

In the survival analysis, the 95% confidence intervals will be estimated using the Klein and Moeschberger equation.

5.9. Additional Analyses

5.9.1. Characteristics of Patients Based on having Received at Least One Targeted Therapy before Inclusion

The characteristics of patients will be described according to the "at least one targeted therapy before inclusion (yes/no)" subgroup in relation to the reference set.

Characteristics of interest are:

- Demographic characteristics,
- ECOG index,
- Comorbidities and history,
- Comorbidities and relevant history,
- Initial diagnosis of the disease,
- Characteristics of the pancreatic neuroendocrine tumour when starting the current line of treatment or line of treatment started at inclusion,

- Previous locoregional cancer treatments,
- Investigations performed most recently,
- Previous cancer treatment lines.

5.9.2. Time Between Diagnosis and Initiation of Ongoing Treatment at Inclusion for Metasynchronous Patients

The time (in years) between the date of diagnosis and initiation of ongoing treatment at inclusion will be presented for metasynchronous patients. A patient is considered as metasynchronous when a metastatic tumour was present at diagnosis.

5.9.3. Therapeutic Pathway of Patient

The therapeutic pathway of the patient will be described based on the three treatments (main treatment line: Targeted therapy, Chemotherapy and Somatostatin analogs).

Targeted therapy

The targeted therapy will be described for each period (overall follow-up, before inclusion, after inclusion) and as follows:

- Number of patients having received at least one targeted therapy.
- Number of patients having received Everolimus at least once.
- Number of patients having received Sunitinib at least once.
- Number of patients having received Pazopanib at least once.
- Number of patients having received Everolimus at least once and Sunitinib at least once.
- Number of patients having received Everolimus at least once, but not Sunitinib or Pazopanib.
- Number of patients having received Sunitinib at least once, but not Everolimus or Pazopanib.
- Number of patients who never received targeted therapy.
- Number of targeted therapies received per patient (quantitative and by class: 0 / 1 / 2 / 3 / 4 and more).

Targeted therapy will be described for the entire follow-up based on:

- Number of patients having received two different targeted therapies (Everolimus and Sunitinib, or Everolimus and Pazopanib, or Sunitinib and Pazopanib).

In addition, the position of the targeted therapy in the care pathway of the patient will be described for the entire follow-up:

- Number of patients having received a targeted therapy as the 1st, 2nd, 3rd, ... nth main treatment line.
- Number of patients having received a targeted therapy immediately before/after chemotherapy.
- Number of patients having received a targeted therapy immediately before/after a somatostatin analog (as main treatment).

The duration of the targeted therapy (in months) and reasons for the discontinuation will also be described irrespective of the targeted therapy and by differentiating between Everolimus and Sunitinib during the period before inclusion then after inclusion.

The total duration of the targeted therapy (obtained by adding the periods before inclusion and after inclusion) will be described.

The analysis and duration of the targeted therapy (irrespective of the targeted therapy) and the reasons for the discontinuation will also be presented based on the following subgroups:

- Main treatment lines during follow-up (1/2/.../n).
- Number of patients with ≤2 lines, >2 main treatment lines for the entire follow-up.
- Ki67 (the most recent prior to inclusion) (≤10% / >10%).
- Liver invasion at initiation of the ongoing treatment line or line started at inclusion (≤50% / >50%).
- Number of metastatic sites when starting the current line of treatment or line of treatment started at inclusion (≤2 / >2). The "not reported" modality will be considered as missing data.

Chemotherapy

Chemotherapy will be described for each period (overall follow-up, before inclusion, after inclusion) and as follows:

- Number of patients having received chemotherapy at least once.
- Number of patients having never received chemotherapy.
- Number of chemotherapies received per patient (quantitative and by class: 0 / 1 / 2 / 3 / 4 and more).

- Number of patients having received chemotherapy and a somatostatin analog as main treatment.

In addition, the position of chemotherapy in the care pathway of the patient will be described for the entire follow-up:

- Number of patients having received chemotherapy as the 1st, 2nd, 3rd, ... nth main treatment line.
- Number of patients having received chemotherapy immediately before/after targeted therapy.
- Number of patients having received chemotherapy immediately before/after a somatostatin analog (as main treatment).
- Number of patients having received chemotherapy as 1st line at inclusion then targeted therapy as 2nd line (yes/no).
- Number of patients having received alkylating chemotherapy after inclusion (yes/no).
- Number of alkylating chemotherapies received after inclusion.

Alkylating agents are listed in Appendix 10.2.

Somatostatin analogs

Somatostatin analogs will be described for each period (entire follow-up, prior to inclusion, after inclusion) overall (main or combination treatment), if received as a main or combination treatment and as follows:

- Number of patients having received at least one somatostatin analog.
- Number of patients having never received a somatostatin analog.
- Number of somatostatin analogs received per patient (quantitative and by class: 0 / 1 / 2 / 3 / 4 and more).

In addition, the position of the somatostatin analog in the care pathway of patients will be described for the entire follow-up:

- Number of patients having received a somatostatin analog as the 1st, 2nd, 3rd, ... nth main treatment line.
- Number of patients having received a somatostatin analog in combination as the 1st, 2nd, 3rd, ... nth main treatment line.
- Number of patients having received a somatostatin analog as the 1st, 2nd, 3rd, ... nth main treatment line or in combination.

- Number of patients having received a somatostatin analog as the main treatment line immediately before/after targeted therapy.

- Number of patients having received a somatostatin analog as the main treatment line immediately before/after chemotherapy.

Surgery

Number and percentage of patients who underwent surgery are described for each period (entire follow-up, before inclusion, after inclusion). Surgery for primary, surgery for liver metastases and surgery recorded under "other treatment" will be considered.

5.9.4. Sequence of Treatment Lines

The main treatment lines (targeted therapy, chemotherapy, somatostatin analog, etc.) will be presented by sequence for the entire follow-up, before inclusion, at inclusion and after inclusion. For each sequence, the number of patients in each sequence will be presented. This analysis will be duplicated by providing details of the targeted therapies (Everolimus, Sunitinib and Pazopanib). The main concomitant treatment lines will also be presented with a detailed description of the targeted therapies.

5.9.5. Discontinuation Due to Toxicity

Discontinuation due to toxicity (AE or death) of the main treatment line will be described for the period after inclusion. The number of patients with at least one discontinuation due to toxicity and the number of discontinuations due to toxicity will be described based on:

- The main treatment ongoing at inclusion (Targeted therapy (of any kind, then Everolimus and Sunitinib), Chemotherapy, Somatostatin analog).

- Number of lines for the entire follow-up (≤2 lines, >2 lines).

- Number of targeted therapies received for the entire follow-up (0, 1, 2, >2).

- Targeted therapy received as 2nd line main treatment vs Chemotherapy received as 2nd line main treatment for the entire the follow-up period.

5.9.6. Main Treatment Lines Received Over the Entire Follow-up Period

For each main treatment line, the number of main treatment lines, the nature of treatments, the duration and reasons for discontinuation will be presented over the entire follow-up (retrospective phase and prospective phase) overall and based on the current treatment at inclusion (targeted therapy/ chemotherapy / somatostatin analog).

The number of main treatment lines received during the study (quantitative and by class), the nature of lines of treatment received during the study (other than those received at inclusion) and the total number of treatment lines received will be shown based on the "at least one targeted therapy before inclusion (yes /no)" subgroup.

5.9.7. Progression-free Survival

Progression-free survival of treatment received at inclusion will be estimated based on the following subgroups:

- At least one targeted therapy before inclusion (yes/no).
- At least one targeted therapy at any time (yes/no).
- Patients receiving chemotherapy as main 2nd line treatment vs patients receiving targeted therapy as main 2nd line treatment.
- Ki67 (≤10%, >10%).
- At least two targeted therapies vs one targeted therapy before inclusion (yes/no).
- At least two targeted therapies vs one targeted therapy at any time of the study (yes/no).
- At least a 1st targeted therapy as line 1 or 2 vs at least a 1st targeted therapy as line 3 or 4 at any time during the study.
- Stage at diagnosis (localised /metastatic).
- At least one surgery at any time of the study (yes/no).
- For 1st line patients at inclusion:
    - Based on targeted therapy/chemotherapy/somatostatin analog at inclusion;
    - At least one targeted therapy at any time of the study (yes/no).
- For 2nd line patients at inclusion:
    - Based on targeted therapy/chemotherapy/somatostatin analog (main treatment) at inclusion;
    - At least one targeted therapy before inclusion (yes/no);
    - At least one targeted therapy at any time of the study (yes/no).
- For metasynchronous patients:
    - Based on current main treatment at inclusion (targeted therapy/ chemotherapy / somatostatin analog);
    - Based on the 1st targeted therapy line at any time of the study (targeted therapy as line 1 or 2, targeted therapy as line 3 or 4).

- For chemotherapy patients at inclusion:
    - Based on line number at inclusion (≤2, >2);
    - Based on the total number of main treatment lines over the entire follow-up (≤2, >2).

Progression-free survival will also be estimated overall for patients receiving targeted therapy at any time of the study based on:

- Liver invasion (≤50%, >50%);
- Number of metastatic sites (≤2, >2).

Analyses of progression-free survival will also be conducted on patient subgroups by main treatment line and by main treatment. These analyses will be calculated from the start of each line (ie, the baseline date will be the start date of the main treatment of any new line after changing the main treatment). Therefore, patients may appear as many times as they have changed their main treatment. Only the lines at inclusion and subsequently will be considered in these analyses, as the information collected for previous lines is not sufficient for a survival analysis. Progression-free survival according to the main treatment lines will not be shown if the start date of the main treatment is later than the date of the last visit. In addition, for this analysis, patients will be censored based on the date of the last tumour assessment or clinical assessment for the line, when patients change line without reporting a progression. When there is no date for the tumour or clinical assessment, patients will be censored on the date they discontinued treatment in relation to the line being analysed.

Progression-free survival by subgroup will be analysed using the method described for analysing progression-free survival in the main analysis, which uses as the baseline date the date of starting the main treatment at inclusion (see above). The Kaplan-Meier method, with right censoring and left truncation, uses the PROC PHREG SAS® procedure.

5.9.8. Overall Survival

In order to better describe the NET patients regardless of their therapeutic management, overall survival will be estimated for all patients, firstly from the time of diagnosis (baseline date = date of diagnosis) and secondly for patients included in the first line of treatment (baseline date = date of 1st line treatment was started if available).

In addition, overall survival (baseline date = date of diagnosis) will also be estimated according to:

- Stage at diagnosis (localised /metastatic),
- Receiving at least one targeted therapy during the data-collection period at any time of the study (yes/no),

- A 1st targeted therapy as line 1 or 2 vs a 1st targeted therapy as line 3 or more at any time of the study,

- Patients having undergone at least one surgery at any time of the study (yes/no).

These analyses will also consider the baseline date as the date of starting treatment at inclusion.

In addition, overall survival will be estimated in metasynchronous patients based on:

- Receiving at least one targeted therapy at any time of the study (yes/no),

- A 1st targeted therapy as line 1 or 2 vs a 1st targeted therapy as line 3 or more.

These two analyses will be duplicated using as the baseline date the date of starting treatment at inclusion, firstly, and the date of diagnosis, secondly.

Overall survival will also be estimated based on the main treatment line by differentiating between the main treatments (baseline date is the start date of each line). Therefore, patients may appear as many times as they have changed their main treatment.

Only the lines at inclusion and subsequently will be considered in the calculation, as the information collected for previous lines is not sufficient to be counted. Overall survival will not be shown if the start date of the main treatment is later than the date of the last visit. Patients still alive when they have completed the line will be censored on the start date of the next line or on the date of receiving the most recent news.

These overall survival analyses will be performed using the method described for analysis of overall survival for the main analysis, the baseline date of which is the date when treatment is started (See above). Analyses will be perfomed for all patients: a Kaplan-Meier estimator of the survival function for left-truncated and right-censored data will be computed using the SAS PROC PHREG procedure on SAS® software.

5.9.9. Changing Main Treatment After Progression

The number and percentage of patients who discontinued their main treatment after progression will be shown for the entire follow-up.

6. LIMITATIONS OF THE STUDY

This protocol has been designed in order to optimally meet the objectives set for this observational study and to meet the requests of the HAS. This however has certain limitations which need to be discussed and should be taken into account when the study is carried out and the results are used.

6.1. Selection Bias

The representativeness of study sample in terms of the target population is a fundamental factor in order to extrapolate the results of the study to the target population. Sample

representativeness depends on the internal validity (precision of estimates and selection criteria for the study population – patients) and external validity (sampling plan and fluctuations).

6.1.1. Representativeness of Included Patients

This also involves the potential selection bias present in observational studies. It is inevitable that patients will be selected for the study by the participating doctors either consciously or subconsciously. The participating doctors will be asked to include all of the initial patients who meet the eligibility criteria for the study sequentially and exhaustively until the subgroup numbers have been reached (targeted therapies group, other treatments group) and the total number nationally for the study in order to reduce this bias.

In order to guarantee that this consecutive approach is used, a register of non-inclusions will be created. Patients who are eligible but not included in the study must be entered in this register throughout the inclusion period and/or until the intended number of patients has been reached. A minimum of number of variables will be collected: sex, year of birth, ECOG performance index and reason for non-inclusion.

It is important to include patients from clinical trials into this study (in some conditions as explained in the study protocol) as follow-up bias (potentially related to the follow-up frequency and conditions imposed by the study) will have less impact than the selection bias which may result from including only those patients who are ineligible for studies.

The decision has also been taken to limit the inclusion of patients by excluding those patients who have received at least 5 or more treatment lines. Whilst this limitation criterion selects the study population, it provides as consistent as possible sample of patients treated for pNET, which we aim to assess in this study. Many of these patients have received very different sequences/lines of treatment, in the absence of an approved sequence. This sample consistency will ensure that the descriptions of the treatment subgroups and, where applicable, the previous lines of treatments received are valid.

6.1.2. Patients Lost to Follow-up During the Follow-up Period

Particular attention will be paid to patients who stop the study or whom the investigator does not review in a visit because of the observational nature of the study (visit frequency for patient follow-up may vary depending on the doctor). For patients who are lost to follow up, an early last news/end of study questionnaire will be completed by the investigator. The statistical analyses will compare the characteristics of included patients who participated throughout the duration of the study with those patients who were included but were lost to follow-up and/or stopped the study.

6.1.3. Left Truncation and Left Censoring

Left truncation bias is present for prevalent patients who started ongoing treatment prior to inclusion into the study because of the impossibility of including patients who have died into the study. The prevalent patients also exhibit left censoring bias because of the lack of retrospective collection of tumour assessment data.

These sources of bias are taken into account in the overall survival analysis and progression-free survival analysis using the statistical method described in Section 5.5.1.

Incident patients contribute to the survival curve from their baseline date. Conversely, prevalent patients are only at risk of developing an event from their inclusion into the study onwards and therefore do not contribute to the survival curve from their baseline date, although do contribute from a later date after their inclusion into the study. All patients from the reference set will therefore be taken into account into the survival analysis although patients whose treatment started two years before the beginning of the study will only be included after a two-year follow-up period and will therefore not be included in the estimation of the two-year survival rate. This is a limitation of the study.

6.2. Measurement Bias

A priori, measurement bias should be minimal, particularly as the study principally involves descriptive objectives and as patient inclusion and data collection will be prospective. Bias may however be present in patients who started treatment (targeted therapy or other treatment) before their inclusion in the study. In these patients, the data will be collected retrospectively until the start date of the ongoing treatment line for the primary objectives of estimating the progression-free survival rate and overall survival rate. This information, which is recorded (progression/response, ongoing treatment) however represents key data in terms of patient survival, which needs to be correctly entered into the patient dossiers. Furthermore, the detailed retrospective collection of response and treatment will only include the treatment which was ongoing at the time of inclusion. The information collected about potential treatment lines prior to inclusion only includes the number of lines and corresponding treatment regimens (not shown).

The estimate of progression-free survival will be less precise than in a clinical trial because of the time intervals between the assessment visits, which are based on real-world conditions and are longer than in clinical trials. Similarly, the assessment of progression/response will be based on the investigator's opinion (which itself will be based on RECIST 1.1 criteria).

The analysis of AEs related to treatment will be partially incomplete for a combination of treatments: the doctor can only enter a single treatment into the CRF and cannot enter which treatment was involved in an action (discontinuation, reduction/increase in dosage).

6.3. Missing Data

The data will be collected using an electronic CRF. This tool firstly enables the number of missing data to be minimised through the use of scrolling lists and fields approved by the Scientific Committee for which completion is mandatory.

Furthermore, the handling of missing data, which is particularly important in longitudinal analyses, will be discussed and the methodology approved prior to conducting the analyses.

6.4. Confusion Bias

Presciption bias is expected in this observational study, in which the choice of treatment between several possible options is not made randomly but according to the choice of the

investigator as a function of the patient's characteristics, the patient's disease and his/her previous treatments. A statistical comparison of the impact of treatments for pNET in terms of morbidity or mortality in this study, is not strictly appropriate as it is clearly subject to confusion bias. For this reason, the study has been designed in order to describe the impact of morbidity and mortality in each of the treatment groups (targeted therapies, other treatments), independently.

Where, however, comparisons were planned, multivariate Cox models will be applied in order to adjust the characteristics of patients potentially associated with the type of treatment received and survival which are liable to cause bias (confusion, change in effect) in the estimates.

6.5. Study Size

Pancreatic neuroendocrine tumours are one of the orphan diseases. The target population is estimated to be 150 patients annually. In this study, the sample size calculation must balance the statistical calculations against the feasibility of the study. According to the information which is available, a number of 150 patients included over a period of 2 years appears to be a feasible objective. Including a total of 150 patients will allow median survival (progression-free survival or overall survival) to be estimated with a precision in the region of 8%. It should be noted that the subgroup analyses (targeted therapy, other treatments) allow median values to be estimated with greater imprecision, as the numbers in the stratification groups are lower.

It is also important to note that these calculations (beyond taking account of practical and actual feasibility of patient recruitment) are based on simulations for the descriptive primary objective of morbidity and mortality assessed in particular from progression-free survival and overall survival. The calculations have not been carried out in order to meet a comparative objective. In practice, the numbers required for a statistically significant comparison based for example on a mortality criterion would require recruitment for over 6 years (on the basis of 4 comparative treatment groups, an assumption of a relative reduction in mortality of 20% and 250 patients per group required ie, 1,000 patients) given the estimated target population of 150 patients annually.

In addition, the estimate of the number of subjects required is based on an approximation using the Klein and Moeschberger equation to calculate the median survival not taking account of left truncation.

7. TABLES, FIGURES AND LISTINGS

8. KEY E-CRF DATA

The table below shows the data required in the eCRF to conduct the main study analysis. As stated in the part describing this analysis (See Section 5.5), particular attention will be paid to recording data on disease progression in the study patients in order to reduce bias.

Parameter	**Data**	**eCRF Variables**
Group (documented treatment in the study)	Main treatment Precision	ITTTRTC EVESUNC
Start date (of line ongoing at the time the patient was included) of treatment with targeted therapy or other treatments	Treatment start date	TSUINDT TINITDT TCHINDT
Disease outcome	Response to treatment, date	Tumour assessment visits: Radiological response: EXTRESP EXTP1DT Clinical response: EXTCRYN EXTCRSP EXTP2DT Dropped out of study: STTRESP STTREDT
	Death, date	Dropped out of study: STTSTAT STTDTDT
Patient status at the end of the study	Patient status 2-year follow-up completed	Dropped out of study: STTSTAT Complete follow-up: VISLVYN
Total duration of exposure to treatment	Treatment start date Treatment end date (permanent discontinuation)	TSUINDT TINITDT TCHINDT FTTEND
Temporary discontinuations	Discontinuation Date discontinuation started Reason for discontinuation Duration of discontinuation	TSUTSYN, TEVTSYN, TIXTSYN, TCHTSYN, TASTSYN, PTST2YN TSTOPDT TSTOPRS TSTOPDU
Permanent discontinuations	Date of permanent discontinuation	FTTEND

Parameter	**Data**	**eCRF Variables**
	Reason for permanent discontinuation	FTTENRS
Adverse events	Description	AEVTERM
	Seriousness	AEVSERC
	Relationship with treatment	AEVRELC
	Death	AEVAES1
	Action on treatment	AEVACTC
	Grade	AEVGRAD

9. TEMPLATES OF TABLES, LISTINGS AND FIGURES

9.1. Demographic Data

9.1.1. Dates of the Study

Table 14.1.1.1: Conduct of the Study

Date of inclusion of the first patient	DD/MM/YYYY
Date of inclusion of the last patient	DD/MM/YYYY
Duration of inclusions (months)	XX.X
Date of last visit of last patient	DD/MM/YYYY
Duration of study (months)	XX.X

Note: duration of study = time between inclusion and last visit.

9.1.2. Distribution of Doctors

Table 14.1.2.1: Study Doctors

	Total (N=XX)
Active doctors	XX (XX.X%)
Inactive doctors	XX (XX.X%)

9.1.3. Distribution of Patients

Table 14.1.3.1: Analysis Sets

		Targeted therapies	Other treatments	Treatment not stated	Total
Not-included patients	N	/	/	XX	XX
Included patients	N	XX	XX	XX	XX
Safety analysis set	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Incident patients	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Prevalent patients	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reference set	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Incident patients	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Prevalent patients	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: The percentages are calculated from the population of included patients.

Incident/ prevalent: eCRF data. In case of a missing data, a patient is prevalent if the inclusion date is after the entered start date.

Programmer note:

- Prevalent patients: those who started the study treatment before the inclusion visit.
- Incident patients: those who started the study treatment on the day or after the inclusion visit.

Table 14.1.3.2: Reason for Non-inclusion into the Safety Analysis Set and Reference Set – Included Patients

		Targeted therapies (N=XX)	Other treatments (N=XX)	Treatment not stated (N=XX)	Total (N=XX)
Patients included in the safety analysis set	N	XX	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason for exclusion from the safety analysis set (1)	N	XX	XX	XX	XX
	Treatment not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Treatment start date missing	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients included in the reference set	N	XX	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason for exclusion from the reference set (1)	N	XX	XX	XX	XX
	Failure to meet the eligibility criteria	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Treatment not received	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No follow-up data	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of patients excluded from the safety analysis set/reference set

Note: A patient may have several reasons for exclusion from the safety analysis set/reference set.

Table 14.1.3.3: Characteristics of Centre – Included Patients

		Number of centres with at least one prevalent patient (N=XX)	Number of centres with at least one incident patient (N=XX)	Total number of centres (N=XX)
Number of centres	N	XX	XX	XX
Number of patients per centre	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Number of patients per centre (N(%))	N	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.1.3.4: Reasons for Dropping Out of the Study – Safety Analysis Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Treatment not stated (N=XX)	Total (N=XX)
Study drop-out	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason for dropping out of the study (1)	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	Alive	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>>	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>>	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Lost to follow-up	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Progression of the disease	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of patients who dropped out of the study.

Table 14.1.3.5: Reasons for Dropping Out of the Study – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Treatment not stated (N=XX)	Total (N=XX)
Study drop-out	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason for dropping out of study (1)	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	Alive	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>>	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>>	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Lost to follow-up	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Progression of the disease	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Missing data	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Alive	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Failure to meet the inclusion-non-inclusion criteria at inclusion into the study	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of patients who dropped out of the study.

TABLE 14.1.3.6: PATIENT STATUS AT THE END OF THE STUDY – SAFETY ANALYSIS SET

		Targeted therapies (N=XX)	Other treatments (N=XX)	Treatment not stated (N=XX)	Total (N=XX)
Status	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	Alive	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> 2-year follow-up completed (1)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Failure to meet the inclusion-non-inclusion criteria at inclusion into the study	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Transfer to another centre not taking part in the study	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Other reason, give details	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Lost to follow-up	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Disease progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Patient PPD was followed up for 2 years. A fatal AE was declared 2 days after the end of this 24-month follow-up period. Patient PPD died after the 2-year follow-up period. Patient PPD died after the 2-year follow-up period.

Table 14.1.3.7: Patient Status at the End of the Study – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Status	N	XX	XX	XX
	Missing data	XX	XX	XX
	Alive	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> 2-year follow-up completed (1)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Failure to meet the inclusion-non-inclusion criteria at inclusion into the study	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Transfer to another centre not taking part in the study	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Other reason, give details	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Lost to follow-up	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Disease progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Patient PPD was followed up for 2 years. A fatal AE was declared 2 days after the end of this 24-month follow-up period. Patient PPD died after the 2-year follow-up period. Patient PPD died after the 2-year follow-up period.

Table 14.1.3.8: Protocol Deviations – Included Patients

		Targeted therapies (N=XX)	Other treatments (N=XX)	Treatment not stated (N=XX)	Total (N=XX)
At least one protocol deviation	N	XX	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Deviation (1)	N	XX	XX	XX	XX
	Breach of inclusion criteria 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Breach of inclusion criteria 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of patients with at least one protocol deviation.

9.1.4. Baseline Characteristics

9.1.4.1. Description of Patients

Programmer note: All tables will be duplicated for the 6 subgroups of patients (everolimus (AFINITOR®), sunitinib (SUTENT®), chemotherapy, somatostatin analogs, interferon alpha and metabolic radiotherapy).

Table 14.1.4.1.1: Demographic Characteristics – Included Patients

		Targeted therapies (N=XX)	Other treatments (N=XX)	Treatment not stated (N=XX)	Total (N=XX)
Age at inclusion (years)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Sex	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Using the same template:

Table 14.1.4.1.2: Demographic Characteristics – Reference Set

Table 14.1.4.1.3: Ecog Index at Inclusion – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
ECOG index	N	XX	XX	XX
	Missing data	XX	XX	XX
	0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	4	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

The ECOG data = unknown data were deemed to be missing data.

Table 14.1.4.1.4: Comorbidities and Past History – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Lung disease	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Treated lung disease (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Heart failure	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
...				

(1) Percentages calculated as a proportion of patients with the disease in question

(2) Percentages calculated as a proportion of patients with treated diabetes

Programmer note: all of the variables contained in the section "Comorbidities and past history at the ongoing treatment line start or at inclusion" of the CRF should be shown in this table. The LVEF (%) value is shown as 2 classes <50% and ≥50%.

Table 14.1.4.1.5: Comorbidities and Past History: Summary – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Patients with a past history of at least one comorbidity (ie: listed in the CRF + Others)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients with a past history of least one comorbidity <u>of interest</u> (ie: listed in the CRF)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of comorbidities of interest in the past history by patient	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
...	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]

Table 14.1.4.1.5: Comorbidities and Past History: Summary – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Number of comorbidities of interest in the past history by patient (classes)	N	XX	XX	XX
	Missing data	XX	XX	XX
	0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	[1-3]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
...	>3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients with a past history of at least one treated comorbidity of interest (ie: listed in the crf)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of treated comorbidities of interest in the past history by patient	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
...	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Number of treated comorbidities of interest in the past history by patient (Classes)	N	XX	XX	XX
	Missing data	XX	XX	XX
	0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	[1-3]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
...	>3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Listing 14.1.4.1.1: Other Comorbidities and Past History – Reference Set

Patient Sex Age	Group	Lung disease	Heart failure	LVEF	Coronary artery disease	CVA	Hyper tension	Hypercholesterolemia	Diabetes	Other	Clearance (ml/min)	Symptoms on starting
XXXX XXXX XX	xxxx											

Table 14.1.4.1.6: Initial Diagnosis of the Disease – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Length of history of disease (years)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Type of tumour at diagnosis	N	XX	XX	XX
	Missing data	XX	XX	XX
	Localised	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Metastatic	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.1.4.1.7: Characteristics of the Pancreatic Neuroendocrine Tumour When Starting the Current Line of Treatment or Line of Treatment Initiated at Inclusion – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Metastases present	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site: lung (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site: bone (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site: liver (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Percentage of liver invasion (2)	N	XX	XX	XX
	Missing data	XX	XX	XX
	≤50%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>50%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site: peritoneum (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site: Other (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Organ 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> …	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Organ N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of patients with metastases.

(2) Percentages calculated as a proportion of patients with localised liver metastases.

Programmer note: for the "Other" site, show the frequency for each of the organs listed (after grouping together the terms 'nodes/lymph nodes' under the term 'Adenopathies').

Table 14.1.4.1.8: Previous Locoregional Cancer Treatments – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Previous locoregional cancer treatments received	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Surgery for primary (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Surgery for liver metastases (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Radio frequency (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Chemo-embolisation/ embolisation (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of patients with cancer treatments.

Listing 14.1.4.1.2: Other Previous Locoregional Cancer Treatments – Reference Set

Patient Sex Age	Group	In the history, has the patient received locoregional treatments?	Locoregional treatment received	Other locoregional treatment received
XXXXX XXXXX XX	XXXX			

Table 14.1.4.1.9: Investigations Performed Most Recently – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Octreoscan	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time since Octreoscan (months) (1)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Octreoscan, uptake (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
PET scan	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time since PET scan (months) (1)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
PET scan, uptake (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ki67 value obtained	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ki67 value (1)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	<3%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	3-20%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>20%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mitotic index value obtained	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mitotic index value (1)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	<2 mitoses/field	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2-20 mitoses/field	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.1.4.1.9: Investigations Performed Most Recently – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
	>20 mitoses/field	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Rereading by TenPath	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of patients concerned.

Table 14.1.4.1.10: Previous Cancer Treatment Lines – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Number of previous lines of treatment by patient	N	XX	XX	XX
	Missing data	XX	XX	XX
	0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients with at least one previous line of treatment per site	N	XX	XX	XX
	Missing data	XX	XX	XX
	No previous line	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Previous first line of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Previous second line of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Previous third line of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients with at least one line of treatment by type of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Sunitinib	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Chemotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Somatostatin analogs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Interferon alpha	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Metabolic radiotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> …	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients by sequences of type of previous treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapy-Chemotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Chemotherapy-somatostatin analog	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Somatostatin analog	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…..			
Reason for discontinuation – by type of treatment regardless of line (0)	N	XX	XX	XX

Table 14.1.4.1.10: Previous Cancer Treatment Lines – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
	Missing data	XX	XX	XX
	Targeted therapies (1)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Planned discontinuation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	….			
First line of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Sunitinib	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Chemotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Somatostatin analogs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Interferon alpha	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Metabolic radiotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> …	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
First line of treatment (combination) (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Treatment 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Treatment N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Duration of first line if targeted therapy (months) (1)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Reason for discontinuation - First line of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Planned discontinuation of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason for discontinuation (0) - First line of treatment by type of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Planned discontinuation of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	….			

Table 14.1.4.1.10: Previous Cancer Treatment Lines – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Second line of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	...	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
...				

(0) Percentages calculated as a proportion of the number of patients in the treatment class concerned.

(1) Percentages calculated as a proportion of the number of patients concerned.

Programmer note:

- For the variable "Previous lines of treatment" show the frequencies for all previous lines of treatment received by the patients: line 1 … line N.
- Also show the duration (if targeted therapy) and reason for stopping the 2nd and 3rd lines of treatment.
- N treatments describe the combination with somatostatin analogs.
- Group together all chemotherapies (combinations of chemotherapies included) under the title 'Chemotherapy'.
- Group together lanreotide and octreotide under somatostatin analogs for all of the analyses in this table and sunitinib then everolimus under the targeted therapies in the analyses of treatment combinations by line of treatment and overall treatment regimen.

Listing 14.1.4.1.3: Other Previous Cancer Treatments – Reference Set

Patient Sex Age	Group	Treatment line	Treatment	Details of treatment
XXXXX XXXXX XX	xxxx	xx	xxxxxx	xxxxxx

Listing 14.1.4.1.4: Other Reasons For Discontinuing Previous Cancer Treatment Lines – Reference Set

Patient Sex Age	Group	Treatment line	Treatment	Treatment: combination	Reason for discontinuation	If Other, give details
XXXXX XXXXX XX	xxxx	xx	xxxxxx	xxxxxx	xx	xxxxx

Table 14.1.4.1.11: Ongoing Treatment At Inclusion – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Targeted therapy	N	XX	NA	NA
	Missing data	XX		
	Everolimus	XX (XX.X%)		
	Sunitinib	XX (XX.X%)		
Other treatment	N	NA	XX	NA
	Missing data		XX	
	Chemotherapy		XX (XX.X%)	
	Somatostatin analogs		XX (XX.X%)	
	Interferon alpha		XX (XX.X%)	NA
	Metabolic radiotherapy		XX (XX.X%)	
Chemotherapy (1)	N	NA	XX	NA
	Missing data		XX	
	5 FU		XX (XX.X%)	
	…		XX (XX.X%)	
	Other		XX (XX.X%)	NA
Chemotherapy combination (1)	N	NA	XX	NA
	Missing data		XX	
	FOLFIRI		XX (XX.X%)	
	…		XX (XX.X%)	
Somatostatin analogs (1)	N	NA	XX	NA
	Missing data		XX	
	Octreotide		XX (XX.X%)	
	Lanreotide		XX (XX.X%)	
Start of treatment	N	XX	XX	XX
	Missing data	XX	XX	XX
	The day of the inclusion consultation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Before the inclusion consultation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time between start of treatment and inclusion (months) (prevalent patients)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]

Table 14.1.4.1.11: Ongoing Treatment At Inclusion – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time between start of treatment and inclusion (days) (incident patients)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time between diagnosis and start of treatment (months)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time between diagnosis and start of treatment (months) (prevalent patients)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time between diagnosis and start of treatment (months) (prevalent patients) – First line of treatment	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time between diagnosis and start of treatment (months) (prevalent patients) – Second line of treatment	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
….				
Time between diagnosis and start of treatment (months) (Incident patients)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time between diagnosis and start of treatment (months) (Incident patients) –First line of treatment	N	XX	XX	XX
	Missing data	XX	XX	XX

Table 14.1.4.1.11: Ongoing Treatment At Inclusion – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
…..				
Treatment decision	N	XX	XX	XX
	Missing data	XX	XX	XX
	RENATEN SmPC	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other SmPC	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Antisecretory treatment	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Type of antisecretory treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Diazoxide	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Proton pump inhibitor	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of the number of patients concerned.

Programmer note: Incident/prevalent: eCRF data. If the data are missing but the inclusion date and start date are entered, derive the information from these dates.

Chemotherapy combination to be identified according to the list of protocols in appendice 10.

Listing 14.1.4.1.5: Details of Other Current Treatments at Inclusion – Reference Set

Patient Sex Age	Group	Treatment subgroup	Chemotherapy: combination	If Other, give details	Somatostatin analog	Others combinations
XXXXX XXXXX XX	xxxx	xx	xxxxxx	xxxxxx		

Listing 14.1.4.1.6: Other Antisecretory Treatments at Inclusion – Reference Set

Patient Sex Age	Group	Has the patient received or is he/she receiving an antisecretory treatment?	Diazoxide	Proton pump inhibitor	Other	If Other, give details
XXXXX XXXXX XX	xxxx	xx	xxxxxx	xxxxxx		

Table 14.1.4.1.12: Ongoing Treatment at Inclusion: Combinations – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Type of treatment	N	XX	XX	XX
	Missing data	XX	XX	XX
	Monotherapy	XX (XX.X%)	0 (0.0%)	XX (XX.X%)
	Combination treatment	XX (XX.X%)	0 (0.0%)	XX (XX.X%)
Treatment received – details of combinations (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Sunitinib+ octreotide	XX (XX.X%)	0 (0.0%)	XX (XX.X%)
	Sunitinib+ lanreotide	XX (XX.X%)	0 (0.0%)	XX (XX.X%)
	Sunitinib+ other	XX (XX.X%)	0 (0.0%)	XX (XX.X%)
	Chemotherapy + octreotide	XX (XX.X%)	0 (0.0%)	XX (XX.X%)
	Chemotherapy + lanreotide	XX (XX.X%)	0 (0.0%)	XX (XX.X%)
	Chemotherapy + other	XX (XX.X%)	0 (0.0%)	XX (XX.X%)
	…			

(1) Percentages calculated as a proportion of the number of patients concerned.

Programmer note: show all of the combinations used in patients in the study.

Table 14.1.4.1.13: Caracteristics of the Main Treatment with Targeted Therapy at Inclusion: Sunitinib – Reference Set

		Sunitinib (N=XX)
Started before the inclusion consultation	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
Treatment started	N	XX
	Missing data	XX
	Monotherapy	XX (XX.X%)
	Combination	XX (XX.X%)
Treatment received – details	N	XX
	Missing data	XX
	Sunitinib alone	XX (XX.X%)
	Sunitinib + octreotide	XX (XX.X%)
	Sunitinib + lanreotide	XX (XX.X%)
	Sunitinib + other	XX (XX.X%)
Time between start of treatment and inclusion (months) (prevalent patients)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Time between start of treatment and inclusion (days) (incident patients)	N	XX
	Missing data	XX

Table 14.1.4.1.13: Caracteristics of the Main Treatment with Targeted Therapy at Inclusion: Sunitinib – Reference Set

		Sunitinib (N=XX)
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Starting dose (N(%))	N	XX
	Missing data	XX
	37.5 mg/day	XX (XX.X%)
	25 mg/day	XX (XX.X%)
	…	XX (XX.X%)
Change in dose step since initiation in prevalent patients	N	XX
	Missing data	XX
	0	XX (XX.X%)
	1	XX (XX.X%)
	…	XX (XX.X%)
Time since last change in dose (days) in prevalent patients (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Type of change of dose steps since starting treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Increase	XX (XX.X%)
	Reduction	XX (XX.X%)
	…	XX (XX.X%)
Dose after increase in treatment in prevalent patients (2)	N	XX
	Missing data	XX
	37.5 mg/day	XX (XX.X%)
	25 mg/day	XX (XX.X%)
	…	XX (XX.X%)
Dose after reducing treatment in prevalent patients (N(%)) (2)	N	XX
	Missing data	XX
	37.5 mg/day	XX (XX.X%)
	25 mg/day	XX (XX.X%)
	…	XX (XX.X%)
At least one dose reduction since starting treatment in prevalent patients	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
At least one dose increase since starting treatment in prevalent patients	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
Reasons for reducing dose since starting treatment in prevalent patients (2)	N	XX
	Missing data	XX

Table 14.1.4.1.13: Caracteristics of the Main Treatment with Targeted Therapy at Inclusion: Sunitinib – Reference Set

		Sunitinib (N=XX)
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)
Reasons for increasing dose since starting treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)
Time between 1st change in dose of treatment (days) in prevalent patients (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Mean time between two changes in dose (days) in treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Discontinuation >7 days since start of treatment in prevalent patients	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
Number of discontinuations prior to inclusion in prevalent patients (1)		N
		Missing data
	1	n (%)
	…	n (%)
Time since last discontinuation of treatment (days) in prevalent patients (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Duration of discontinuations of treatment in prevalent patients (days) (2)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]

Table 14.1.4.1.13: Caracteristics of the Main Treatment with Targeted Therapy at Inclusion: Sunitinib – Reference Set

		Sunitinib (N=XX)
Reasons for discontinuations of treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)

(1) As a proportion of number of patients concerned.

(2) As a proportion of the number of changes/increases/reductions.

Programmer note:

- For the variable "Treatment received", show all of the combinations listed.
- For the variable "Dose (N(%))", show all of the doses reported (including those in "Others").
- "Type of change in dose step since initiation": N=total number of changes in dose step (there may be several of these in any one patient).
- "Duration of discontinuations (days)" and "Reasons for discontinuations": N=total number of discontinuations (there may be several of these in the same patient).
- Time between the 1st change in dose = date of first change in dose – date treatment was started.
- Mean time before change in dose = mean time between two different consecutive doses.

Using the same template:

Table 14.1.4.1.14: Details of the Main Treatment by Targeted Therapy at Inclusion: Everolimus – Reference Set

Programmer note: for the variables "Reasons for reduction in dose since starting", "Reasons for increase in dose since starting" and "Reasons for discontinuation" the modalities are "Adverse event related to everolimus", "Adverse event not related to everolimus", "Adverse event (relationship with everolimus not stated)", "Patient's choice" and "Doctor's choice."

Table 14.1.4.1.15: Details of the Main Treatment with Chemotherapy at Inclusion – Reference Set

		Chemotherapy (N=XX)
Started before the inclusion consultation	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
Treatment started	N	XX
	Missing data	XX
	Monotherapy	XX (XX.X%)
	Combination	XX (XX.X%)
Treatment received	N	XX
	Missing data	XX
	Chemotherapy alone	XX (XX.X%)
	Chemotherapy + somatostatin analog	XX (XX.X%)
	Chemotherapy + Other	XX (XX.X%)
Treatment received – Details	N	XX
	Missing data	XX
	5FU	XX (XX.X%)
	5FU + capecitabine	XX (XX.X%)
	…	XX (XX.X%)
Time between start of treatment and inclusion (months) (prevalent patients)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Time between start of treatment and inclusion (days) (incident patients)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Number of treatment cycles given to prevalent patients	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Number of treatment cycles given to prevalent patients (N(%))	N	XX
	Missing data	XX
	1	XX (XX.X%)
	2	XX (XX.X%)
	…	XX (XX.X%)
Frequency of treatment cycles in prevalent patients	N	XX
	Missing data	XX
	7 days	XX (XX.X%)
	14 days	XX (XX.X%)
	…	XX (XX.X%)

Table 14.1.4.1.15: Details of the Main Treatment with Chemotherapy at Inclusion – Reference Set

		Chemotherapy (N=XX)
Change in dose step since starting treatment in prevalent patients	N	XX
	Missing data	XX
	0	XX (XX.X%)
	1	XX (XX.X%)
	…	XX (XX.X%)
Time since last change in dose (days) of treatment in prevalent patients (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Type of change of dose step since starting treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Increase	XX (XX.X%)
	Reduction	XX (XX.X%)
	…	XX (XX.X%)
At least one reduction in dose since starting treatment in prevalent patients	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
At least one increase in dose since starting treatment in prevalent patients	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	Non	XX (XX.X%)
Reasons for reduction in dose in dose since starting treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)
Reasons for increase in dose in dose since starting treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)
Time before 1st change in dose (days) of treatment in prevalent patients (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Mean time before change in dose (days) of treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)

Table 14.1.4.1.15: Details of the Main Treatment with Chemotherapy at Inclusion – Reference Set

		Chemotherapy (N=XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Time difference of at least 7 days since starting treatment in prevalent patients	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
Reasons for time differences in treatment for prevalent patients (2)	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)

(1) As a proportion of the number of prevalent patients.

(2) As a proportion of the number of patients concerned.

(3) As a proportion of the number of changes/increases/reductions.

Programmer note:

- For the variable "Frequency of cycles", show all of the frequencies reported (including those in "Others").

Table 14.1.4.1.16: Details of the Main Treatment with Interferon Alpha at Inclusion – Reference Set

		Interferon alpha (N=XX)
Started before the inclusion consultation	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
Treatment started	N	XX
	Missing data	XX
	Monotherapy	XX (XX.X%)
	Combination	XX (XX.X%)
Treatment received – Details	N	XX
	Missing data	XX
	Interferon alpha alone	XX (XX.X%)
	Interferon alpha + Somatostatin analog	XX (XX.X%)
	Interferon alpha+ Other	XX (XX.X%)
Type of treatment	N	XX
	Missing data	XX
	Pegylated	XX (XX.X%)

Table 14.1.4.1.16: Details of the Main Treatment with Interferon Alpha at Inclusion – Reference Set

		Interferon alpha (N=XX)
	Standard	XX (XX.X%)
Time between start of treatment and inclusion (months) (prevalent patients)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Time between start of treatment and inclusion (days) (incident patients)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Starting dose (N(%))	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Change in dose step since starting treatment in prevalent patients	N	XX
	Missing data	XX
	0	XX (XX.X%)
	1	XX (XX.X%)
	…	XX (XX.X%)
Time since last change in dose (days) of treatment in prevalent patients (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Reasons for change in dose since starting treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)
Time before 1st change in dose (days) of treatment in prevalent patients (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]

Table 14.1.4.1.16: Details of the Main Treatment with Interferon Alpha at Inclusion – Reference Set

		Interferon alpha (N=XX)
Mean time before change in dose (days) of treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Time difference of at least 7 days since starting treatment in prevalent patients	N	XX
	Missing data	XX
	No	XX (XX.X%)
	Yes	XX (XX.X%)
Reasons for time differences in treatment for prevalent patients (2)	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)

(1) As a proportion of the number of patients concerned.

(2) As a proportion of the number of changes/increases/reductions.

Table 14.1.4.1.17: Details of the Main Treatment with Somatostatin Analog at Inclusion – Reference Set

		Somatostatin analog (N=XX)
Started before the inclusion consultation	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
Treatment started	N	XX
	Missing data	XX
	Monotherapy	XX (XX.X%)
	Combination	XX (XX.X%)
Treatment received	N	XX
	Missing data	XX
	Octreotide alone	XX (XX.X%)
	Octreotide + Treatment 1	XX (XX.X%)
	…	XX (XX.X%)
Time between start of treatment and inclusion (months) (prevalent patient)s	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]

Table 14.1.4.1.17: Details of the Main Treatment with Somatostatin Analog at Inclusion – Reference Set

		Somatostatin analog (N=XX)
Time between start of treatment and inclusion (days) (prevalent patients)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Dose of octreotide (N(%))	N	XX
	Missing data	XX
	10 mg/28d	XX (XX.X%)
	20 mg/28d	XX (XX.X%)
	…	XX (XX.X%)
Dose of lanreotide (N(%))	N	XX
	Missing data	XX
	60 mg/28d	XX (XX.X%)
	90 mg/28d	XX (XX.X%)
	…	XX (XX.X%)
Change in dose step since starting treatment in prevalent patients	N	XX
	Missing data	XX
	0	XX (XX.X%)
	1	XX (XX.X%)
	…	XX (XX.X%)
Time before 1st change in dose (days) of treatment in prevalent patients (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Reasons for change in dose since starting treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)
Time before 1st change in dose (days) of treatment in prevalent patients (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Mean time before change in dose (days) of treatment in prevalent patients (2)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]

Table 14.1.4.1.17: Details of the Main Treatment with Somatostatin Analog at Inclusion – Reference Set

		Somatostatin analog (N=XX)
Time difference of at least 7 days since starting treatment in prevalent patients	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
Reasons for time differences in treatment for prevalent patients (2)	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)

(1) As a proportion of the number of patients concerned.

(2) As a proportion of the number of changes/increases/reductions.

Table 14.1.4.1.18: Details of the Main Treatment by Metabolic Radiotherapy at Inclusion – Reference Set

		Metabolic radiotherapy (N=XX)
Started before the inclusion consultation	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
Treatment started	N	XX
	Missing data	XX
	Monotherapy	XX (XX.X%)
	Combination	XX (XX.X%)
Treatment received	N	XX
	Missing data	XX
	Metabolic radiotherapy alone	XX (XX.X%)
	Metabolic radiotherapy + somatostatin analog	XX (XX.X%)
	Metabolic radiotherapy + other	XX (XX.X%)
Time between start of treatment and inclusion (months) (prevalent patients)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Time between start of treatment and inclusion (days) (incident patients)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]

Table 14.1.4.1.18: Details of the Main Treatment by Metabolic Radiotherapy at Inclusion – Reference Set

		Metabolic radiotherapy (N=XX)
Place of treatment	N	XX
	Missing data	XX
	France	XX (XX.X%)
	Netherlands	XX (XX.X%)
	Switzerland	XX (XX.X%)
	Other	XX (XX.X%)
Number of courses since start of treatment in prevalent patients	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Number of courses since start of treatment in prevalent patients (N(%))	N	XX
	Missing data	XX
	1	XX (XX.X%)
	2	XX (XX.X%)
	…	XX (XX.X%)
Radio-isotope	N	XX
	Missing data	XX
	Lutetium	XX (XX.X%)
	Indium	XX (XX.X%)
	Yttrium	XX (XX.X%)

Listing 14.1.4.1.7: Other Reasons for Changing or Temporarily Discontinuing Treatment at Inclusion – Reference Set

Patient Sex Age	**Group**	**Subgroup**	**Change/Temporary discontinuation**	**Other reasons**
XXXXX XXXXX XX	xxxx	xxxxxx	xxxxxxxx	xxxxxx

9.1.4.2. Description of Doctors

Table 14.1.4.2.1: Characteristics of Participating Doctors

		Total (N=XX)
Specialty	N	XX
	Missing data	XX
	Oncology	XX (XX.X%)
	Gastroenterology	XX (XX.X%)
	Endocrinology	XX (XX.X%)
	Other	XX (XX.X%)
Type of practice	N	XX
	Missing data	XX
	Public	XX (XX.X%)
	Private	XX (XX.X%)
Type of facility*	N	XX
	Missing data	XX
	Hospital	XX (XX.X%)
	Primary care/clinic	XX (XX.X%)
	Cancer Centre	XX (XX.X%)
Estimated number of patients suffering from a pancreatic neuroendocrine tumour (treated at the time the participation agreement was completed)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]

* Several answer options are possible.

9.1.4.3. Representativeness of the Samples of Patients and Doctors

Table 14.1.4.3.1: Representativeness of Sample of Doctors

		Active doctors (N=XX)	Inactive doctors (N=XX)	Standardised difference*
Specialty	N	XX	XX	
	Missing data	XX	XX	
	Oncology	XX (XX.X%)	XX (XX.X%)	XX.X
	Gastroenterology	XX (XX.X%)	XX (XX.X%)	XX.X
	Endocrinology	XX (XX.X%)	XX (XX.X%)	XX.X
	Other	XX (XX.X%)	XX (XX.X%)	XX.X
Type of practice	N	XX	XX	
	Missing data	XX	XX	
	Public	XX (XX.X%)	XX (XX.X%)	XX.X
	Private	XX (XX.X%)	XX (XX.X%)	XX.X
Type of facility	N	XX	XX	
	Missing data	XX	XX	
	Hospital	XX (XX.X%)	XX (XX.X%)	XX.X
	Primary care/clinic	XX (XX.X%)	XX (XX.X%)	XX.X
	Cancer Centre	XX (XX.X%)	XX (XX.X%)	XX.X

Table 14.1.4.3.1: Representativeness of Sample of Doctors

		Active doctors (N=XX)	Inactive doctors (N=XX)	Standardised difference*
Estimated number of patients suffering from a pancreatic neuroendocrine tumour (treated at the time the participation agreement was completed)	N	XX	XX	
	Missing data	XX	XX	
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.X
	Median	XX.X	XX.X	
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	

* Standardised difference: rapid interpretation: 0.2-0.3: weak, 0.3-0.8: moderate, >0.8: strong.

Table 14.1.4.3.2: Representativeness of Sample of Patients: Comparison of Non-Included and Included Patients

		Non-included patients* (N=XX)	Included patients (N=XX)	Standardised difference**
Age at inclusion (years)	N	XX	XX	
	Missing data	XX	XX	
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.X
	Median	XX.X	XX.X	
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	
Sex	N	XX	XX	
	Missing data	XX	XX	
	Male	XX (XX.X%)	XX (XX.X%)	XX.X
	Female	XX (XX.X%)	XX (XX.X%)	XX.X
Reason for non-inclusion	N	XX		
	Missing data	XX		
	Patient refusal	XX (XX.X%)		
	Other	XX (XX.X%)		

* data collected in the non-inclusion register.

*** Standardised difference: rapid interpretation: 0.2-0.3: weak, 0.3-0.8: moderate, >0.8: strong.

Listing 14.1.4.3.1: Other Reasons for Non-Inclusion – Non-Included Patients

Centre No.	Registration no.	Age	Sex	Others reasons for non-inclusion
XXXXX	1	XXXXX	XXXXX	XXXXX
	2	XXXXX	XXXXX	XXXXX

Table 14.1.4.3.3: Representativeness of the Samples of Patients: Comparison of Patients Lost to Follow-Up and/or Who Discontinued the Study Treatment Early (For a Reason Other than Death) and Patients with Full Follow-Up

		Patients lost to follow-up and/or dropped out of the study (for reason other than death) (N=XX)	Patients with complete follow-up** (N=XX)	Standardised difference*
Age at inclusion (years)	N	XX	XX	
	Missing data	XX	XX	
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.X
	Median	XX.X	XX.X	
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	
Sex	N	XX	XX	
	Missing data	XX	XX	
	Male	XX (XX.X%)	XX (XX.X%)	XX.X
	Female	XX (XX.X%)	XX (XX.X%)	XX.X
ECOG index at inclusion	N	XX	XX	
	Missing data	XX	XX	
	0	XX (XX.X%)	XX (XX.X%)	XX.X
	1	XX (XX.X%)	XX (XX.X%)	XX.X
	2	XX (XX.X%)	XX (XX.X%)	XX.X
	3	XX (XX.X%)	XX (XX.X%)	XX.X
	4	XX (XX.X%)	XX (XX.X%)	XX.X
Group	N	XX	XX	
	Missing data	XX	XX	
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX.X
	Other treatments	XX (XX.X%)	XX (XX.X%)	XX.X

The ECOG data = unknown entries were deemed to be missing data.

* Standardised difference rapid interpretation: 0.2-0.3: weak, 0.3-0.8: moderate, >0.8: strong.

** Patients who have complete follow-up (followed up until disease progression, death, end of main treatment ongoing at the time of inclusion or 2-year cutoff date).

9.1.5. Additional Analyses

9.1.5.1. Characteristics of Patients Based on having Received at Least One Targeted Therapy before Inclusion

Table 14.1.5.1.1: Demographic Characteristics – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Age at inclusion (years)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Sex	N	XX	XX	XX
	Missing data	XX	XX	XX
	Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.1.5.1.2: ECOG Index at Inclusion – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
ECOG index	N	XX	XX	XX
	Missing data	XX	XX	XX
	0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	4	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

ECOG data = Unknown were considered as missing data.

Table 14.1.5.1.3: Comorbidities and Past History – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Lung disease	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Treated lung disease (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Heart failure	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
...				

(1) Percentages calculated as a proportion of patients with the disease in question.

(2) Percentages calculated as a proportion of patients with treated diabetes.

Programmer note: all of the variables contained in the section “Comorbidities and past history at the start of the ongoing treatment line or at inclusion” on the CRF should be shown in this table. The LVEF (%) value is shown as 2 classes <50%, >=50%.

Table 14.1.5.1.4: Comorbidities and Past History: Summary – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Patients with a past history of at least one comorbidity (ie: listed on the CRF + others)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients with a past history of at least one comorbidity <u>of interest</u> (ie: listed on the CRF)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of comorbidities of interest in the past history by patient	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
...	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Number of comorbidities of interest in the past history by patient (classes)	N	XX	XX	XX
	Missing data	XX	XX	XX
	0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	[1-3]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
...	>3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients with a past history of at least one treated comorbidity of interest (i.e.: listed on the CRF)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of treated comorbidities of interest in the past history by patient	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
...	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Number of treated comorbidities of interest in the past history by patient (classes)	N	XX	XX	XX
	Missing data	XX	XX	XX
	0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	[1-3]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
...	>3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Listing 14.1.5.1.1: Other Comorbidities and Past History – Reference Set – Analysis of Patients with at Least One Targeted Therapy Before Inclusion

Patient Sex Age	Treatment group at inclusion	Lung disease	Heart failure	LVEF	Coronary artery disease	CVA	Hypertension	Hypercholesterolemia	Diabetes	Other	Clearance (ml/min)	Symptoms at start
XXXX XXXX XX	- xxxx - xxxx											

Using the same template:

Listing 14.1.5.1.2: Other Comorbidities and Past History – Reference Set – Analysis of Patients Who Did Not Receive Targeted Therapy before Inclusion

Table 14.1.5.1.5: Initial Diagnosis of Disease – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Length of the disease (years)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Type of tumour at diagnosis	N	XX	XX	XX
	Missing data	XX	XX	XX
	Localised	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Metastatic	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.1.5.1.6: Characteristics of the Pancreatic Neuroendocrine Tumour When Starting the Current Line of Treatment or Line of Treatment Started at Inclusion – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Metastases present	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site: lung (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site: bone (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site: liver (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Percentage of liver invasion (2)	N	XX	XX	XX
	Missing data	XX	XX	XX
	≤50%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>50%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site: peritoneum (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site: other (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Organ 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> …	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Organ N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of patients with metastases.

(2) Percentages calculated as a proportion of patients with localised liver metastases.

Programmer note: for the "Other" site, show the frequency for each of the organs listed (after grouping together the terms 'nodes/lymph nodes' under the term 'Adenopathies').

Table 14.1.5.1.7: Previous Locoregional Cancer Treatments – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Previous locoregional cancer treatments received	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Surgery for primary (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Surgery for liver metastases (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Radio frequency (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Chemo-embolisation/ embolisation (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of patients with cancer treatments.

Listing 14.1.5.1.3: Other Previous Locoregional Cancer Treatments – Reference Set – Analysis of Patients with at Least One Targeted Therapy before Inclusion

Patient Sex Age	At least one targeted therapy before inclusion (yes/no) Treatment group at inclusion	In the history, has the patient received locoregional treatments?	Locoregional treatment received	Other locoregional treatment received
XXXXX XXXXX XX	XXXX			

Using the same template:

Listing 14.1.5.1.4: Other Previous Locoregional Cancer Treatments – Reference Set – Analysis Of Patients Who Did Not Receive Targeted Therapy Before Inclusion

Table 14.1.5.1.8: Investigations Performed Most Recently – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Octreoscan	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time since Octreoscan (months) (1)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Octreoscan, uptake (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
PET scan	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time since PET scan (months) (1)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
PET scan, uptake (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ki67 value obtained	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ki67 value (1)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	<3 %	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	3-20 %	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>20 %	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mitotic index value obtained	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.1.5.1.8: Investigations Performed Most Recently – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Mitotic index value (1)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	<2 mitoses/field	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2-20 mitoses/field	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>20 mitoses/field	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Rereading by TenPath	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Not stated	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) Percentages calculated as a proportion of patients concerned.

Table 14.1.5.1.9: Previous Cancer Treatment Lines – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Number of previous lines of treatment by patient	N	XX	XX	XX
	Missing data	XX	XX	XX
	0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients with at least one previous line of treatment per site	N	XX	XX	XX
	Missing data	XX	XX	XX
	No previous line	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Previous first line of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Previous second line of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Previous third line of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients with at least one line of treatment by type of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Sunitinib	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Chemotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Somatostatin analoganalogs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Interferon alpha	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Metabolic radiotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> …	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.1.5.1.9: Previous Cancer Treatment Lines – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Patients by sequences of type of previous treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapy-chemotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Chemotherapy-Somatostatin analoganalog	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Somatostatin analoganalog	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…..			
Reason for discontinuation – by type of treatment regardless of line (0)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies (1)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Planned discontinuation of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	….			
First line of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Sunitinib	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Chemotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Somatostatin analoganalogs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Interferon alpha	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Metabolic radiotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> …	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
First line of treatment (combination) (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Treatment 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Treatment N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Duration of first line if targeted therapy (months) (1)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Reason for discontinuation – First line of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Planned discontinuation of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.1.5.1.9: Previous Cancer Treatment Lines – Reference Set – Subgroup Analysis Based on the Presence of Targeted Therapy before Inclusion

		Targeted therapy before inclusion (N=XX)	No targeted therapy before inclusion (N=XX)	Total (N=XX)
Reason for discontinuation (0) – First line of treatment by type of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Planned discontinuation of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	….			
Second line of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	...	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
...				

(0) Percentages calculated as a proportion of the number of patients in the treatment class concerned.

(1) Percentages calculated as a proportion of patients concerned.

Programmer notes:

- For the variable “Previous lines of treatment” show the frequencies for all previous lines of treatment received by patients: line 1 … line N.
- Also show the duration (if targeted therapy) and reason for stopping the 2nd and 3rd lines of treatment.
- N treatments describe the combination with somatostatin analoganalogs.
- Group together all chemotherapies (combinations of chemotherapies included) under the title ‘Chemotherapy’.
- Group together lanreotide and Octreotide under Somatostatin analoganalogs for all of the analyses in this table and Sunitinib and Everolimus under the targeted therapies in the analyses of treatment combinations by line of treatment and overall treatment regimen.

Listing 14.1.5.1.5: Other Previous Cancer Treatments – Reference Set – Analysis of Patients with at Least One Targeted Therapy before Inclusion

Patient Sex Age	At least one targeted therapy before inclusion (yes/no) Treatment group at inclusion	Treatment line	Treatment	Details of treatment
XXXXX XXXXX XX	xxxx xxxx	xx	xxxxxx	xxxxxx

Using the same template:

Listing 14.1.5.1.6: Other Previous Cancer Treatments – Reference Set – Analysis of Patients Who Did Not Receive Targeted Therapy before Inclusion

Listing 14.1.5.1.7: Other Reasons for Discontinuing Previous Cancer Treatment Lines – Reference Set – Analysis of Patients having Received at Least One Targeted Therapy before Inclusion

Patient Sex Age	At least one targeted therapy before inclusion (yes/no) Treatment group at inclusion	Treatment line	Treatment	Treatment: Association	Reason for discontinuation	If other, give details
XXXXX XXXXX XX	xxxx xxxx	xx	xxxxxx	xxxxxx	xx	xxxxx

Using the same template:

Listing 14.1.5.1.8: Other Reasons for Discontinuing Previous Cancer Treatment Lines – Reference Set – Analysis Of Patients Not having Received Targeted Therapy before Inclusion

9.1.5.2. Time between Diagnosis and Initiation of Ongoing Treatment at Inclusion for Metasynchronous Patients

Table 14.1.5.2.1: Length of the Disease at Initiation of Ongoing Treatment at Inclusion for Metasynchronous Patients – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Length of the disease at initiation of ongoing treatment at inclusion (years)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]

(1) Length of disease: (current treatment start date – diagnosis date) / 365.25.

9.2. Analysis of the Primary Objective

Table 14.2.1.1: Analysis of Progression-Free Survival – Reference Set – Overall

	Total (N=XX)
N	XX
Missing data	XX
Number of events*	XX
>> Number of disease progressions	XX
>> Number of deaths	XX
Number of censored data	XX
>> Number of patients lost to follow-up	XX
>> Number of censored data for other reason	XX
Q3 (months) [95% CI]	XX.X [XX.X - XX.X]
Median (months) [95% CI]	XX.X [XX.X - XX.X]
Q1 (months) [95% CI]	XX.X [XX.X - XX.X]
Minimum survival time (months)	XX.X
Maximum survival time (months)	XX.X
Survival rate at 3 months (N at risk, survival rate, (SE))	XX - XX.X% (X.X%)
Survival rate at 6 months (N at risk, survival rate, (SE))	XX - XX.X% (X.X%)
Survival rate at 9 months (N at risk, survival rate, (SE))	XX - XX.X% (X.X%)
Survival rate at 12 months (N at risk, survival rate, (SE))	XX - XX.X% (X.X%)
Survival rate at 18 months (N at risk, survival rate,(SE))	XX - XX.X% (X.X%)
Survival rate at 24 months (N at risk, survival rate ,(SE))	XX - XX.X% (X.X%)
….. (72 months)	

Kaplan-Meier estimate with right censoring and left truncation.

* Event related to main treatment at inclusion.

Table 14.2.1.2: Analysis of Progression-Free Survival – Reference Set – Targeted Therapies vs Other Treatments Group

	Targeted therapies (N=XX)	Other treatments (N=XX)
N	XX	XX
Missing data	XX	XX
Number of events*	XX	XX
>> Number of disease progressions	XX	XX
>> Number of deaths	XX	XX
Number of censored data	XX	XX
>> Number of patients lost to follow-up	XX	XX
>> Number of censored data for other reasons	XX	XX
Q3 [95% CI]	XX.X [XX.X - XX.X]	XX.X [XX.X - XX.X]
Median [95% CI]	XX.X [XX.X - XX.X]	XX.X [XX.X - XX.X]
Q1 [95% CI]	XX.X [XX.X - XX.X]	XX.X [XX.X - XX.X]
Minimum survival time (months)	XX.X	XX.X
Maximum survival time (months)	XX.X	XX.X
Survival rate at 3 months (N at risk, survival rate)	XX - XX.X% [XX.X]	XX - XX.X% [XX.X]
Survival rate at 6 months (N at risk, survival rate])	XX - XX.X% [XX.X]	XX - XX.X% [XX.X]
Survival rate at 9 months (N at risk, survival rate	XX - XX.X% [XX.X]	XX - XX.X% [XX.X
Survival rate at 12 months (N at risk, survival rate [	XX - XX.X% [XX.X]	XX - XX.X% [XX.X]
Survival rate at 18 months (N at risk, survival rate	XX - XX.X% [XX.X]	XX - XX.X% [XX.X
Survival rate at 24 months (N at risk, survival rate	XX - XX.X% [XX.X]	XX - XX.X% [XX.X]
….. (72 months)		

Kaplan-Meier estimator with right censoring and left truncation and stabilising the estimate for small sample sizes (Lai and Ying method).

* Event related to main treatment at inclusion.

Using a similar template:

Table 14.2.1.3: Analysis of Progression-Free Survival – Reference Set – Targeted Therapy Groups

Table 14.2.1.4: Analysis of Progression-Free Survival – Reference Set – Other Treatments Groups

Table 14.2.1.5: Analysis of Overall Survival – Reference Set – Overall

Table 14.2.1.6: Analysis of Overall Survival – Reference Set – Targeted Therapies Group Vs Other Treatments

Table 14.2.1.7: Analysis of Overall Survival – Reference Set – Targeted Therapies Groups

Table 14.2.1.8: Analysis of Overall Survival – Reference Set – Other Treatments Groups

Programmer note:

- The Kaplan-Meier curves associated with the analyses.
- Show the 95% confidence interval (log-log transformation) of the survival function for the total population analyses.

Table 14.2.1.9: Best Overall Response to the Main Treatment At Inclusion – Reference Set – Analysis Based on Targeted Therapies and Other Treatments

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Best overall response	N	XX	XX	XX
	Missing data	XX	XX	XX
	CR	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	PR	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Clinical response	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	SD	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	PD	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Using the same template:

Table 14.2.1.10: Best Overall Response with Main Treatment at Inclusion – Reference Set – Analysis by Treatment Subgroup

Table 14.2.1.11: Best Overall Response During Follow-Up – Reference Set

		Total (N=XX)
Best overall response	N	XX
	Missing data	XX
	CR	XX (XX.X%)
	PR	XX (XX.X%)
	Clinical response	XX (XX.X%)
	SD	XX (XX.X%)
	PD	XX (XX.X%)

9.3. Analysis of the Secondary Objectives

9.3.1. Management of Patients

Table 14.2.2.2.1: Number and Frequency of Tumour Assessment Visits – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Number of tumour assessments	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Number of tumour assessments (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Frequency of investigations (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	X/year	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Time between investigations (months)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time between investigations (1) (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	≤4 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>4 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	1st decile	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2nd decile	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

(1) calculated as a proportion of the total number of investigations performed and not the number of patients.

Programmer note: for the variables “Time between investigations”, N=number of times between investigations . The inclusion visits are not counted as a tumour assessment but are retained in the calculation of times between investigations in order to obtain the first time between the inclusion visit and the first tumour assessment.

Frequency of investigations = number of investigations / ((date of last visit–date of inclusion)/365.25).

Table 14.2.2.2.2: Investigations Used for the Tumour Assessment – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
CT Scan – performed at least once during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
CT Scan – number of times performed by patient during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
CT Scan – number of times performed by patient during the study regardless of treatment received (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
CT Scan – number of times performed by patient receiving the main treatment line at inclusion (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
	…..			
CT Scan – Frequency of investigations (per year) by class during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	X/year	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…..			
CT Scan – Frequency of investigations (per year) during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]

Table 14.2.2.2.2: Investigations Used for the Tumour Assessment – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
MRI – performed at least once during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
MRI – number of times performed per patient during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
MRI – number of times performed per patient during the study regardless of treatment received (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
MRI - number of times performed per patient receiving the main treatment line at inclusion (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
MRI - frequency of investigations (per year) by class during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	X/year	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
MRI - frequency of investigations (per year) during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
PET Scan – performed at least once during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.2.2.2.2: Investigations Used for the Tumour Assessment – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
PET Scan – number of times performed per patient during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
PET Scan – number of times performed per patient during the study regardless of treatment received (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
PET Scan – number of times performed per patient receiving the main treatment line at inclusion (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
PET Scan – frequency of investigations per year during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	X/year	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
		XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
PET Scan – frequency of investigations (per year) during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Octreoscan – Performed at least once during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.2.2.2.2: Investigations Used for the Tumour Assessment – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Octreoscan – Number of times performed by patient during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Octreoscan – Number of times performed by patient during the study regardless of treatment received (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Octreoscan – Number of times performed by patient receiving the main treatment line at inclusion (N(%))	AT	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Octreoscan – Frequency of investigations (per year) during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	X/year	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
		XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Octreoscan – Frequency of investigations per year during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Ultrasound– performed at least once during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ultrasound– Number of times performed per patient during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]

Table 14.2.2.2.2: Investigations Used for the Tumour Assessment – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Ultrasound– Number of times performed per patient during the study regardless of treatment received (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Ultrasound– Number of times performed per patient receiving the main treatment line at inclusion (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ultrasound– Frequency of investigations per year during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	X/year	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
		XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ultrasound– Frequency of investigations (per year) during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Imaging (CT or MRI) – Number of times performed per patient during the study regardless of treatment received (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Imaging (CT or MRI) – Number of uses per patient receiving the main treatment line at inclusion (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Imaging (CT or MRI) – Frequency of investigations during the study regardless of treatment received	N	XX	XX	XX
	Missing data	XX	XX	XX
	X/year	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
		XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.2.2.2.2: Investigations Used for the Tumour Assessment – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Imaging (CT or MRI) – Frequency of investigations (per year) during the study regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Imaging (CT or MRI) – Time between 2 imaging investigations by patient during the study, regardless of treatment received	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			

Programmer note: the number of uses of an investigation should be analysed in the population of patients with at least one investigation (this applies for all investigations).

Frequency of investigations = number of investigations (by type or all)/((study end date-inclusion date)/365.25).

Time between 2 imaging investigations per patient = date of the second imaging assessment – date of the 1st imaging investigation in the same patient.

Table 14.2.2.2.3: Changes to Treatment Documented in the Study – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Change in ongoing treatment at inclusion	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
At least one change in concomitant treatment	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.2.2.2.4: Changes in the Dose of Treatment Started or Ongoing at Inclusion During the Study: Sunitinib – Reference Set

		Sunitinib (N=XX)
Change in dose step during the study	N	XX
	Missing data	XX
	0	XX (XX.X%)
	1	XX (XX.X%)
	…	XX (XX.X%)
Type of change in dose step during the study*	N	XX
	Missing data	XX
	Increase	XX (XX.X%)
	Reduction	XX (XX.X%)
	…	XX (XX.X%)
Dose after increase (N(%))*	N	XX
	Missing data	XX
	37.5 mg/day	XX (XX.X%)
	25 mg/day	XX (XX.X%)
	…	XX (XX.X%)
Dose after reduction (N(%))*	N	XX
	Missing data	XX
	37.5 mg/day	XX (XX.X%)
	25 mg/day	XX (XX.X%)
	…	XX (XX.X%)
At least one dose reduction during the study	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	Non	XX (XX.X%)
At least one dose increase during the study	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	Non	XX (XX.X%)
Reasons for dose reduction during the study	N	XX

Table 14.2.2.2.4: Changes in the Dose of Treatment Started or Ongoing at Inclusion During the Study: Sunitinib – Reference Set

		Sunitinib (N=XX)
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)
Reasons for dose increase during the study*	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)
Time between inclusion and the 1st change in dose (days)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Time between inclusion and the 1st change in dose (days) - incident patients	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Time between inclusion and the 1st change in dose (days) - prevalent patients	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Mean time between 2 changes in dose (days)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Mean time between 2 changes in dose (days) – incident patients	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Mean time between 2 changes in dose (days) – prevalent patients	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]

* The same patient may be counted several times if several changes/increases/reductions took place.

Programmer note:

- Time between inclusion and the 1st change in dose = date of 1st change in dose – inclusion date.
- Mean time between change in dose = mean of times between two different consecutive doses per patient (after inclusion).

Using the same template:

Table 14.2.2.2.5: Changes in the Dose of Treatment Started or Ongoing at Inclusion During the Study: Everolimus – Reference Set

Programmer note: for the variables "Reasons for dose reduction during the study" and "Reasons for dose increase during the study", the modalities are "Adverse event related to everolimus," "Adverse event not related to everolimus," "Adverse event (relationship with everolimus not stated)", "Patient's choice" and "Doctor's choice".

Table 14.2.2.2.6: Changes in the Dose of Treatment Started or Ongoing at Inclusion During the Study: Interferon Alpha– Reference Set

Programmer note: do not show changes in dose by increase and decrease.

Table 14.2.2.2.7: Changes in the Dose of Treatment Started or Ongoing at Inclusion During the Study: Chemotherapy – Reference Set

		Chemotherapy (N=XX)
Change in dose step during the study	N	XX
	Missing data	XX
	0	XX (XX.X%)
	1	XX (XX.X%)
	…	XX (XX.X%)
Type of change in dose step during the study*	N	XX
	Missing data	XX
	Increase	XX (XX.X%)
	Decrease	XX (XX.X%)
	…	XX (XX.X%)
At least one dose reduction during the study	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
At least one dose increase during the study	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
Reasons for dose reduction during the study*	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)

Table 14.2.2.2.7: Changes in the Dose of Treatment Started or Ongoing at Inclusion During the Study: Chemotherapy – Reference Set

		Chemotherapy (N=XX)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)
Reasons for dose increase during the study	N	XX
	Missing data	XX
	Adverse event	XX (XX.X%)
	Patient's choice	XX (XX.X%)
	Doctor's choice	XX (XX.X%)
	Other	XX (XX.X%)
Time between inclusion and the 1st change in dose (days)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Time between inclusion and the 1st change in dose (days)-incident patients	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Time between inclusion and the 1st change in dose (days) –prevalent patients	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Mean time between change in dose (days)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Mean time between change in dose (days) – incident patients	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Mean time between change in dose (days) – prevalent patients	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]

* The same patient may be counted several times if several changes/increases/reductions took place.

Programmer note:

- Time between inclusion and the 1st change in dose = date of 1st dose modification – date of inclusion.

- Mean time between change in dose = mean of times between two different consecutive doses (after inclusion).

Using the same template:

Table 14.2.2.2.8: Changes in the Dose of Treatment Started or Ongoing at Inclusion During the Study: Somatostatin Analog – Reference Set

Programmer note: do not show changes in dose by increase and decrease.

Table 14.2.2.2.9: Number of Courses During the Study of Metabolic Radiotherapy Initiated or Ongoing at Inclusion – Reference Set

		Metabolic radiotherapy (N=XX)
Number of courses since initiation	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Median	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Number of courses since initiation (N(%))	N	XX
	Missing data	XX
	1	XX (XX.X%)
	2	XX (XX.X%)
	…	XX (XX.X%)
Number of courses during the study*	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Mean	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Number of courses during the study (N(%))	N	XX
	Missing data	XX
	1	XX (XX.X%)
	2	XX (XX.X%)
	…	XX (XX.X%)

* only post-inclusion courses are shown.

Table 14.2.2.2.10: Lines of Treatment Received During the Study – Reference Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Number of lines of treatment received during the study	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Number of lines of treatment received during the study (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Type of lines of treatment received during the study (other than those being received at inclusion)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Line 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Line 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Total number of lines of treatment received*	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Total number of lines of treatment received* (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			

* Previous lines and lines received during the study.

Note: The lines of treatment will need to be reviewed prior to the analysis (data review) in order to identify these as such in planning the analyses.

Using the same template:

Table 14.2.2.2.11: Main Concomitant Treatment Lines Received During the Study – Reference Set

Listing 14.2.2.2.1: Treatment Regimen (Previous Lines of Treatment and Administered During the Study) – Reference Set

Patient Sex Age	Reference set	Group	Diagnosis date - Type of tumour at diagnosis	Type of treatment	No. of main treatment line	No. of the main concomitant treatment line	Main treatment	Concomitant treatment	Start date	End Date (Duration of treatment (months))*	Reason for discontinuation
XXXX X XXXX X XX	Yes/No	XXX	Xxxx	- xxxx	- xxxx	- xxxx	- xxxx	- xxxx	- xxxx	- xxxx	- xxxx

Programmer note:

* In the case of previous treatment, the length of the targeted therapies is to be taken directly from the e-CRF (data not calculated).

Table 14.2.2.2.12: Treatments Received at Least Once During the Study According to the Treatment at Inclusion – Reference Set

	Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Number of patient receiving a main treatment at least once during the study (N(%)):	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Targeted therapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Sunitinib	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Other treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Chemotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Somatostatin analog	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Metabolic radiotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Interferon alpha	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of patients receiving at least one main treatment and/or a combination during the study (N(%)):	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Targeted therapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Sunitinib	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Other treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.2.2.2.12: Treatments Received at Least Once During the Study According to the Treatment at Inclusion – Reference Set

	Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
- Chemotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Somatostatin analog	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Metabolic radiotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Interferon alpha	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of patients receiving at least once during the study:			
Treatment XX alone	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Combination 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Combination 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
…			

Using the same template:

Table 14.2.2.2.13: Treatments Received at Least Once During the Study According to Treatment at Inclusion – Safety Analysis Set

9.3.2. Analyses of Subgroups/additional Analyses

9.3.2.1. Therapeutic Pathway of Patient

9.3.2.1.1. Targeted Therapy

Table 14.2.2.2.1.1: Number of Patients with Targeted Therapy – Reference Set – Analysis of the Period before Inclusion

		Total (N=XX)
Number of patients having received at least one targeted therapy before inclusion		XX (XX.X%)
Number of patients having received Everolimus at least once before inclusion		XX (XX.X%)
Number of patients having received Sunitinib at least once before inclusion		XX (XX.X%)
Number of patients having received Pazopanib at least once before inclusion		XX (XX.X%)
Number of patients having received Everolimus at least once and Sunitinib at least once before inclusion		XX (XX.X%)
Number of patients having received Everolimus at least once but not Sunitinib or Pazopanib before inclusion		XX (XX.X%)
Number of patients having received Sunitinib at least once but not Everolimus or Pazopanib before inclusion		XX (XX.X%)
Number of patients who never received targeted therapy before inclusion		XX (XX.X%)
Number of targeted therapies received per patient before inclusion	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Mean	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
	0	XX (XX.X%)
	1	XX (XX.X%)
	2	XX (XX.X%)
	3	XX (XX.X%)
	>3	XX (XX.X%)
Number of patients having received two different targeted therapies* before inclusion		XX (XX.X%)

* Two different targeted therapies: Everolimus and Sunitinib, or Everolimus and Pazopanib, or Sunitinib and Pazopanib.

Using the same template:

Table 14.2.2.2.1.2: Number of Patients with Targeted Therapy – Reference Set – Analysis of the Period at Inclusion and after Inclusion

Table 14.2.2.2.1.3: Number of Patients with Targeted Therapy – Reference Set – Analysis of the Overall Follow-Up Period

Table 14.2.2.2.1.4: Position of the Targeted Therapy in the Care Pathway of Patients Throughout Follow-Up – Reference Set

	Total (N=XX)
Number of patients having received a targeted therapy as the 1st main treatment line	XX (XX.X%)
Number of patients having received a targeted therapy as the 2nd main treatment line	XX (XX.X%)
Number of patients having received a targeted therapy as the ... main treatment line	XX (XX.X%)
Number of patients having received a targeted therapy as the nth main treatment line	XX (XX.X%)
Number of patients having received a targeted therapy immediately before chemotherapy	XX (XX.X%)
Number of patients having received a targeted therapy immediately after chemotherapy	XX (XX.X%)
Number of patients having received a targeted therapy immediately before a somatostatin analoganalog (as main treatment)	XX (XX.X%)
Number of patients having received a targeted therapy immediately after a somatostatin analoganalog (as main treatment)	XX (XX.X%)

Programmer note: add as a footnote the list of patients whose start date for their last main treatment line falls after the date of the last visit.

Table 14.2.2.2.1.5: Length and Reason for Discontinuation of Targeted Therapy – Reference Set – Analysis of the Period before Inclusion

		Total (N=XX)
Length of targeted therapy before inclusion (months) (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Mean	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Length of Everolimus targeted therapy before inclusion (months) (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Mean	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Length of Sunitinib targeted therapy before inclusion (months) (1)	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Mean	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
Reason for discontinuation of targeted therapy before inclusion (2)	N	XX
	Missing data	XX
	Adverse event*	XX (XX.X%)
	Progression	XX (XX.X%)
	Planned discontinuation of treatment	XX (XX.X%)
	Patient decision	XX (XX.X%)
	Other	XX (XX.X%)
Reason for discontinuation of Everolimus targeted therapy before inclusion (2)	N	XX
	Missing data	XX
	Adverse event*	XX (XX.X%)
	Progression	XX (XX.X%)
	Planned discontinuation of treatment	XX (XX.X%)
	Patient decision	XX (XX.X%)
	Other	XX (XX.X%)
Reason for discontinuation of Sunitinib targeted therapy before inclusion (2)	N	XX
	Missing data	XX
	Adverse event*	XX (XX.X%)
	Progression	XX (XX.X%)
	Planned discontinuation of treatment	XX (XX.X%)
	Patient decision	XX (XX.X%)
	Other	XX (XX.X%)

* The "Total" column shows all of the targeted therapies.

(1) Data reported directly from the e-CRF, total of data if several targeted therapies.

(2) The number of reasons for discontinuation will be higher than the set having received targeted therapy (ie, patients having discontinued Everolimus and Sunitinib).

(3) Total duration representing the entire follow-up period (before and after inclusion).

Using the same template:

Table 14.2.2.2.1.6: Length and Reason for Discontinuation of Targeted Therapy in the Care Pathway of Patients – Reference Set – Analysis of the Period before and after Inclusion

Table 14.2.2.2.1.7: Length and Reason for Discontinuation of Targeted Therapy in the Care Pathway of Patients – Reference Set – Analysis of the Entire Follow-Up Period

Table 14.2.2.2.1.8: Length and Reason for Discontinuation of Targeted Therapy – Reference Set – Subgroup Analysis Based on the Number of Main Treatment Line Throughout Follow-Up

		1st Line (N=XX)	2nd Line (N=XX)	… (N=XX)	Nth Line (N=XX)
Length of targeted therapy (months)	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Reason for discontinuation of targeted therapy	N	XX	XX	XX	XX XX
	Missing data	XX	XX	XX	
	Adverse event*	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Planned discontinuation of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Using the same template:

Table 14.2.2.2.1.9: Length and Reason for Discontinuation of Targeted Therapy Over the Entire Follow-Up Period – Reference Set – Subgroup Analysis Based on the Number of Main Treatment Lines Throughout Follow-Up (≤2 Lines, >2 Lines)

Table 14.2.2.2.1.10: Length and Reason for Discontinuation of Targeted Therapy Over the Entire Follow-Up Period – Reference Set – Subgroup Analysis Based on the Ki67 (≤10%, >10%)

Table 14.2.2.2.1.11: Length and Reason for Discontinuation of Targeted Therapy Over the Entire Follow-Up Period – Reference Set – Subgroup Analysis Based on the Percentage of Liver Invasion (≤50%, >50%)

Table 14.2.2.2.1.12: Length and Reason for Discontinuation of Targeted Therapy Over the Entire Follow-Up Period – Reference Set – Subgroup Analysis Based on the Number of Metastatic Sites at Initiation of the Current Treatment Line or Treatment Line Started at Inclusion (≤2 Sites, >2 Sites)

9.3.2.1.2. Chemotherapy

Table 14.2.2.2.2.1: Number of Chemotherapy Patients – Reference Set – Analysis of the Period before Inclusion

		Total (N=XX)
Number of patients having received chemotherapy at least once before inclusion		XX (XX.X%)
Number of patients who never received chemotherapy before inclusion		XX (XX.X%)
Number of chemotherapies received per patient before inclusion		XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Mean	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
	0	XX (XX.X%)
	1	XX (XX.X%)
	2	XX (XX.X%)
	3	XX (XX.X%)
	>3	XX (XX.X%)
Number of patients having received chemotherapy and a somatostatin analoganalog as main treatment before inclusion		XX (XX.X%)

Using the same template:

Table 14.2.2.2.2.2: Number of Chemotherapy Patients – Reference Set – Analysis of the Period at Inclusion and after Inclusion

Table 14.2.2.2.2.3: Number of Chemotherapy Patients – Reference Set – Analysis of the Overall Follow-Up Period

Table 14.2.2.2.2.4: Position of Chemotherapy in the Care Pathway of Patients for the Entire Follow-Up – Reference Set –

		Total (N=XX)
Number of patients having received chemotherapy as the 1st main treatment line		XX (XX.X%)
Number of patients having received chemotherapy as the 2nd main treatment line		XX (XX.X%)
Number of patients having received chemotherapy as the ...nth main treatment line		XX (XX.X%)
Number of patients having received chemotherapy as the nth main treatment line		XX (XX.X%)
Number of patients having received chemotherapy immediately before targeted therapy		XX (XX.X%)
Number of patients having received chemotherapy immediately after targeted therapy		XX (XX.X%)
Number of patients having received chemotherapy immediately after a somatostatin analoganalog (as main treatment)		XX (XX.X%)
Number of patients having received chemotherapy immediately after a somatostatin analoganalog (as main treatment)		XX (XX.X%)
Number of patients having received chemotherapy as 1st line, then targeted therapy as 2nd line (at inclusion)		XX (XX.X%)
Number of patients having received alkylating chemotherapy at least once after inclusion		XX (XX.X%)
Number of alkylating chemotherapies received after inclusion	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Mean	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
	0	XX (XX.X%)
	1	XX (XX.X%)
	2	XX (XX.X%)
	3	XX (XX.X%)
	>3	XX (XX.X%)

Programmer note: add as a footnote the list of patients whose start date for their last main treatment line falls after the date of the last visit.

9.3.2.1.3. Somatostatin Analoganalogs

Table 14.2.2.2.3.1: Number of Somatostatin-Analoganalog Patients – Reference Set – Analysis of the Period before Inclusion

		Total (N=XX)
Number of patients having received at least one somatostatin analoganalog as main treatment before inclusion		XX (XX.X%)
Number of patients having never received at least one somatostatin analoganalog as main treatment before inclusion		XX (XX.X%)
Number of somatostatin analoganalogs received as main treatment per patient before inclusion	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Mean	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
	0	XX (XX.X%)
	1	XX (XX.X%)
	2	XX (XX.X%)
	3	XX (XX.X%)
	>3	XX (XX.X%)
Number of patients having received at least one somatostatin analoganalog in combination before inclusion		XX (XX.X%)
Number of patients having never received at least one somatostatin analoganalog in combination before inclusion		XX (XX.X%)
Number of somatostatin analoganalogs received in combination per patient before inclusion	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Mean	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]
	0	XX (XX.X%)
	1	XX (XX.X%)
	2	XX (XX.X%)
	3	XX (XX.X%)
	>3	XX (XX.X%)
Number of patients having received at least one somatostatin analoganalog (as main treatment or in combination) before inclusion		XX (XX.X%)
Number of patients having never received at least one somatostatin analog (as main treatment or in combination) before inclusion		XX (XX.X%)
Number of somatostatin analogs received in combination per patient before inclusion	N	XX
	Missing data	XX
	Mean (SD)	XX.XX (X.XX)
	Mean	XX.X
	[Min; Max]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]

Table 14.2.2.2.3.1: Number of Somatostatin-Analoganalog Patients – Reference Set – Analysis of the Period before Inclusion

	Total (N=XX)
0	XX (XX.X%)
1	XX (XX.X%)
2	XX (XX.X%)
3	XX (XX.X%)
>3	XX (XX.X%)

Using the same template:

Table 14.2.2.2.3.2: Number of Somatostatin-Analog Patients – Reference Set – Analysis of the Period at Inclusion and after Inclusion

Table 14.2.2.2.3.3: Number of Somatostatin-Analog Patients – Reference Set – Analysis of Entire Follow-Up Period

Table 14.2.2.2.3.4: Position of Somatostatin Analog as Main Treatment in the Care Pathway of Patients for the Entire Follow-Up – Reference Set

	Total (N=XX)
Number of patients having received a somatostatin analog as the 1st main treatment line	XX (XX.X%)
Number of patients having received a somatostatin analog as the 2nd main treatment line	XX (XX.X%)
Number of patients having received a somatostatin analog as the ...nth main treatment line	XX (XX.X%)
Number of patients having received a somatostatin analog as the nth main treatment line	XX (XX.X%)
Number of patients having received a somatostatin analog immediately before targeted therapy	XX (XX.X%)
Number of patients having received a somatostatin analog immediately after targeted therapy	XX (XX.X%)
Number of patients having received a somatostatin analog immediately before chemotherapy	XX (XX.X%)
Number of patients having received a somatostatin analog immediately after chemotherapy	XX (XX.X%)

Programmer note: add as a footnote the list of patients whose start date for their last main treatment line falls after the date of the last visit.

Using the same template:

Table 14.2.2.2.3.5: Position of Somatostatin-Analog in Combination in the Care Pathway of Patients Throughout Follow-Up – Reference Set

Programmer note: only show the treatment lines

Table 14.2.2.2.3.6: Position of Somatostatin Analog as Main Treatment or in Combination in the Care Pathway of Patients Throughout Follow-Up – Reference Set

Programmer note: only show the treatment lines

9.3.3. Sequence of Treatment Lines

Table 14.2.2.3.1: Sequence of Main Treatment Lines Per Period – Reference Set

Before inclusion	Inclusion	After inclusion	Number of patients (N=XX)
	XXX	XXX	XX
	XXX	XXX + XXX	XX
XXX	XXX	XXX+XXX+XXX	XX

Using the same template:

Table 14.2.2.3.2: Sequence of Main Treatment Lines Per Period Differentiating Between Targeted Therapies – Reference Set

Table 14.2.2.3.3: Sequence of Main Treatment Lines for the Entire Follow-Up – Reference Set

	Number of patients (N=XX)
Targeted therapy	XX
Chemotherapy	XX
Somatostatin analogs	XX
Targeted therapy – Chemotherapy	XX
Targeted therapy	XX
….	

Using the same template:

Table 14.2.2.3.4: Sequence of Main Treatment Lines Differentiating Between Targeted Therapies for the Entire Follow-Up – Reference Set

Table 14.2.2.3.5: Sequence of Main Concomitant Treatment Lines for the Entire Follow-Up – Reference Set

	Number of patients (N=XX)
Targeted therapy	XX
Chemotherapy	XX
Somatostatin analogs	XX
Targeted therapy – Chemotherapy	XX
Targeted therapy + combination with Somatostatin analog	XX
Targeted therapy in combination with Somatostatin analog – chemotherapy	XX
….	

Using the same template:

Table 14.2.2.3.6: Sequence of Main Concomitant Treatment Lines Differentiating Between Targeted Therapies for the Entire Follow-Up – Reference Set

9.3.4. Discontinuation Due to Toxicity

Table 14.2.2.4.1: Discontinuation Due to Toxicity During Follow-Up (Post Inclusion) – Reference Set – Subgroup Analysis Based on the Number of Main Treatment Lines Throughout Follow-Up (≤2 Lines, >2 Lines)

		≤2 lines (N = XX)	>2 lines (N = XX)	Total (N = XX)
Patients who have discontinued at least once due to toxicity*	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
If yes, number of discontinuations per patient due to toxicity**	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	1			
	2			
	3			
	…			

* Discontinuation due to toxicity corresponds to discontinuation for an AE or Death.

** A patient may record several discontinuations due to toxicity.

Using the same template:

Table 14.2.2.4.2: Discontinuation Due to Toxicity During Follow-Up (Post Inclusion) – Reference Set – Subgroup Analysis Based on the Number of Targeted Therapies Received Throughout Follow-Up (0, 1, 2, >2)

Table 14.2.2.4.3: Discontinuation Due to Toxicity During Follow-Up (Post Inclusion) – Reference Set – Subgroup Analysis Based on the Number of Patients Having Received Targeted Therapies as a 2nd Line and Patients Having Received Chemotherapy as a 2nd Line Throughout Follow-Up

9.3.5. Treatment Lines Received Throughout the Follow-up

Table 14.2.2.5.1: Treatment Lines Received Throughout the Follow-Up Based on Treatment Groups at Inclusion – Reference Set

		Targeted therapies (N=XX)	Other (N=XX)	Total (N=XX)
Number of main treatment lines by patient	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients with at least one main line of treatment per site	N	XX	XX	XX
	Missing data	XX	XX	XX
	First main line of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Second main line of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients with at least one main line of treatment by type of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Sunitinib	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Chemotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Somatostatin analogs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Interferon alpha	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Metabolic radiotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> …	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	….			
First main line of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Sunitinib	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Chemotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Somatostatin analogs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Interferon alpha	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Metabolic radiotherapy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Combination with this line of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Treatment 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Treatment N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Duration of first main line of treatment (months) (1)(2)	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]

Table 14.2.2.5.1: Treatment Lines Received Throughout the Follow-Up Based on Treatment Groups at Inclusion – Reference Set

		Targeted therapies (N=XX)	Other (N=XX)	Total (N=XX)
Reason for discontinuation – First main line of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Planned discontinuation of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason for discontinuation (0) – First main line of treatment by type of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Planned discontinuation of treatment	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Patient decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	….			
Second main line of treatment (1)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Targeted therapies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>> Everolimus	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	...	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
...				

(0) Percentages calculated as a proportion of the number of patients in the treatment class concerned.

(1) Percentages calculated as a proportion of patients concerned.

(2) Not available for the duration of previous treatments other than targeted therapies.

Programmer notes:

- For the variable “Lines of treatment” show the frequencies for all previous lines of treatment received by patients: line 1 … line N.
- Also show the duration (if targeted therapy) and reason for discontinuing the lines of treatment.
- N treatments describe the combination with somatostatin analogs.
- Group together all chemotherapies (combinations of chemotherapies included) under the title ‘Chemotherapy’.
- Group together Lanreotide and Octreotide under somatostatin analogs for all of the analyses in this table and sunitinib and Everolimus under the targeted therapies in the analyses of treatment combinations by line of treatment and overall treatment regimen.

Using the same template:

Table 14.2.2.5.2: Main Treatment Lines Received Throughout the Follow-Up Based on Treatment Groups at Inclusion – Reference Set – Treatment Subgroup Analysis

Table 14.2.2.5.3: Main Treatment Lines Received Throughout the Follow-Up – Reference Set – Subgroup Analysis Based on at Least One Targeted Therapy before Inclusion (Yes/No)

		At least one targeted therapy received before inclusion (N=XX)	No targeted therapy received before inclusion (N=XX)	Total (N=XX)
Number of main treatment lines received during the study	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Number of main treatment lines received during the study (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Nature of the main treatment lines received during the study (other than those received at inclusion)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Line 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Line 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Total number of main treatment lines received*	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Total number of main treatment lines received* (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			

9.3.6. Progression-free Survival

Table 14.2.2.6.1: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving at Least One Targeted Therapy before Inclusion (Yes/No)

Figure 14.2.2.6.1: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving at Least One Targeted Therapy before Inclusion (Yes/No)

Table 14.2.2.6.2: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving at Least One Targeted Therapy at Any Time (Yes/No)

Figure 14.2.2.6.2: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving at Least One Targeted Therapy at Any Time (Yes/No)

Table 14.2.2.6.3: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving Chemotherapy as 2nd Line Vs Receiving Targeted Therapy as 2nd Line

Figure 14.2.2.6.3: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving Chemotherapy as 2nd Line Vs Receiving Targeted Therapy as 2nd Line

Table 14.2.2.6.4: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on the Ki67 (≤10%, >10%)

Figure 14.2.2.6.4: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based the Ki67 (≤10%, >10%)

Table 14.2.2.6.5: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving Two Targeted Therapies Vs One Targeted Therapy before Inclusion (Yes/No)

Figure 14.2.2.6.5: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving Two Targeted Therapies Vs One Targeted Therapy before Inclusion (Yes/No)

Table 14.2.2.6.6: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based On Receiving Two Targeted Therapies Vs One Targeted Therapy at Any Time (Yes/No)

Figure 14.2.2.6.6: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving Two Targeted Therapies Vs One Targeted Therapy at Any Time (Yes/No)

Table 14.2.2.6.7: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving at Least Two Targeted Therapies Vs One Targeted Therapy at Any Time During the Study (Yes/No)

Figure 14.2.2.6.7: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Receiving at Least Two Targeted Therapies Vs One Targeted Therapy at Any Time During the Study (Yes/No)

Table 14.2.2.6.8: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on The Stage at Diagnosis (Localised/Metastatic)

Figure 14.2.2.6.8: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on the Stage at Diagnosis (Localised/Metastatic)

Table 14.2.2.6.9: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Having Undergone Any Surgery at Any Time During the Study (Yes/No)

Figure 14.2.2.6.9: Analysis of Survival-Free Progression of Treatment at Inclusion – Reference Set – Subgroup Analysis Based on Having Undergone Any Surgery at Any Time During the Study (Yes/No)

Table 14.2.2.6.10: Analysis of Survival-Free Progression of Treatment at Inclusion for 1st Line Patients at Inclusion – Reference Set – Subgroup Analysis Based on Receiving at Least One Targeted Therapy at Any Time During the Study (Yes/No)

Figure 14.2.2.6.10: Analysis of Survival-Free Progression of Treatment at Inclusion for 1st Line Patients at Inclusion – Reference Set – Subgroup Analysis Based on Receiving at Least One Targeted Therapy at Any Time During the Study (Yes/No)

Table 14.2.2.6.11: Analysis of Survival-Free Progression of Treatment at Inclusion for 1st Line Patients at Inclusion – Reference Set – Analysis by Treatment Subgroup (Targeted Therapy, Chemotherapy, Somatostatin Analog)

Figure 14.2.2.6.11: Analysis of Survival-Free Progression of Treatment at Inclusion for 1st Line Patients at Inclusion – Reference Set – Analysis by Treatment Subgroup (Targeted Therapy, Chemotherapy, Somatostatin Analog)

Table 14.2.2.6.12: Analysis of Survival-Free Progression of Treatment at Inclusion for 2nd Line Patients at Inclusion – Reference Set – Subgroup Analysis Based on Receiving Targeted Therapy before Inclusion (Yes/No)

Figure 14.2.2.6.12: Analysis of Survival-Free Progression of Treatment at Inclusion for 2nd Line Patients at Inclusion – Reference Set – Subgroup Analysis Based on Receiving Targeted Therapy before Inclusion (Yes/No)

Table 14.2.2.6.13: Analysis of Survival-Free Progression of Treatment at Inclusion for 2nd Line Patients at Inclusion – Reference Set – Subgroup Analysis Based on Receiving Two Targeted Therapies Vs One Targeted Therapy at Any Time During the Study (Yes/No)

Figure 14.2.2.6.13: Analysis of Survival-Free Progression of Treatment at Inclusion for 2nd Line Patients at Inclusion – Reference Set – Subgroup Analysis Based on Receiving Two Targeted Therapies Vs One Targeted Therapy at Any Time During the Study (Yes/No)

Table 14.2.2.6.14: Analysis of Survival-Free Progression of Treatment at Inclusion for 2nd Line Patients at Inclusion – Reference Set – Analysis by Treatment Subgroup (Targeted Therapy, Chemotherapy, Somatostatin Analog) at Inclusion

Figure 14.2.2.6.14: Analysis of Survival-Free Progression of Treatment at Inclusion for 2nd Line Patients at Inclusion – Reference Set – Analysis by Treatment Subgroup (Targeted Therapy, Chemotherapy, Somatostatin Analog) at Inclusion

Table 14.2.2.6.15: Analysis of Survival-Free Progression of Treatment at Inclusion for Metasynchronous Patients – Reference Set – Analysis by Treatment Subgroup at Inclusion (Targeted Therapy, Chemotherapy, Somatostatin Analog)

Figure 14.2.2.6.15: Analysis of Survival-Free Progression of Treatment at Inclusion for Metasynchronous Patients – Reference Set – Analysis by Treatment Subgroup at Inclusion (Targeted Therapy, Chemotherapy, Somatostatin Analog)

Table 14.2.2.6.16: Analysis of Survival-Free Progression of Treatment at Inclusion for Metasynchronous Patients – Reference Set – Analysis by Treatment Subgroup Based on the Targeted-Therapy Lines at Any Time During the Study (1st Targeted Therapy as Line 1 or 2 Vs 1st Targeted Therapy as Line 3 or More)

Figure 14.2.2.6.16: Analysis of Survival-Free Progression of Treatment at Inclusion for Metasynchronous Patients – Reference Set – Analysis by Treatment Subgroup Based on the Targeted-Therapy Lines at Any Time During the Study (1st Targeted Therapy as Line 1 or 2 Vs 1st Targeted Therapy as Line 3 or More)

Table 14.2.2.6.17: Analysis of Overall Progression-Free Survival for Patients Receiving Targeted Therapy at Any Time During the Study – Reference Set – Subgroup Analysis Based on Liver Invasion (≤50%, >50%)

Figure 14.2.2.6.17: Analysis of Overall Progression-Free Survival for Patients Receiving Targeted Therapy at Any Time During the Study – Reference Set – Subgroup Analysis Based on Liver Invasion (≤50%, >50%)

Table 14.2.2.6.18: Analysis of Overall Progression-Free Survival for Patients Receiving Targeted Therapy at Any Time During the Study – Reference Set – Subgroup Analysis Based on Number of Metastatic Sites (≤2, >2)

Figure 14.2.2.6.18: Analysis of Overall Progression-Free Survival for Patients Receiving Targeted Therapy at Any Time During the Study – Reference Set – Subgroup Analysis Based on Number of Metastatic Sites (≤2, >2)

Table 14.2.2.6.19: Analysis of Progression-Free Survival for Patients Receiving Chemotherapy at Inclusion – Reference Set – Subgroup Analysis Based the Number of the Main Treatment Line at Inclusion (≤2, >2)

Figure 14.2.2.6.19: Analysis of Progression-Free Survival for Patients Receiving Chemotherapy at Inclusion – Reference Set – Subgroup Analysis Based the Number of the Main Treatment Line at Inclusion (≤2, >2)

Table 14.2.2.6.20: Analysis of Progression-Free Survival for Patients Receiving Chemotherapy at Inclusion – Reference Set – Subgroup Analysis Based the Number of the Main Treatment Line Throughout Follow-Up (≤2, >2)

Figure 14.2.2.6.20: Analysis of Progression-Free Survival for Patients Receiving Chemotherapy at Inclusion – Reference Set – Subgroup Analysis Based the Number of the Main Treatment Line Throughout Follow-Up (≤2, >2)

Table 14.2.2.6.21: Analysis of Progression-Free Survival of the 1st Treatment Line – Reference Set – Analysis by Main Treatment Line Subgroup

Figure 14.2.2.6.21: Analysis of Progression-Free Survival of the 1st Treatment Line – Reference Set – Analysis by Main Treatment Line Subgroup

Table 14.2.2.6.22: Analysis of Progression-Free Survival of the 2nd Treatment Line – Reference Set – Analysis by Main Treatment Line Subgroup

Figure 14.2.2.6.22: Analysis of Progression-Free Survival of the 2nd Treatment Line – Reference Set – Subgroup Analysis of the Main Treatment Line

Table 14.2.2.6.23: Analysis of Progression-Free Survival of the ... Nth Treatment Line – Reference Set – Subgroup Analysis of the Main Treatment Line

Figure 14.2.2.6.23: Analysis of Progression-Free Survival of the ... Nth Treatment Line – Reference Set – Subgroup Analysis of the Main Treatment Line

Table 14.2.2.6.24: Analysis of Progression-Free Survival of the ... Nth Treatment Line – Reference Set – Subgroup Analysis of the Main Treatment Line

Figure 14.2.2.6.24: Analysis of Progression-Free Survival of the ... Nth Treatment Line – Reference Set – Subgroup Analysis of the Main Treatment Line

9.3.7. Overall Survival

Table 14.2.2.7.1: Analysis of Overall Survival (Baseline Date = Date of Starting the First Treatment Line) – Reference Set – Patients Included as 1st Treatment Line

Figure 14.2.2.7.1: Analysis of Overall Survival (Baseline Date = Date of Starting the First Treatment Line) – Reference Set – Patients Included as 1st Treatment Line

Table 14.2.2.7.2: Analysis of Overall Survival (Baseline Date = Date of Starting the Second Treatment Line) – Reference Set – Patients Included as 2nd Treatment Line

Figure 14.2.2.7.2: Analysis of Overall Survival (Baseline Date = Date of Starting the Second Treatment Line) – Reference Set – Patients Included as 2nd Treatment Line

Table 14.2.2.7.3: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) – Reference Set – Overall

Figure 14.2.2.7.3: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) – Reference Set – Overall

Table 14.2.2.7.4: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) – Reference Set – Subgroup Analysis Based on the Stage at Diagnosis (Localised/Metastatic)

Figure 14.2.2.7.4: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) – Reference Set – Subgroup Analysis Based on the Stage at Diagnosis (Localised/Metastatic)

Table 14.2.2.7.5: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) – Reference Set – Subgroup Analysis Based on Receiving at Least One Targeted Therapy During the Data-Collection Period at Any Time During the Study (Yes/No)

Figure 14.2.2.7.5: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) – Reference Set – Subgroup Analysis Based on Receiving at Least One Targeted Therapy During the Data-Collection Period at Any Time During the Study (Yes/No)

Table 14.2.2.7.6: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) – Reference Set – Analysis by Treatment Subgroup Based on a 1st Targeted Therapy as Line 1 or 2 Vs 1st Targeted Therapy as Line 3 or More at Any Time During the Study

Figure 14.2.2.7.6: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) – Reference Set – Analysis by Treatment Subgroup Based on a 1st Targeted Therapy as Line 1 or 2 Vs 1st Targeted Therapy as Line 3 or More at Any Time During the Study

Table 14.2.2.7.7: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) – Reference Set – Subgroup Analysis Based on Patients Having Received Surgery at Least Once at Any Time During the Study (Yes/No)

Figure 14.2.2.7.7: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) – Reference Set – Subgroup Analysis Based on Patients Having Received Surgery at Least Once at Any Time During the Study (Yes/No)

Table 14.2.2.7.8: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) – Reference Set – Subgroup Analysis Based on the Stage at Diagnosis (Localised/Metastatic)

Figure 14.2.2.7.8: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) – Reference Set – Subgroup Analysis Based on the Stage at Diagnosis (Localised/Metastatic)

Table 14.2.2.7.9: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) – Reference Set – Subgroup Analysis Based on Receiving at Least One Targeted Therapy During the Data-Collection Period at Any Time During the Study (Yes/No)

Figure 14.2.2.7.9: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) – Reference Set – Subgroup Analysis Based on Receiving at Least One Targeted Therapy During the Data-Collection Period at Any Time During the Study (Yes/No)

Table 14.2.2.7.10: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) – Reference Set – Analysis by Treatment Subgroup Based on a 1st Targeted Therapy as Line 1 or 2 Vs 1st Targeted Therapy as Line 3 or More at Any Time During the Study

Figure 14.2.2.7.10: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) – Reference Set – Analysis by Treatment Subgroup Based on a 1st Targeted Therapy as Line 1 or 2 Vs 1st Targeted Therapy as Line 3 or More at Any Time During the Study

Table 14.2.2.7.11: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) – Reference Set – Subgroup Analysis Based on Patients Having Received Surgery at Least Once at Any Time During the Study (Yes/No)

Figure 14.2.2.7.11: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) – Reference Set – Subgroup Analysis Based on Patients Having Received Surgery at Least Once at Any Time During the Study (Yes/No)

Table 14.2.2.7.12: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) in Metasynchronous Patients – Reference Set – Subgroup Analysis Based on Patients Having Received Targeted Therapy at Any Time During the Study (Yes/No)

Figure 14.2.2.7.12: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) in Metasynchronous Patients – Reference Set – Subgroup Analysis Based on Patients Having Received Targeted Therapy at Any Time During the Study (Yes/No)

Table 14.2.2.7.13: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) in Metasynchronous Patients – Reference Set – Analysis by Treatment Subgroup Based on a 1st Targeted Therapy as Line 1 or 2 Vs 1st Targeted Therapy as Line 3 or More at Any Time During the Study

Figure 14.2.2.7.13: Analysis of Overall Survival (Baseline Date = Date of Diagnosis) in Metasynchronous Patients – Reference Set – Analysis by Treatment Subgroup Based on a 1st Targeted Therapy as Line 1 or 2 Vs 1st Targeted Therapy as Line 3 or More at Any Time During the Study

Table 14.2.2.7.14: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) in Metasynchronous Patients – Reference Set – Subgroup Analysis Based on Patients Having Received Targeted Therapy at Any Time During the Study (Yes/No)

Figure 14.2.2.7.14: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) in Metasynchronous Patients – Reference Set – Subgroup Analysis Based on Patients Having Received Targeted Therapy at Any Time During the Study (Yes/No)

Table 14.2.2.7.15: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) in Metasynchronous Patients – Reference Set – Analysis by Treatment Subgroup Based on a 1st Targeted Therapy as Line 1 or 2 Vs 1st Targeted Therapy as Line 3 or More at Any Time During the Study

Figure 14.2.2.7.15: Analysis of Overall Survival (Baseline Date = Date of Starting Treatment at Inclusion) in Metasynchronous Patients – Reference Set – Analysis by Treatment Subgroup Based on a 1st Targeted Therapy as Line 1 or 2 Vs 1st Targeted Therapy as Line 3 or More at Any Time During the Study

Table 14.2.2.7.16: Analysis of Overall Survival of the 1st Main Treatment Line (Baseline Date = Date of Starting Main Treatment) – Reference Set – Subgroup Analysis Based on the Main Treatment Line

Figure 14.2.2.7.16: Analysis of Overall Survival of the 1st Main Treatment Line (Baseline Date = Date of Starting Main Treatment) – Reference Set – Subgroup Analysis Based on the Main Treatment Line

Table 14.2.2.7.17: Analysis of Overall Survival of the 2nd Main Treatment Line (Baseline Date = Date of Starting Main Treatment) – Reference Set – Subgroup Analysis Based on the Main Treatment Line

Figure 14.2.2.7.17: Analysis of Overall Survival of the 2nd Main Treatment Line (Baseline Date = Date of Starting Main Treatment) – Reference Set – Subgroup Analysis Based on the Main Treatment Line

Table 14.2.2.7.18: Analysis of Overall Survival of the ... Nth Main Treatment Line (Baseline Date = Date of Starting Main Treatment) – Reference Set – Subgroup Analysis Based on the Main Treatment Line

Figure 14.2.2.7.18: Analysis of Overall Survival of the ... Nth Main Treatment Line (Baseline Date = Date of Starting Main Treatment) – Reference Set – Subgroup Analysis Based on the Main Treatment Line

Programmer note: Show the 95% confidence interval (log-log transformation) of the survival function for the analyses on the overall population (Figures 14.2.7.1 and 14.2.7.3).

9.3.8. Change of Main Treatment after Progression

Table 14.2.2.8.1: Discontinuation of Main Treatment after Progression Over the Entire Period – Reference Set

		Total (N=XX)
Patients having registered a progression at least once	N	XX
	Missing data	XX
	Yes	XX (XX.X%)
	No	XX (XX.X%)
If yes, Discontinuation of the main treatment at the time of the progression	N(%)	XX (XX.X%)
If yes, Discontinuation after progression	N(%)	XX (XX.X%)

9.3.9. Supportive Analyses

Table 14.2.2.9.1: Analysis of Progression-Free Survival – Reference Set – Overall and Targeted Therapies Vs Other Treatments Group

Figure 14.2.2.9.1: Analysis of Progression-Free Survival – Reference Set – Overall and Targeted Therapies Vs Other Treatments Group

Table 14.2.2.9.2: Analysis of Progression-Free Survival – Incident Patients – Reference Set – Overall and Targeted Therapies Vs Other Treatments Group

Figure 14.2.2.9.2: Analysis of Progression-Free Survival – Incident Patients – Reference Set – Overall and Targeted Therapies Vs Other Treatments Group

9.4. Safety Data

9.4.1. Treatment Drop-outs and Reasons for Dropping Out Documented for the Study

Table 14.3.1.1: Total Duration of Exposure to the Main Treatment Received at the Inclusion Since Starting the Documented Treatment in the Study – Safety Analysis Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Total duration of treatment exposure (months)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Total duration of treatment exposure (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	]0-3] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]3-6] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]6-12] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]12-24] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	> 24 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Total duration of exposure = (Date of last dose of treatment – Date of first dose of treatment +1)/30.4375.

For patients still on treatment at 2 years, the date of the last treatment dose used is the date of the last visit.

For patients who dropped out of the study, the date of the last treatment dose used is the date of the last visit.

Using the same template:

Table 14.3.1.2: Total Duration of Exposure to the Main Treatment Received at the Inclusion Since Starting the Documented Treatment in the Study – Reference Set

Table 14.3.1.3: Total Duration of Exposure to the Treatment Received at Least Once During the Study – Safety Analysis Set

Add the footnote: As the start/end dates of combinations reported during a treatment line are not available, the visit dates were used to calculate the duration of the combination treatments. Exposure to combinations is overestimated.

Table 14.3.1.4: Total Duration of Exposure to the Treatment Received at Least Once During the Study – Reference Set

Table 14.3.1.5: Temporary Discontinuations of the Main Treatment at Inclusion Documented in the Study – Safety Analysis Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
At least one temporary discontinuation	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of temporary discontinuations per patient	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time to the first temporary discontinuation since inclusion (months)	N	XX	NA	XX
	Missing data	XX		XX
	Mean (SD)	XX.XX (X.XX)		XX.XX (X.XX)
	Median	XX.X		XX.X
	[Min; Max]	[XX.X; XX.X]		[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]		[XX.X; XX.X]
Time to the first temporary discontinuation since inclusion (N(%))	N	XX	NA	XX
	Missing data	XX		XX
	]0-3] months	XX (XX.X%)		XX (XX.X%)
	]3-6] months	XX (XX.X%)		XX (XX.X%)
	> 6 months	XX (XX.X%)		XX (XX.X%)
Time to the first temporary discontinuation since inclusion (months) – incident patients	N	XX	NA	XX
	Missing data	XX		XX
	Mean (SD)	XX.XX (X.XX)		XX.XX (X.XX)
	Median	XX.X		XX.X
	[Min; Max]	[XX.X; XX.X]		[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]		[XX.X; XX.X]
Time to the first temporary discontinuation since inclusion (N(%)) – incident patients	N	XX	NA	XX
	Missing data	XX		XX
	]0-3] months	XX (XX.X%)		XX (XX.X%)
	]3-6] months	XX (XX.X%)		XX (XX.X%)
	> 6 months	XX (XX.X%)		XX (XX.X%)
	…			
Time to the first temporary discontinuation since inclusion (months) – prevalent patients	N	XX	NA	XX
	Missing data	XX		XX

Table 14.3.1.5: Temporary Discontinuations of the Main Treatment at Inclusion Documented in the Study – Safety Analysis Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
	Mean (SD)	XX.XX (X.XX)		XX.XX (X.XX)
	Median	XX.X		XX.X
	[Min; Max]	[XX.X; XX.X]		[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]		[XX.X; XX.X]
Time to the first temporary discontinuation since inclusion (N(%)) – prevalent patients	N	XX	NA	XX
	Missing data	XX		XX
	]0-3] months	XX (XX.X%)		XX (XX.X%)
	]3-6] months	XX (XX.X%)		XX (XX.X%)
	> 6 months	XX (XX.X%)		XX (XX.X%)
	…			
Reasons for temporary discontinuations	N	XX	XX	XX
	Missing data	XX	XX	XX
	Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Patient's choice	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Doctor's choice	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Duration of temporary discontinuations (days)	N	XX	NA	XX
	Missing data	XX		XX
	Mean (SD)	XX.XX (X.XX)		XX.XX (X.XX)
	Median	XX.X		XX.X
	[Min; Max]	[XX.X; XX.X]		[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]		[XX.X; XX.X]

For chemotherapies, interferons and somatostatin analogs, a difference of more than 7 consecutive days is deemed to be a temporary discontinuation.

Programmer note:

- For the variables "Time to first temporary discontinuation", N=number of patients with at least one temporary discontinuation.
- For the variables "Reasons for temporary discontinuations" and "Duration of temporary discontinuations", N=number of temporary discontinuations.

Table 14.3.1.6: Temporary Discontinuations of the Main Treatment Received at Least Once During the Study – Safety Analysis Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
At least one temporary discontinuation	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of temporary discontinuations per patient	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Reasons for temporary discontinuations	N	XX	XX	XX
	Missing data	XX	XX	XX
	Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Patient's choice	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Doctor's choice	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Duration of temporary discontinuations (days)	N	XX	NA	XX
	Missing data	XX		XX
	Mean (SD)	XX.XX (X.XX)		XX.XX (X.XX)
	Median	XX.X		XX.X
	[Min; Max]	[XX.X; XX.X]		[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]		[XX.X; XX.X]

The temporary discontinuations were not recorded for patients on "Other" treatments shown in the "Other treatments" column.

Table 14.3.1.7: Permanent Discontinuations of the Treatment at Inclusion Documented in the Study – Safety Analysis Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Permanent discontinuation	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time to permanent discontinuation since inclusion (months)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]

Table 14.3.1.7: Permanent Discontinuations of the Treatment at Inclusion Documented in the Study – Safety Analysis Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Time to permanent discontinuation since inclusion (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	]0-1] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]1-2] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]2-3] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Time to permanent discontinuation since inclusion (months) – incident patients	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time to permanent discontinuation since inclusion (N(%)) – incident patients	N	XX	XX	XX
	Missing data	XX	XX	XX
	]0-1] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]1-2] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]2-3] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Time to permanent discontinuation since inclusion (months) – prevalent patients	N	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time until permanent discontinuation from inclusion (N(%)) – prevalent patients	N	XX	XX	XX
	Missing data	XX	XX	XX
	]0-1] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]1-2] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]2-3] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Time until permanent discontinuation from initiation (months)	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time until permanent discontinuation from initiation (N(%))	N	XX	XX	XX
	Missing data	XX	XX	XX
	]0-3] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]3-6] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]6-12] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]12-24] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>24 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time until permanent discontinuation from initiation (months) – incident patients	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]

Table 14.3.1.7: Permanent Discontinuations of the Treatment at Inclusion Documented in the Study – Safety Analysis Set

		Targeted therapies (N=XX)	Other treatments (N=XX)	Total (N=XX)
Time until permanent discontinuation from initiation (N(%)) – incident patients	N	XX	XX	XX
	Missing data	XX	XX	XX
	]0-3] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]3-6] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]6-12] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]12-24] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>24 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	…			
Time until permanent discontinuation from initiation (months) – prevalent patients	N	XX	XX	XX
	Missing data	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Mean	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Time until permanent discontinuation from initiation (N(%)) – prevalent patients	N	XX	XX	XX
	Missing data	XX	XX	XX
	]0-3] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]3-6] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]6-12] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]12-24] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>24 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reasons for permanent discontinuation	N	XX	XX	XX
	Missing data	XX	XX	XX
	Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Patient's choice	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Doctor's choice	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	OtherLost to follow-up	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients who have discontinued due to toxicity*	N	XX	XX	XX
	Missing data	XX	XX	XX
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

* Discontinuation due to toxicity corresponds to discontinuation for an AE or Death.

Programmer note: analysis of the time to permanent discontinuation since inclusion will be shown by class by month at 12 months and then every 3 months up to 24 months.

Using the same template:

Table 14.3.1.8: Permanent Discontinuations of the Treatment at Inclusion Documented in the Study – Safety Analysis Set – Treatment Subgroup Analysis

Table 14.3.1.9: Total Duration of Exposure Since Starting the Documented Treatment in the Study by Ecog Index at Inclusion – Reference Set

		ECOG=0 (N=XX)	**...**	**ECOG=4 (N=XX)**	**Total (N=XX)**
Total duration of exposure to treatment (months)	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Total duration of exposure to treatment (N(%))	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	]0-3] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]3-6] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]6-12] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]12-24] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>24 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Total duration of exposure = (Date of last dose of treatment – Date of first dose of treatment + 1) / 30.4375.

For patients still on treatment at 2 years, the date of the last treatment dose used is the date of the last visit.

Table 14.3.1.10: Total Duration of Exposure Since Starting the Documented Treatment in the Study by Ecog Index at Inclusion – Incident Patients – Reference Set

		ECOG=0 (N=XX)	...	ECOG=4 (N=XX)	Total (N=XX)
Total duration of exposure to treatment (months)	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Total duration of exposure to treatment (N(%))	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	]0-3] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]3-6] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]6-12] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]12-24] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>24 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Total duration of exposure = (Date of last dose of treatment – Date of first dose of treatment + 1)/ 30.4375.

For patients still on treatment at 2 years, the date of the last treatment dose used is the date of the last visit.

Table 14.3.1.11: Total Duration of Exposure Since Starting the Documented Treatment in the Study by Ecog Index at Inclusion – Prevalent Patients – Reference Set

		ECOG=0 (N=XX)	...	ECOG=4 (N=XX)	Total (N=XX)
Total duration of exposure to treatment (months)	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	Mean (SD)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)	XX.XX (X.XX)
	Median	XX.X	XX.X	XX.X	XX.X
	[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
	[Q1; Q3]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Total duration of exposure to treatment (N(%))	N	XX	XX	XX	XX
	Missing data	XX	XX	XX	XX
	]0-3] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]3-6] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]6-12] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	]12-24] months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>24 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Total duration of exposure = (Date of last dose of treatment – Date of first dose of treatment + 1) / 30.4375.

9.4.2. Adverse Events

Programmer note: All of the tables below are shown:

- By treatment at inclusion: Targeted therapy/Other treatments (somatostatin analogs/ chemotherapy /…)/ Total.
- By treatment at inclusion: Everolimus/Sunitinib/chemotherapy/somatostatin analogs/ interferon alpha/somatostatin analog/metabolic radiotherapy/total.
- By treatment received at least once during the study: Targeted therapy/Other treatments (somatostatin analogs/chemotherapy/…).
- By treatment received at least once during the study: Everolimus/Sunitinib/chemotherapy /somatostatin analogs/interferon alpha/somatostatin analog/metabolic radiotherapy.

As a result, the summary tables will be duplicated.

Table 14.3.2.1: General Overview of Adverse Events – Safety Analysis Set

		Targeted therapies (N=XX)	…	Total (N=XX)
At least one adverse event	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events	N	XX	XX	XX
At least one serious adverse event	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of serious adverse events	N	XX	XX	XX
At least one adverse event suspected to be related to the study treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events suspected to be related to the study treatment	N	XX	XX	XX
At least one adverse event resulting in death	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events resulting in death	N	XX	XX	XX
At least one adverse event resulting in permanent discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events resulting in permanent discontinuation of treatment	N	XX	XX	XX
At least one adverse event leading to change in dosage/temporary discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events leading to change in dosage/temporary discontinuation of treatment	N	XX	XX	XX
At least one adverse event suspected to be related to the study treatment leading to permanent discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.3.2.1: General Overview of Adverse Events – Safety Analysis Set

		Targeted therapies (N=XX)	**…**	**Total (N=XX)**
Number of adverse events suspected to be related to the study treatment leading to permanent discontinuation of treatment	N	XX	XX	XX
At least one adverse event suspected to be related to the study treatment resulting in a change in dosage/temporary discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events suspected to be related to the study treatment leading to change in dosage/temporary discontinuation of treatment	N	XX	XX	XX
At least one adverse event suspected to be related to the study treatment leading to temporary discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events suspected to be related to the study treatment leading to temporary discontinuation of treatment	N	XX	XX	XX
At least one serious adverse event suspected to be related to the study treatment leading to permanent discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of serious adverse events suspected to be related to the study treatment leading to permanent discontinuation of treatment	N	XX	XX	XX
At least one serious adverse event suspected to be related to the study treatment leading to change in dosage/temporary discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of serious adverse events suspected to be related to the study treatment leading to change in dosage/temporary discontinuation of treatment	N	XX	XX	XX
At least one serious adverse event suspected to be related to the study treatment leading to temporary discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of serious adverse events suspected to be related to the study treatment leading to temporary discontinuation of treatment	N	XX	XX	XX

Table 14.3.2.2: General Overview of Grade ≥3 Adverse Events – Safety Analysis Set

		Targeted therapies (N=XX)	Other treatments (N=XX	Total (N=XX)
At least one adverse event	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events	N	XX	XX	XX
At least one serious adverse event	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of serious adverse events	N	XX	XX	XX
At least one adverse event suspected to be related to the study treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events suspected to be related to the study treatment	N	XX	XX	XX
At least one adverse event resulting in death	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events resulting in death	N	XX	XX	XX
At least one adverse event leading to permanent discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events leading to permanent discontinuation of treatment	N	XX	XX	XX
At least one adverse event leading to change in dosage/temporary discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events leading to change in dosage/temporary discontinuation of treatment	N	XX	XX	XX
At least one adverse event suspected to be related to the study treatment leading to permanent discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events suspected to be related to the study treatment leading to permanent discontinuation of treatment	N	XX	XX	XX
At least one adverse event suspected to be related to the study treatment leading to change in dosage/temporary discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events suspected to be related to the study treatment leading to change in dosage/temporary discontinuation of treatment	N	XX	XX	XX
At least one adverse event suspected to be related to the study treatment leading to temporary discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of adverse events suspected to be related to the study treatment leading to temporary discontinuation of treatment	N	XX	XX	XX
At least one serious adverse event suspected to be related to the study treatment leading to permanent discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of serious adverse events suspected to be related to the study treatment leading to permanent discontinuation of treatment	N	XX	XX	XX

Table 14.3.2.2: General Overview of Grade ≥3 Adverse Events – Safety Analysis Set

		Targeted therapies (N=XX)	Other treatments (N=XX	Total (N=XX)
At least one serious adverse event suspected to be related to the study treatment leading to change in dosage/temporary discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of serious adverse events suspected to be related to the study treatment leading to change in dosage/temporary discontinuation of treatment	N	XX	XX	XX
At least one serious adverse event suspected to be related to the study treatment leading to temporary discontinuation of treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of serious adverse events suspected to be related to the study treatment leading to temporary discontinuation of treatment	N	XX	XX	XX
At least one grade 3 adverse event	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of grade 3 adverse events	N	XX	XX	XX
At least one serious grade 3 adverse event	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of serious grade 3 adverse events	N	XX	XX	XX
At least one grade 3 adverse event suspected to be related to the study treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of grade 3 adverse events suspected to be related to the study treatment	N	XX	XX	XX
At least one serious grade 3 adverse event suspected to be related to the study treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of serious grade 3 adverse events suspected to be related to the study treatment	N	XX	XX	XX
At least one grade 4 or higher adverse event	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of grade 4 or greater adverse events	N	XX	XX	XX
At least one grade 4 or greater adverse event suspected to be related to the study treatment	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of grade 4 or greater adverse events suspected to be related to the study treatment	N	XX	XX	XX

Programmer note: All of the tables below are shown:

- By treatment received at least once during the study: Targeted therapy/Other treatments (somatostatin analogs/chemotherapy/etc).
- By treatment received at least once during the study: Everolimus/Sunitinib/chemotherapy /somatostatin analogs/interferon alpha/somatostatin analog/metabolic radiotherapy.

Table 14.3.2.3: Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set

	Targeted therapies (N=XX)	…	Total (N=XX)
SOC 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
…			
…			

Using the same template:

Table 14.3.2.4: Adverse Events Suspected to be Related to the Study Treatment by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.5: Adverse Events Grade =3 by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.6: Serious Adverse Events Grade =3 by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.7: Adverse Events Grade ≥4 by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.8: Adverse Events Grade =3 Suspected to be Related to the Treatment by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.9: Serious Adverse Events Grade =3 Suspected to be Related to the Treatment by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.10: Adverse Events Grade ≥4 Suspected to be Related to the Treatment by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.11: Serious Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.12: Non-Serious Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.13: Adverse Events which Resulted in Temporary Discontinuation of Treatment by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.14: Adverse Events which Resulted in Permanent Discontinuation of Treatment by System Organ Class and Preferred Term – Safety Analysis Set

Table 14.3.2.15: Adverse Events Resulting in Death of the Patient by System Organ Class and Preferred Term – Safety Analysis Set

9.5. Listings

Listing 16.2.1: Protocol Deviations

Patient Sex Age	Reference set	Deviations
XXXXX XXXXX XX	Yes/No	XXXXXXXXXXXX XXXXXXXXXXXX

Listing 16.2.2: Patients Excluded from the Analysis Sets

Patient Sex Age	Reference set	Safety analysis set	Reason for exclusion from the analysis sets
XXXXX XXXXX XX	Yes/No	Yes/No	XXXXXXXXXXXX XXXXXXXXXXXX

Listing 16.2.3: Previous Lines of Treatment

Patient Sex Age	Reference set	Treatment group	Previous lines of treatment
XXXXX XXXXX XX	Yes/No	XXXXXXXXXX	Line 1: XXXXXXXXXXXX Line 2: XXXXXXXXXXXX Line 3: XXXXXXXXXXXX

Listing 16.2.4: Lines of Treatment Received Since Starting the Treatment Documented in the Study

Patient Sex Age Initiation - Incident / Prevalent - Reference set	Group	- Visit - Date of visit - Date of tumour assessment	- Radiological response - Clinical response	- Main treatment - Details - Start date - Initial dosage Combination somatostatin analog - Other combination	- Treatment continued - If no, reason	- Concomitant treatment entered - ongoing?	- New concomitant treatment entered - Somatostatin analog? - Other?	- Start date - End date	New Line?	New treatment	Temp. discontinuation
XXXXX	XXX	xxxx	xx	xxxx	xxx			xxxx			
XXXXX XX		xxxx	xx					xxxx			

Listing 16.2.5: Main Treatment Lines Documented in the Study

Patient Sex Age Start Incident / Prevalent Reference set	Period	No. of main treatment line No. of main concomitant treatment line	Main treatment	Combination with the line	Initiation date	Stop date	Reason for discontinuation
xxxxx xxxxx xx	xxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx

Listing 16.2.6: Adverse Events

Patient **Sex** **Age**	**- Safety analysis set** **- Reference set**	**- Start date of study treatment** **- End date of study treatment**	**At least one adverse event**	**- SOC** **- PT** **- Verbatim statement**	**- Start date** **- End date**	**Severity [1]**	**Outcome [2]**	**Intensity [3]**	**CTCAE Grade [4]**	**Causality**	**Action on study treatment [5]**	**Prospective AE (Yes/No)**	**-Treatments received when the AE developed** **- Treatments deemed to be received at the time the AE developed (limit 28 days post-discontinuation date)**
XXXXX XXXXX XX	Yes/No Yes/No		Yes/no							Not related to treatment/ Related to treatment XXXX			

[1] Serious, non-serious.
[2] Recovered, recovered with complications, currently recovering, subject not recovered, unknown.
[3] Mild, moderate, severe.
[4] 0, 1, 2, 3, 4, 5.
[5] Temporary discontinuation, permanent discontinuation, increase of dosage, reduction of dosage, continued unchanged, unknown, not applicable.

Using the same template:

Listing 16.2.7: Adverse Events Reported in Patients Excluded from the Safety Analysis Set

Listing 16.2.8: Adverse Events, Grade ≥3

Listing 16.2.9: Serious Adverse Events

Listing 16.2.10: Adverse Events Suspected to be Related to the Study Treatment Leading to Permanent Discontinuation of Treatment

LISTING 16.2.11: Adverse Events Suspected to be Related to the Study Treatment Leading to Temporary Discontinuation of Treatment

Listing 16.2.12: Deaths

Patient Sex Age	- Safety analysis set - Reference set	Date of death	Reason for death	Details if Other
XXXXX XXXXX XX	Yes/No Yes/No	DDMMYYYY	Related to the disease/Related to treatment /Other	XXXXXXXXXXXXXXXXXXX

10. APPENDICES

10.1. Appendix 1: List of Main Chemotherapy Protocols

- ✓ LV5FU2-streptozotocin
- ✓ 5 FU- streptozotocin
- ✓ Interferon alpha-2
- ✓ Adriamycin-streptozotocin
- ✓ Dacarbazine
- ✓ Temozolomide
- ✓ Temozolomide-capecitabine (TEM-CAP)
- ✓ LV5FU2-dacarbazine
- ✓ FOLFIRI = irinotecan + simplified LV5FU2
- ✓ Simplified FOLFOX 4 (or modified FOLFOX 6) = oxaliplatin (EloxatineR) + (EloxatineR) + simplified LV5FU2
- ✓ Simplified LV5FU2
- ✓ XELOX
- ✓ GEMOX = gemcitabine + oxaliplatin
- ✓ CDDP-etoposide
- ✓ Carboplatin-etoposide
- ✓ Irinotecan-CDDP
- ✓ Capecitabine-bevacizumab
- ✓ 5 FU-streptozotocin-bevacizumab
- ✓ Chemo-embolisation

Further information about the chemotherapy protocols above:

- ✓ FOLFIRI = Folinic acid + 5FU + irinotecan
- ✓ *Simplified* FOLFOX *4 (or modified FOLFOX 6)* = Folinic acid + 5FU + oxaliplatin (Eloxatine®)
- ✓ XELOX = capecitabine (Xeloda)+ Oxaliplatin (Eloxatine®)

  LV5FU2 = Leucovernin = Levamisol = folinic acid = 5FU
  5FU = 5 Fluorouracil
- ✓ GEMOX = gemcitabine (Gemzar®) + oxaliplatin
- ✓ Irinotecan-CDDP = CCDP = Cisplatin
- ✓ Temozolomide-capecitabine (TEM-CAP) = Temodal®+Xeloda®
- ✓ Carboplatin-etoposide; etoposide=VP16
- ✓ Adriamycin-streptozotocin
- ✓ Adriamycin = doxorubicin
- ✓ Dacarbazine = Deticene® = DTIC
- ✓ Bevacizumab = Avastin®

10.2. Appendix 2: Alkyating Agents and Alkylating Treatment Protocols

Alkyating agents and alkylating treatment protocols are shown below:

- ✓ Dacarbazine
- ✓ Temozolomide
- ✓ Temozolomide-capecitabine (TEM-CAP)
- ✓ LV5FU2-dacarbazine
- ✓ Simplified FOLFOX 4 (or modified FOLFOX 6) = oxaliplatin (EloxatineR) + (EloxatineR) + simplified LV5FU2
- ✓ XELOX
- ✓ GEMOX = gemcitabine + oxaliplatin
- ✓ CDDP-etoposide
- ✓ Carboplatin-etoposide
- ✓ Irinotecan-CDDP

- ✓ Simplified FOLFOX 4 (or modified FOLFOX 6) = Folinic acid + 5FU + oxaliplatin (Eloxatine®)
- ✓ XELOX = capecitabine (Xeloda)+ Oxaliplatin (Eloxatine®)
- ✓ GEMOX = gemcitabine (Gemzar®) + oxaliplatin
- ✓ Irinotecan-CDDP (CCDP = Cisplatin)
- ✓ Temozolomide-capecitabine (TEM-CAP) = Temodal®+Xeloda®
- ✓ Carboplatin-etoposide; (etoposide=VP16)
- ✓ Dacarbazine = Deticene® = DTIC

11. REFERENCES

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