NOVARTIS

Department of Medical Oncology

Afinitor®, everolimus

Non-Interventional Final Report

CRAD001JFR38

TANGO study

Observational prospective study in post-menopausal women with advanced HR+/HER2- breast cancer treated with a combination of Afinitor® + exemestane to describe the management of two Adverse Events, non-infectious lung disease and stomatitis

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PASS information

Title	TANGO study Observational prospective study in post-menopausal women with advanced HR+/HER2- breast cancer treated with a combination of Afinitor® + exemestane to describe the management of two Adverse Events, non-infectious lung disease and stomatitis.
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Active substance	L01XE10, everolimus
Medicinal product	Afinitor®
Product reference	RAD001
Procedure number	Not applicable
Marketing authorization holder	Novartis Europharm Limited
Joint PASS	Yes
Research question and objectives	This observational study aimed to describe two specific adverse events, non-infectious lung disease and stomatitis, and their management in women with HR+/HER2- advanced breast cancer treated with Afinitor® + exemestane. **Primary objective:** To describe the patterns of management for stomatitis and non-infectious lung disease (therapeutic classes, specific management). **Secondary objectives:** To describe characteristics of stomatitis and non-infectious lung disease in clinical practice (incidence, time to occurrence, evolution).

To describe previous treatments for metastatic disease.

To describe for Afinitor® + exemestane:

- Overall duration of Afinitor®.
- Main reasons for dose reduction and interruption / discontinuation.
- Response rate, clinical benefit rate, progression-free survival.
- Safety of Afinitor® + exemestane.

To describe sequential therapies prescribed after discontinuation of the Afinitor® + exemestane combination, discontinuation of either Afinitor® or exemestane.

Country of study France

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1 Abstract

Title

TANGO: Observational prospective study in post-menopausal women with advanced HR+/HER2- breast cancer treated with a combination of Afinitor® + exemestane to describe the management of two Adverse Events, non-infectious lung disease and stomatitis.

Version and date

Version 00 dated 21 March 2018

Name and affiliation of main author

Main author: [redacted], Medical Advisor, Novartis Pharma S.A.S.

Keywords

Afinitor®, breast cancer, non-interventional, stomatitis, non infectious lung disease

Rationale and background

Afinitor® received approval from the European Medicines Agency (EMA) for women with advanced HR+/HER2- breast cancer in July 2012 following the phase III randomised double-blind study BOLERO-2. In this study, the most frequent adverse events (AE) leading to dose reduction or treatment discontinuation were stomatitis and non-infectious pneumopathy (NIP). Their overall incidence was 59% (Grade 3: 8%) and 16% (Grade 3: 3%), respectively. Considering these safety results, it was important to collect data related to stomatitis and NIP and their management in clinical practice.

Research question and objectives

The primary objective was to describe the patterns of management for these two AE. Overall safety of Afinitor® (excluding stomatitis/NIP), treatment duration and progression-free survival (PFS) were part of secondary objectives.

Study design

National, multicentre, observational, prospective, joint post-authorisation safety study (PASS).

Setting

This study was conducted in 112 centres in France from 06-Nov-2014 to 28-Apr-2017.

Patients and study size, including dropouts

This study included post-menopausal women (≥ 18-year-old) with metastatic or locally advanced HR+/HER2- breast cancer, for whom the physician decided to initiate Afinitor® + exemestane under their EMA labels. It was planned to enroll ~639 patients.

Variables and data sources

Data were recorded on paper case report forms completed by physicians. Treatment duration was defined as the time from the first dose of treatment until documented treatment discontinuation (at least one drug discontinued) or follow-up discontinuation and PFS as the time elapsed between the first dose of Afinitor® and tumour progression, death from any cause or follow-up discontinuation.

Statistical methods

Descriptive analyses were mainly performed. The Kaplan-Meier method was used for survival analysis.

Results

596 patients were included in the safety population (patients with at least one dose of Afinitor® and one post-baseline safety assessment) and 562 in the efficacy population (patients with at least one dose of Afinitor® and one documented follow-up visit).

In the safety population, 305/596 patients (51.2%) experienced 400 episodes of stomatitis and 80/596 (13.4%) experienced 88 episodes of NIP. The 3 most common medications used to treat stomatitis episodes were mouthwashes (309/400, 77.3%), topical analgesics (74/400, 18.5%), and antifungals (60/400, 15.0%). NIP were mainly treated with corticosteroids (35/88, 39.8%) and to a lesser extent with antibiotics (9/88, 10.2%).

418/596 patients (70.1%) experienced at least one AE (excluding stomatitis/NIP) related to Afinitor®, the most common ones being *asthenia* (11/596, 18.6%), *diarrhoea* (67/596, 11.2%), and *rash* (61/596, 10.2%). 55/596 patients (9.2%) experienced at least one serious AE (excluding stomatitis/NIP) related to Afinitor®, the most common one being *asthenia* (9/596, 1.5%). 5/596 patients (0.8%) experienced a total of 6 fatal AE related to Afinitor®: *general physical health deterioration*, *multiple organ dysfunction syndrome*, *epistaxis*, *interstitial lung disease, metastases to pleura*, and *disorientation*.

In the efficacy population, the median duration of exposure to Afinitor® + exemestane was 5.3 months (95% confidence interval [CI]: 4.8−6.0).

The median PFS was 6.9 months (95% CI: 6.2−7.8).

Discussion

Safety and efficacy results provided by TANGO supported those obtained in BOLERO-2 and in real-life observational studies (such as BRAWO).

Conclusion

TANGO results reinforce the known safety profile of Afinitor® and complement existing data on the management of stomatitis and NIP occurring during Afinitor® treatment.

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Name(s) and Affiliation(s) of Principal Investigator(s)

Not applicable.

2 List of abbreviations

AIP	Analyzable Included Population
CCTIRS	Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé / French Committee on Information Processing in Material Research in the Field of Health
CI	Confidence interval
CNIL	Commission Nationale de l'Informatique et des Libertés / French National Commission on Informatics and Liberty
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DS&E	Drug Safety & Epidemiology
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
EFF	Efficacy Population
EMA	European Medicines Agency
ER+	Estrogen receptor-positive
FPFV	First patient first visit
GCP	Good Clinical Practice
HER2-	Human epidermal growth factor receptor 2-negative
HR+	Hormone receptor-positive
ICH	International Council for Harmonisation
LPFV	Last patient first visit
M	Month
Max	Maximum
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mTOR	Mammalian Target of Rapamycin
NIP	Non-infectious pneumopathy
NSAI	Non-steroidal aromatase inhibitor
NR	Not reached
OS	Overall Survival
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PFS	Progression-Free Survival
PRC	Promotional Review Committee
PT	Preferred Term
Q1 & Q3	First and third quartiles
RECIST	Response Evaluation Criteria In Solid Tumors
(S)AE	(Serious) Adverse Event
SAF	Safety Population
(S)AI	(Steroidal) Aromatase Inhibitor
SAP	Statistical Analysis Plan
SBR	Scarff-Bloom-Richardson

SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
TTP	Time To Progression
V	Visit
VEGF	Vascular Endothelial Growth Factor

PREAMBLE

The text of **Sections 3** to **9.10** describes the reality of how the study was conducted and analysed, *i.e.*, takes into account the changes in the study conduct and analyses up to the database lock (30-Nov-2017). The protocol version 04 (dated 21-Jul-2015) as well as the statistical analysis plan (SAP) version 3 (dated 15-Mar-2018) were used to prepare this report.

3 Study physicians

This study was conducted by 112 physicians in France. The list of all study physicians together with their contact details can be found in **Annex 2**.

4 Other responsible parties

The study was sponsored by *Novartis Pharma S.A.S.* (2−4 rue Lionel Terray, 92506 Rueil-Malmaison, France). Key persons composing the Sponsor's study team are listed in the table below:

Function	Company/Organisation	Name
Medical Advisor	Novartis Pharma S.A.S, France	[redacted]
Scientific and Medical Project Manager	Novartis Pharma S.A.S, France	[redacted]
Local Study Coordinator	Novartis Pharma S.A.S, France	[redacted]
Data Management Coordinator	IT&M Stats, France, on behalf of Novartis	[redacted]
Biostatistician	Novartis Pharma S.A.S, France	[redacted]
Pharmacovigilance Expert	Experis IT, France, on behalf of Novartis	[redacted]

In addition, the following roles and responsibilities were given to a contract research organisation (CRO), Keyrus Biopharma, which followed its own internal standard operating procedures (SOP) reviewed and approved by Novartis:

Role/Responsibility	Company/Organisation	Name
Project Management & Monitoring[1]	Keyrus Biopharma, France	[redacted]
Data Management	Keyrus Biopharma, France	[redacted]
Statistical Analysis	Keyrus Biopharma, France	[redacted]
Medical Writing	Keyrus Biopharma, Belgium	[redacted]

[1]Keyrus Biopharma was in charge of recruiting study physicians, setting-up participating centres, providing cases report forms, and initiating and monitoring participating centres.

A scientific committee was also established by the Sponsor and was composed of the following 2 members:

[redacted]	[redacted]
	France
[redacted]	[redacted]
	France

The role of the scientific committee was to define and approve the methodology and procedures for carrying out this study and to review and approve the SAP. In case of abnormalities in the data control process, the scientific committee reviewed all the actions judged necessary in order to improve data quality. The scientific committee was involved and will continue to be involved in the communication of study results.

5 Milestones

Table 5-1. Study milestones

Milestone	Planned date/duration[1]	Actual date/duration	Comments
CCTIRS approval (protocol version 00)	-	09-Jan-2014	
CNIL approval (protocol version 02)	-	13-Aug-2014	
Registration in the EU PAS register	-		
Recruitment of physicians	1 month	1 month	-
Recruitment of patients	16 months	16.5 months	Initial recruitment period was planned to last for 12 months. Due to delays in inclusion, the recruitment period was extended by 4 months as described in protocol amendment 3 (see **Section 8**).
First patient IN (Start of data collection)	Nov-2014	06-Nov-2014	-
Last patient IN	Mar-2016	23-Mar-2016	
Last patient OUT (excluding last contact forms)	Mar-2017	28-Apr-2017	
Database lock (End of data collection)	-	30-Nov-2017	

Milestone	Planned date/duration[1]	Actual date/duration	Comments
Interim analysis (baseline data)	Jun-2016	22-Dec-2016	Delayed delivery due to delays in database cleaning, in particular for inclusion visit
Final analysis	-	20-Dec-2017	-
Final report of study results	2017	Mar-2018	Delayed delivery due to delays in database lock and data availability

[1]Planned dates/durations are those indicated in the last version in use of the study protocol (Version 04 dated 21-Jul-2015).
CCTIRS: Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé ; CNIL: Commission Nationale de l'Informatique et des Libertés; PAS: Post-Autorisation Study.

6 Rationale and background

Breast cancer is the most frequent cancer in women with an estimated 54,000 new cases in 2015 in France. Median age at diagnosis was 63-year-old in 2012 (Institut National du Cancer, 2016).

There was a constant progression in the incidence rate between 2000 and 2005, in parallel with a decrease in mortality rate over the same period. This inversed trend is partially due to screening campaigns which have led to earlier diagnosis and to the improved efficacy of available treatments.

Around 40% of diagnosed patients will progress to metastatic breast cancer. Treatment of metastatic breast cancer is palliative with a median life expectancy of 21 to 31 months for first-line therapy (Saad et al, 2010).

Afinitor® (everolimus) is a selective inhibitor of mTOR (mammalian target of rapamycin) protein, a serine-threonine kinase having an essential role in the signalling cascade PI3K-Akt-mTOR, a pathway which is de-regulated in most human cancers. Afinitor® acts directly by inhibiting the proliferation of cell lines and tumor growth and indirectly by inhibiting angiogenesis (by strongly inhibiting vascular endothelial growth factor receptor [VEGF] production by tumour cells and endothelial cell proliferation induced by VEGF) (Escudier and Thompson, 2009; Saby and Bukowski, 2009).

There is ever increasing evidence in favour of an interaction between the PI3K-Akt-mTOR signalling pathway and hormone receptors. Pre-clinical studies have shown that in breast cancer cells having an Akt pathway with positive feedback, response to hormonal therapy can be restored by treatment with everolimus or other mTOR inhibitors (Baselga et al, 2009). Pre-clinical research has demonstrated that mTOR inhibitors administered in combination with aromatase inhibitors (AI) induce synergistic inhibition of cell proliferation and apoptosis (Boulay et al, 2005).

In addition, research has shown that breast cancer cells which are resistant to hormonal therapy have an over-active PI3KAkt-mTOR signaling pathway and treatment with mTOR inhibitors, including rapamycin analogs can reverse this resistance (Miller et al, 2010).

The results of recent clinical studies confirm these findings. In a neoadjuvant setting, the combination of everolimus and letrozole resulted in a better response rate than letrozole alone in post-menopausal women with estrogen receptor-positive (ER+) breast cancer (Baselga et al, 2009). A randomised phase II study in patients with disease progression after previous treatment with an AI has demonstrated a longer time to progression (TTP) and improved overall survival (OS) with a combination of everolimus and tamoxifen compared to tamoxifen alone (Bachelot et al, 2012). An ongoing study evaluating everolimus and fulvestrant in post-menopausal women with ER+ breast cancer has also shown encouraging results (Badin et al, 2010).

Afinitor® received approval from the European Medicines Agency (EMA) on 23 July 2012 under the following label: “The treatment of hormone receptor-positive, HER2/neu-negative advanced breast cancer, in combination with exemestane, in post-menopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor” (EMA, 2012).

This approval was obtained following the phase III randomised double-blind study BOLERO-2, comparing the association of everolimus and exemestane *versus* exemestane and placebo in post-menopausal women with locally advanced or metastatic ER+ breast cancer resistant to letrozole or anastrozole treatment. The addition of everolimus to exemestane lengthened the median progression-free survival (PFS) from 3.2 to 7.8 months, when evaluated locally by the investigator (relative risk: 0.45; 95% confidence interval (CI): 0.38-0.54; $P < 0.0001$) and from 4.1 to 11 months by independent centralised reading (relative risk: 0.38; 95% CI: 0.31-0.48; $P < 0.0001$) (Yardley et al, 2013). The recommended posology for Afinitor® is 10 mg orally daily in association with 25 mg exemestane. The treatment should be continued as long as there is a clinical benefit or until unacceptable toxicity is reached. Dose modulation is possible in case of toxicity (Summary of Product Characteristics [SmPC] dated 13-Sep-2017). The most frequent adverse events (AE) with the combination of everolimus and exemestane were: stomatitis, skin rash, fatigue, diarrhoea, nausea and decreased appetite (Yardley et al, 2013). The incidence of serious adverse events (SAE, Grades 3 or 4) was 23% for everolimus and exemestane compared to 12% for placebo and exemestane. The most frequent SAE were stomatitis (8% *versus* 1%), anaemia (6% *versus* < 1%), hyperglycaemia (4% *versus* < 1%), dyspnoea (4% *versus* 1%), fatigue (4% *versus* 1%), and non-infectious lung disease (3% *versus* 1%). In addition, there were more treatment discontinuations with everolimus and exemestane and more SAE related to treatment (11% *versus* 1%) (Baselga et al, 2012). The incidence (all grades) was 59% and 16% for stomatitis and non-infectious lung disease, respectively (Grade 3: 8% and 3%, respectively). The 2 most frequent AE leading to dose reduction or treatment discontinuation of Afinitor® were stomatitis and non-infectious lung disease (Yardley et al, 2013).

Therefore, it was considered important to collect data related to the management in medical centres of patients with hormone receptor-positive (HR+) / human epidermal growth factor receptor 2-negative (HER2-) breast cancer treated with everolimus and exemestane, in relation to the treatment and follow-up of AE, in particular for the two most frequent AE, stomatitis and non-infectious lung disease.

7 Research question and objectives

The primary objective of this observational study was to describe the management of 2 specific AE, non-infectious lung disease and stomatitis, in post-menopausal women with advanced HR+/HER2- breast cancer treated with Afinitor® + exemestane (prescribed treatments: therapeutic class, specific actions taken).

The secondary objectives were to describe the following:

- Characteristics of stomatitis and non-infectious lung disease in clinical practice, in particular:
  - Incidence, time to occurrence, evolution
  - The relationship between severity, management type, and evolution
- Previous treatments for metastatic disease:
  - Adjuvant hormonal therapy (if applicable)

  - Systemic treatments during metastatic phase (chemotherapy, hormonal therapy)
  - Best tumoural response with treatment (judged by the investigator)

- Afinitor® + exemestane treatment:
  - Overall duration of Afinitor® + exemestane treatment from first dose of treatment until treatment discontinuation or end-of-study
  - Doses and main reasons for dose reduction
  - Reason for interruption / treatment discontinuation (Afinitor® and/or exemestane)
  - Response rate using RECIST 1.1[1] criteria
  - Clinical benefit rate (response or disease stabilisation)
  - PFS
  - Safety of Afinitor® + exemestane (Grades CTCAE v4.0[2])
  - Subsequent anti-cancer therapies(s) prescribed after discontinuation of the Afinitor® + exemestane combination, discontinuation of either Afinitor® or exemestane

[1]RECIST (Response Evaluation Criteria in Solid Tumors): Version 1.1 2009.
[2]CTCAE (Common Terminology Criteria for Adverse Events): Version 4.0 2009.

8 Amendments and updates to the protocol

There were 4 protocol amendments, all non substantial, following finalisation of the original protocol (Version 00) dated 13-Nov-2013. All amendments were initiated prior to interim/final analyses of the study. The 4 protocol amendments are listed in **Table 8-1**, along with the reasons for the amendments.

Table 8-1. Summary of protocol amendments or updates

Number	Date	Amendment or Update	Section of Study Protocol	Reason(s)
1	28-Jan-2014 (submitted to CCTIRS/CNIL)	Amendment 1 (protocol version 01)	• 4, 9.2.1.3, 9.4 • 4, 6 • First page and headers • Annex	• To answer to the CCTIRS comments: the name of the CRO in charge of the study was precised (KEYRUS BIOPHARMA). • The dates of FPFV and LPFV were updated. • Update of the Novartis code of the study: CRAD001JFR38. • The patient information note was completed by an informed consent form.
2	15-Jul-2014 (submitted to CCTIRS/CNIL)	Amendment 2 (protocol version 02)	• 10	• Comment from the CNIL: inconsistency between the protocol and the information note concerning the intervention of a third party to collect consent (page 26 of the protocol version 01, it was precised that in case of impossibility for the patient, the collection of consent would be obtained from a legal representative, however this hypothesis was not present in the submitted information note).
3	29-Jun-2015 (submitted to PRC[1])	Amendment 3 (protocol version 03)	• 9.7 • 4, 6 • 9.2.1, 9.2.1.3, 9.5, 9.8	• Addition of the subgroup 'number of previous lines of treatment in metastatic disease' to the safety analysis. • Increase of the duration of inclusion: the period of inclusion was extended by 4 months, until Mar-2016. • Increase of the maximal number of patients that can be included per centre: from 20 to 30 patients.

Number	Date	Amendment or Update	Section of Study Protocol	Reason(s)
			• 9.2.1.3	• Deletion of paragraphs recommending the closure of centres inactive for 3 months. Centres inactive for 3 months and more will remain open. Nonetheless, they could be closed upon investigator's request.
4	21-Jul-2015 (submitted to CCTIRS/CNIL)	Amendment 4 (protocol version 04)	• 4, 6	• Upon request of PRC, clarification of the date of interim analysis of baseline data.

[1]Amendment 3 was submitted for internal review and validation by Novartis PRC. This amendment was not implemented. Based on PRC comments, amendment 4 was prepared and submitted to CCTIRS and CNIL.
CCTIRS: Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé; CNIL: Commission Nationale de l'Informatique et des Libertés; CRO: Contract Research Organisation; FPFV: First patient first visit; LPFV: Last patient first visit; PRC: Promotional Review Committee.

9 Research methods

9.1 Study design

9.1.1 Overall study design

The TANGO study (CRAD001JFR38) was a strictly observational multicentre study in France involving physicians with experience with anticancer drugs (mainly medical or radiotherapy oncologists) managing patients with metastatic or locally advanced breast cancer.

This study included post-menopausal women (≥ 18-year-old) with metastatic or locally advanced HR+/HER2- breast cancer, for whom the physician decided to initiate Afinitor® + exemestane treatment under their EMA labels.

It was planned to enroll approximately 639 patients in 150 French centres, with one physician per centre. Each physician/centre had to include consecutively at least 4 patients (maximum 30 patients) with metastatic breast cancer and treated with Afinitor®. The observation period was from the date of inclusion into the study until disease progression, death, or withdrawal. Each patient was to be followed up for 12 months after inclusion into the study. Patient's monitoring in the study stopped if both treatments were discontinued (Afinitor® AND exemestane) before the end of the 12-month observation period. If only one of the treatments was discontinued, monitoring continued until 12 months or until discontinuation of the second treatment.

The total study duration was expected to be at maximum 30 months, including the periods necessary for physician recruitment (1 month), recruitment of patients by the physicians (16 months), 12 months of patient monitoring and 1 month for collecting last forms.

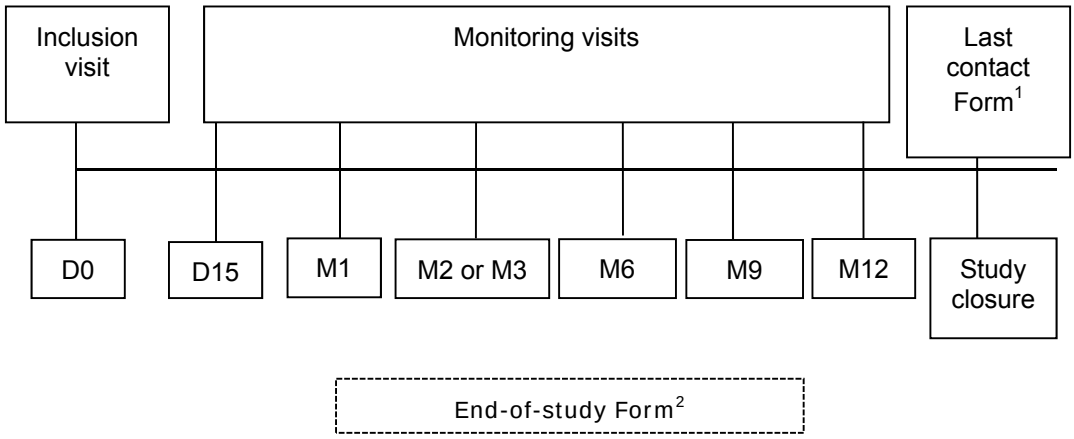
As the study was observational, no therapeutic protocol, diagnosis/therapeutic examinations or strict visit calendar was imposed. Physicians were free to prescribe and care for their patients as usual. Patient care followed the usual physician practice, with visits at inclusion, 15 days (D), one month (M1), 2−3 months (M2−3), 6 months (M6), 9 months (M9), and 12 months (M12), or treatment discontinuation. Assessments performed at each study visit were part of routine care and only these data were collected as part of the study. Case report forms (CRF) were to be completed by the treating physician, if possible, at every patient visit (**Figure 9-1**).

A study discontinuation or end-of-study form had to be completed at the 12-month monitoring visit or in case of treatment discontinuation before the 12-month monitoring visit. At study closure, physicians had to complete a last contact form for the patients continuing treatment at the 12-month monitoring visit (**Figure 9-1**).

The study received favourable opinion of the CCTIRS (French Committee on Information Processing in Material Research in the Field of Health) on 09-Jan-2014 and authorisation of the CNIL (French National Commission on Informatics and Liberty) on 13-Aug-2014. All patients provided written informed consent before inclusion into the study. The study was conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP), the

guiding principles of the 'Declaration of Helsinki', and other applicable guidelines for non-interventional studies.

Figure 9-1. Study design



[1]For patients continuing treatment after the 12-month monitoring period.
[2]In case of study withdrawal between planned visits or at the 12-month monitoring visit.
D: Day; M: Month.

9.1.2 Discussion of the study design

The study design chosen for TANGO study was observational because its main objective was to describe 2 specific AE, non-infectious lung disease and stomatitis, and their management in women with HR+/HER2- breast cancer treated with Afinitor® + exemestane in routine clinical practice. Consequently, no mandatory visits or mandatory assessments were required.

9.2 Setting

The study was conducted in 112 centres in France between 06-Nov-2014 (date of first patient included) to 28-Apr-2017 (last visit date of the last patient), which corresponds to a study duration of 29.7 months.

For patients continuing treatment at the 12-month monitoring visit, a last contact form was sent to the physician in order to collect additional follow-up data. The date of last visit of the last patient who continued the treatment after M12 was 28-Aug-2017. Therefore, the duration of the study, including the last contact forms, was 33.7 months.

Enrolment commenced on 06-Nov-2014 and was completed on 23-Mar-2016 (date of last patient included), which corresponds to a recruitment period of 16.5 months (**Table 1.1.1**, refer to **Annex 1**).

9.3 Patients

9.3.1 Inclusion criteria

Patients were consecutively included in each centre if the answer to all of the following statements was 'yes':

- Post-menopausal women (≥ 18-year-old) with advanced HR+/HER2- breast cancer.
- Patients for whom it was decided to initiate Afinitor® + exemestane treatment under their EMA labels.
- Patients informed and having provided their consent to participate in the study.

9.3.2 Exclusion criteria

Patients with any of the following criteria were not included:

- Patients previously or currently treated with a mTOR inhibitor.
- Patients having a contra-indication to Afinitor® treatment as specified in the SmPC.
- Patients already participating in a clinical study at inclusion.

9.4 Variables

9.4.1 Data related to physicians

Data concerning physicians of this study were collected in an observatory physician identification form, with the following characteristics: age, gender, specialty, region, practice type, structure type, current practices for the management of stomatitis and non-infectious lung disease.

9.4.2 Data related to patients

Data collected by the physician in the CRF were described hereafter and are summarised in **Table 9-1**.

9.4.2.1 Data collected at inclusion

- Demography data: age.
- Co-morbidities: liver insufficiency (presence and severity).
- Data related to the pathology: breast cancer diagnosis date, histological type at diagnosis, stage at diagnosis (localised, locally advanced or metastatic), Scarff-Bloom-Richardson score (SBR), hormone receptor status (HR, HER2).
- Oral cavity and lung examination and action taken if stomatitis or lung disease present.
- Data related to treatment during adjuvant phase (if applicable): treatment type (hormonal or other), description, initiation date, discontinuation date.
- Data related to recurrence: date and progression type.

- Location and symptomatic nature of metastases.
- Data related to treatment during metastasis: treatment type, treatment start and end dates, best tumoural response using RECIST 1.1 criteria and reason for treatment discontinuation.
- Data at initiation of Afinitor® + exemestane treatment: ECOG-PS (Eastern Cooperative Oncology Group − Performance Status), treatment initiation date and posology.

9.4.2.2 Data collected at the monitoring visit at D15

- Patient status (alive or not).
- Clinical data: ECOG-PS.
- Data related to Afinitor® + exemestane treatment:
  - Dose reduction of Afinitor® and/or exemestane, temporary interruption / reason...
  - Discontinuation of Afinitor® and/or exemestane: date and reason for discontinuation.
  - Sequential treatment prescribed after Afinitor® + exemestane or after either of these 2 treatments.
  - Overall safety with collection of AE (severity, relationship, start and end of event, outcome and action taken).
  - Detailed monitoring and follow-up of stomatitis and non-infectious lung disease (severity, relationship, start and end of event, evolution and action taken).

9.4.2.3 Data collected at the monitoring visits at M1, M2, M3, M6, M9 or M12

The same information as monitoring visit at D15 were collected.

Additional clinical data were also collected:

- Best tumoural response using RECIST 1.1 criteria.
- New metastases locations, if any.

9.4.2.4 Data collected on the end-of-study form

In case of discontinuation of Afinitor® and exemestane or end of the study's 12-month monitoring period or early withdrawal, an end-of-study form was completed. The following data were collected: date and the reason for study withdrawal (treatment discontinuation, follow-up discontinuation / lost to follow-up, death, patient request, other reason).

9.4.2.5 Data collected on the last contact form at study closure

For patients continuing Afinitor® and/or exemestane treatment after M12, the following data data were collected on a last contact form:

- Continuation, at last contact, of Afinitor® + exemestane.

- In case of treatment discontinuation: date of last treatment by Afinitor® and/or exemestane and main reason for treatment discontinuation.
- Sequential treatment prescribed after Afinitor® + exemestane or after either of these 2 treatments.
- Patient status at last contact (alive or not).
- Detailed monitoring and follow-up of stomatitis and non-infectious lung disease (episodes occurring between the visit at M12 and discontinuation of Afinitor®, or at last contact): severity, start and end of episode, action taken...
- Safety (overall, AE occurring between the visit at M12 and discontinuation of Afinitor®, or at last contact).

Table 9-1. Flowchart of study observations

Visits	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**		
Month	**Inclusion (M0)**	**D15**	**M1**	**M2**	**M3**	**M6**	**M9**	**M12**	**End of study**	**Study closure**
Demography data	X									
Co-morbidities	X									
Data related to breast cancer	X									
Monitoring and follow-up of stomatitis and non-infectious lung disease	X	X	X	X	X	X	X	X		X
Data related to treatment during:										
adjuvant phase	X									
metastasis	X									
Recurrence	X									
Metastases	X		X	X	X	X	X	X		
Initiation and follow-up of Afinitor® + exemestane treatment	X	X	X	X	X	X	X	X		X
ECOG-PS	X	X	X	X	X	X	X	X		
AE		X	X	X	X	X	X	X		X
Best tumoural response (RECIST 1.1)			X	X	X	X	X	X		
Date and reason for study withdrawal									X	
Patient status		X	X	X	X	X	X	X		X

V: Visit; D: Day; M: Month; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; AE: Adverse Event; RECIST1.1: Response Evaluation Criteria In Solid Tumors version 1.1.

9.4.3 Definition and reporting of adverse events

9.4.3.1 Adverse events

An AE is any untoward medical occurrence in a patient administered the drugs of interest Afinitor® (everolimus) + Aromasine® (exemestane) which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Novartis drug, whether or not related to the medicinal product(s).

Medical conditions/diseases present before starting the drugs of interest were only considered AE if they worsened after starting the drugs of interest. The cancer progressions were to be exempted from the AE reporting except for those with a fatal outcome.

Information about common adverse effects already known about the medicinal product can be found in the SmPC. This information was included in the patient informed consent and should have been discussed with the patient during the study as needed.

All AE, including SAE and safety endpoints (stomatitis and non-infectious lung disease), were collected and recorded in the study database, irrespective of causal association. All AE and SAE occurring in association with exposure to another Novartis drug (e.g. Aromasine®, exemestane) were also notified for recording in the Novartis safety database.

Information on AE occurring during the study was collected though different ways: on-directive questioning of the patient at each visit (visits D15, M1, M2−3, M6, M9, and M12, and also at the end-of-study visit and last contact), voluntary declaration of AE by the patient during or between visits, or detection of AE through physical exmanination, laboratory test or other assessments.

All AE were recorded on the AE report form of the CRF with the following information:

- The severity grade (grade 1−5).
- Its relationship to Afinitor® (suspected/not suspected).
- Its duration (start and end dates or if continuing at final exam).
- Whether it constituted a SAE.
- Its treatment, i.e. no action taken, Afinitor® dosage adjusted/temporarily interrupted, Afinitor® permanent discontinuation, drug or non-drug therapy given, patient hospitalised/patient's hospitalisation prolonged.

In addition, forms relating to AE were to be completed: comments, medical history and co-morbidities, concomitant medication and results of additional examinations and laboratory results.

Once an AE was detected, it should have been followed until its resolution or until it is judged to be permanent, and assessment should have been made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

Information on all AE written in the CRF was to be transferred to Novartis Drug Safety & Epidemiology (DS&E) department on a periodic basis and no later than once a month.

9.4.3.2 Serious adverse event

An SAE is defined as an event which:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation, unless hospitalisation is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in patient's condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Is medically significant, i.e., defined as an event that jeopardises the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
- Transmission of infectious agent via medicinal product.

Information about all SAE was to be collected and recorded on the Serious Adverse Event Report Form. Every SAE, regardless of causality assessment, occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation (defined as time of last dose of the drug of interest taken or last visit whichever is later) was to be reported to Novartis DS&E Department within 24 hours of learning of its occurrence.

Any SAE experienced after this 4-week period should have only been reported to Novartis if the treating physician or other involved health care professional suspected a causal relationship to the drug of interest.

Recurrent episodes, complications, or progression of the initial SAE were to be reported as follow-up to the original episode, regardless of when the event occurred. This report was to be submitted within 24 hours of receiving the follow-up information by the treating physician or other involved health care professional. The report was to be sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this was a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should have described whether the event had resolved or continued, if and how it had been treated, whether the patient continued or withdrew from study participation.

For Afinitor®, the following events are of special interest for targeted follow-up: non-infectious pneumonitis, severe infections, hypersensitivity (anaphylactic reactions), increased creatinine/renal failure/proteinuria, cardiac failure, female fertility (including secondary amenorrhoea), patients with pre-existing infections (reactivation, aggravation or exacerbation), post-natal developmental toxicity, pregnant or breast-feeding women, patient with renal impairment. Any AE of special interest (serious or non serious) was to be notified to Novartis DS&E within the same timelines as a SAE.

9.5 Data sources and measurement

Sites enrolling patients in this study recorded data on paper CRF provided by the designated CRO (Keyrus Biopharma). These data were checked, stored, and analysed in a validated database.

Each included patient was identified by an unique number which was written on each page of each visit of the CRF. Each paper CRF consisted of several « forms » corresponding to inclusion, monitoring and end-of-study visits, last contact, follow-up of study treatment, AE, episodes of stomatitis and episodes of non-infectious lung disease.

Data were collected from inclusion of the first patient and until the last forms were completed.

Safety data were to be transferred to Novartis DS&E Department at a frequency as defined in **Section 9.4.3**. Clinical data were to be transferred to Novartis after closure of the study.

A database quality control was performed at the end of the inclusion period and at the end of the study, before the final database lock (See **Section 9.10**).

9.6 Bias

In order to limit selection bias, physicians were asked to enroll consecutive patients who met the eligibility criteria.

9.7 Study size

The sample size calculation was based on the results of the phase III BOLERO-2 study, with an incidence of 59% for stomatitis and 16% for non-infectious lung disease (Yardley et al, 2013).

The primary objective of the study was to describe the therapeutical management of stomatitis and non-infectious lung disease in patients with HR+/ HER2- metastatic or locally advanced breast cancer who were treated with Afinitor®. To answer this objective, it was key to describe with sufficient precision the proportion of patients with stomatitis and non-infectious lung disease treated with different types of treatments or various combinations of these treatments.

The number of patients necessary to estimate a proportion p with a CI of 95% and an absolute accuracy i, is calculated using the formula:

$$n = p \times (1 - p) \times \left(\frac{1.96}{i} \right)^2$$

For a given number of patients, the proportion with the least absolute accuracy was 50%. The minimum absolute accuracy was set at 10%. Therefore, 97 patients were necessary to describe a proportion of 50% with an absolute accuracy of 10% (nQuery Advisor® 7.0).

Of the 2 events of interest, non-infectious lung disease is the rarest. In order to obtain 97 patients with such an event, 607 patients were required based on the hypothesis of an expected incidence of 16%. In the case of stomatitis, 358 patients were necessary based on expected incidence of 59%.

The following table presents the absolute accuracies obtained for different proportions with 97 and 358 patients:

Table 11 1. Absolute accuracies obtained for different proportions with 97 and 358 patients

		Proportion						
		10%	25%	33%	50%	67%	75%	90%
Number of patients	97	6.0%	8.6%	9.4%	10.0%	9.4%	8.6%	6.0%
	358	3.1%	4.5%	4.9%	5.2%	4.9%	4.5%	3.1%

Taking into account the proportion of CRF not returned or CRF returned but not evaluable normally encountered in this type of survey (around 5%), the number of patients to be included in the TANGO study by 150 specialist physicians was 639 patients.

9.8 Data transformation

9.8.1 Derivate variables

For this study, an extensive list of derivate variables was created. For all details on calculations of derivate variables, refer to Section 4.6 of the SAP version 3.

9.8.2 Analysis populations

For this study, different analysis populations were defined:

- **Included population:** all patients in the study with at least one data filled in the CRF.
- **Analyzable Included Population:** all patients except those from centres 102 and 107, for which physicians did not pursue the study. However, AE of these patients were listed.
- **Safety population:** all patients from the analyzable included population who received at least one dose of Afinitor® and had at least one post-baseline safety assessment. The fact that a patient had no AE throughout her follow-up until M12 also constituted a safety assessment.

  Patient demographics, other baseline characteristics, and safety evaluations were performed on the safety population.

  Note: Patients who started Afinitor® more than 14 days before the inclusion were excluded from the safety population.

- **Efficacy population:** all patients from the analyzable included population who received at least one dose of Afinitor® and had at least one documented follow-up visit.

  Patient demographics, other baseline characteristics, and efficacy evaluations were performed on the efficacy population.

  Note: Patients who started Afinitor® more than 14 days before the inclusion or patients with an artificial interruption were excluded from the efficacy population. An artificial interruption was defined as 'other' in the end-of-study form and specification of 'other' contained 'INCLUS A TORT'. Patients without an non-steroidal aromatase inhibitor (NSAI) administered before the inclusion for whom the radiological assessment highlighted an interstitial pneumopathy or patients identified as HER2+ or taking Herceptin® before inclusion were also excluded from this population.

9.8.3 Main analyses

9.8.3.1 Study duration, study centres and patient disposition

Based on the main study dates (first patient included, last patient included, last visit date of the last patient), duration of inclusion and duration of the study were calculated.

The number of active centres and number of patients by centres globally and by class (1, 2, 3, 4, 5, 6, 7 and ≥ 7 patients) were presented.

Patient disposition was summarised by computing:

- The number of patients included in the study.
- The number of patients included in the 3 analysis populations: analyzable included population, safety population, efficacy population. Reasons for exclusion from these 3 analysis populations were also presented.
- The numbers (%) of patients who discontinued the study prematurely in the 3 analysis populations. Reasons for premature study discontinuation were also presented.
- The duration of exposure to treatment (Afinitor®, exemestane or their combination) in the 3 analysis populations, only for patients who discontinued the treatment.
- The number (%) of patients presenting at least one non-compliance to protocol.

  Non-compliances to protocol were assessed during the pre-analysis data review meeting of the database. All decisions concerning the potential withdrawal of a patient due to protocol deviation(s) were discussed with the sponsor before database lock.

9.8.3.2 Physician characteristics

The characteristics of the physicians involved in the study (i.e. centres with at least one patient included in the analyzable included population) were presented: type of facility, region, current practices for the prevention of stomatitis and non-infectious lung disease.

9.8.3.3 Patient demographics and clinical characteristics at inclusion

Patient demographics and clinical characteristics were summarised in the safety and efficacy populations.

The following data were extracted from these populations:

- **Demography:** age.
- **Breast cancer history:** time since initial diagnosis, histologic type, stage at diagnosis, SBR score, HR status, HER2 receptor status, Ki67 (if available).
- **Initial therapy – locoregional treatments:** surgery and time since surgery, radiotherapy.
- **Initial therapy – treatment in adjuvant phase:** chemotherapy, hormonotherapy, number, type, duration of previous hormonal treatments, interval to recurrence with respect to stop of adjuvant hormonal treatment.
- **Breast cancer relapse:** history of relapse and type.
- **Metastases:** presence of metastases at inclusion, location, symptomatic character of the metastases.
- **Previous treatments in metastatic phase:** number of lines of treatment, and for each line, type, duration of treatment, interval to recurrence, response rate (using RECIST 1.1 criteria).
- **Hepatic concomitant pathology:** presence of liver failure and severity.
- **ECOG-PS**
- **Initial evaluation of the oral cavity:** visit to the dentist and presence of stomatitis before study treatment initiation, type of previous stomatitis, current stomatitis at inclusion, type of current stomatitis at inclusion, measures prescribed to prevent new stomatitis episodes.
- **Initial evaluation of the lungs:** presence of and details about pulmonary symptoms at inclusion, consultation of pulmonologist before inclusion and details about imaging examinations performed.

9.8.3.4 Safety analysis

Safety analyses were performed on the safety population.

9.8.3.4.1 Management of stomatitis and non-infectious lung disease − Primary objective

Management of these two AE, more specifically therapeutic classes of prescribed treatments, was described overall (regardless of severity grades) and for grade > 1 events only.

9.8.3.4.2 Characteristics of stomatitis and non-infectious lung disease in clinical practice – Secondary objective

The following characteristics were summarised:

- Incidence and time to first occurrence of stomatitis/non-infectious lung disease.
- Duration and outcome of stomatitis/non-infectious lung disease episodes (if at least 5 patients by episode, except episode 1).
- The number (%) of patients for whom the most severe episode was classified as grade 1, 2, 3, 4 and 5 or grades 1−2, grade 3, grades 4−5 (after grouping severity grades).

Characteristics of stomatitis and non-infectious lung disease were described overall and in the following subgroups of interest:

Parameters	**Subgroups**
Age	< 70 years *versus* ≥ 70 years < 75 years *versus* ≥ 75 years
Number of previous lines of treatment in metastatic setting	0, 1−2 *versus* ≥ 3 lines
Previous chemotherapy, **for stomatitis only**	Presence *versus* absence
Pulmonary metastases at inclusion, **for non-infectious lung disease only**	Presence *versus* absence
Dose of the first Afinitor® intake	5 mg *versus* 10 mg
Pulmonary or hepatic metastases at inclusion	Presence *versus* absence
Bone metastases at inclusion	Presence of bone-only metastases *versus* Presence of bone and non-bone metastases *versus* Absence of bone metastases

9.8.3.4.3 Overall safety

AE were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology, version 12.1.

Only treatment-emergent AE encountered during the study were summarised, using descriptive statistics. For the classification of AE as emergent/non-emergent, refer to **Section 9.9.3**. Not-related AEs occurring 28 days post-treatment and AE interrupted before the first administration of treatment were not summarised as they were not directly related to the TANGO study. However, these events were listed.

The overall safety, according to the Grades CTCAE v4.0, of Afinitor® and/or exemestane was described.

The following analyses were performed:

- Number (%) of patients having at least one AE, SAE, AE leading to death, AE leading to a dose reduction or temporary interruption of Afinitor®, AE leading to permanent discontinuation of Afinitor®.
- Number (%) of patients with AE, SAE, AE leading to death, AE leading to a dose reduction or temporary interruption of Afinitor®, AE leading to permanent discontinuation of Afinitor® by system organ class (SOC) / preferred term (PT).

- Number (%) of patients with AE by SOC/PT and severity (graded using the CTCAE version 4.0).

9.8.3.5 Description of study treatment

Treatment characteristics were summarised in the efficacy population.

The dose of Afinitor® prescribed at inclusion and the first dose of Afinitor® actually taken by patients were described.

The duration of exposure to Afinitor® + exemestane combination (months) was also described and was defined as the time from the first dose of treatment until documented treatment discontinuation (at least one drug discontinued) or end of observation period. The duration of exposure was computed using Kaplan-Meier method (refer to **Section 9.9.2.3.1** for further details).

Two analyses were performed to estimate the duration of exposure: 1) a **main analysis** including the whole dataset and 2) a **sensitivity analysis** for which treatment data collected after M12 (i.e. data reported in the last contact form) were excluded.

Finally, the duration of exposure was described overall and in the following subgroups of interest:

Parameters	**Subgroups**
Age	< 70 years *versus* ≥ 70 years < 75 years *versus* ≥ 75 years
Number of previous lines of treatment in metastatic setting	0, 1−2 *versus* ≥ 3 lines 0, 1, 2, 3 *versus* > 3 lines
Visceral metastases at inclusion	Presence *versus* absence
Type of previous hormonal therapy	≥1 SAI *versus* ≥ 1 antioestrogen
Interval to recurrence with respect to stop of adjuvant hormonal treatment	0 month,]0−12 months] *versus* > 12 months
Duration of response to previous hormonal therapy	≤ 6 months *versus* > 6 months
Dose of the first Afinitor® intake	5 mg *versus* 10 mg
Pulmonary or hepatic metastases at inclusion	Presence *versus* absence
Bone metastases at inclusion	Presence of bone-only metastases *versus* Presence of bone and non-bone metastases *versus* Absence of bone metastases

SAI: Steroidal aromatase inhibitor.

9.8.3.6 Anticancer therapies prescribed after discontinuation of study treatment (Afinitor®, exemestane or their combination)

Anticancer therapies prescribed after discontinuation of study treatment (Afinitor®, exemestane or their combination) were described for the efficacy population, in particular in partients for whom the date of last intake of Afinitor® and/or exemestane was confirmed.

9.8.3.7 Efficacy

Efficacy analyses were performed on the efficacy population.

Response rates evaluated using RECIST 1.1 criteria, PFS, and OS were each described overall and by subgroup of interest (refer to subgroups defined for duration of exposure, **Section 9.8.3.5**).

PFS and OS were computed using Kaplan-Meier method (refer to **Section 9.9.2.3.1** for further details). PFS time was defined as the time elapsed between the first dose of Afinitor® and tumour progression, death from any cause or follow-up discontinuation, whichever came first. OS time was defined as the time elapsed between the first dose of Afinitor® and death from any cause or follow-up discontinuation, whichever came first.

Two analyses were performed to estimate PFS: 1) a **main analysis** for which treatment data collected after M12 (i.e. data reported in the last contact form) were excluded and 2) a **sensitivity analysis** including the whole dataset.

Finally, the maximum ECOG value reported by patients during the observation period was described and a shift data table describing ECOG class at inclusion versus highest ECOG class during follow-up was generated.

Table 9-2. Summary of analyses performed for each study variable

Variable	Analysis population(s)	Analyses
Patient disposition and clinical characteristics at inclusion		
Patient disposition Patient demographics and clinical characteristics at inclusion	Analyzable included, safety & efficacy populations	
Safety		
Management of stomatitis and non-infectious lung disease (**primary objective**)	Safety population	
Incidence, time to first occurrence, duration, outcome, highest severity of stomatitis and non-infectious lung disease	Safety population	Overall and by subgroup
Overall safety of Afinitor® and/or exemestane	Safety population	
Description of study treatment		
Afinitor® dose	Efficacy population	
Duration of exposure to Afinitor® + exemestane combination	Efficacy population	Overall and by subgroup Main and sensitivity analyses
Anticancer therapies prescribed after discontinuation of study treatment		
Anticancer therapies prescribed after treatment discontinuation	Efficacy population	
Efficacy		
Response rates	Efficacy population	Overall and by subgroup
PFS	Efficacy population	Overall and by subgroup Main and sensitivity analyses
OS	Efficacy population	Overall and by subgroup
ECOG-PS	Efficacy population	

ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; OS: Overall survival; PFS: Progression-free survival.

9.8.4 Interim/final analyses

The following analyses were performed for this study:

1) Baseline Analysis at the end of the recruitment period. This analysis aimed to assess the demographic and clinical characteristics of enrolled patients. No interim report was written; only statistical tables were generated (22-Dec-2016).
2) Final Analysis at the end of the study, whose results are described in the present report.

9.9 Statistical methods

9.9.1 Main summary measures

Standard descriptive statistics were used for quantitative and categorical variables.

Quantitative variables were presented using the number of observed values, number of missing observations, mean, standard deviation (SD), and median, first quartile (Q1), third quartile (Q3), minimum (Min) and maximum (Max). When required, 95% CI were computed based on the Wald method.

Categorical variables were presented using counts and percentages of patients. The number of missing observations was also presented. Missing observations were included in the calculation of percentages, unless otherwise specified. When required, 95% CI were computed based on the Wald method.

9.9.2 Main statistical methods

9.9.2.1 Hypotheses

As this is a prospective observational study, no formal hypothesis was tested.

9.9.2.2 Statistical calculations

All statistical analyses were performed using SAS® software (SAS Institute Inc., Cary, NC, USA) version 9.4.

9.9.2.3 Statistical methods

9.9.2.3.1 Kaplan-Meier survival analyses

The Kaplan-Meier method was used for time-to-event variables, i.e. duration of exposure, PFS, and OS. Estimates for the median time to event and the two-sided 95% CI were calculated based on the nonparametric Brookmeyer-Crowley method. Survival analyses were also displayed graphically. Further details on survival analyses are provided for each variable (i.e. duration of exposure, PFS, and OS) in Section 4.6 of the SAP version 3.

9.9.3 Missing values

For the dates of previous treatment and the date of diagnosis of the breast cancer:

- If the day was missing, it was replaced by the 15th of the month.

- If both day and month were missing, they were replaced by the 1st July of the year.
- If day, month and year were missing, date remained missing.

For the dates of Afinitor® or exemestane administration (except the start date of administration):

- If day was missing:
  - If the patient was not dead or the month of the administration was different from the month of the death, it was replaced by the 15th of the month.
  - If patient was dead and the month of the administration was equal to the month of the death, it was replaced by the day of death.
- If day and month were missing, date remained missing.
- If day, month and year were missing, date remained missing.

For the date of death:

- If the day was missing, it was replaced by the 15th of the month.
- If day and month were missing, date remained missing.
- If day, month and year were missing, date remained missing.

For the date of the first Afinitor® administration:

- If the day was missing, it was replaced by the 1st of the month.
- If both day and month were missing, date remained missing.
- If day, month and year were missing, date remained missing.

For the dates of AE, missing dates were not replaced; however the following rules were applied for the classification of AE as emergent/non-emergent:

- If the start day was missing, and start month/year was prior to the first administration of Afinitor®, then AE was considered as non-emergent.
- If the start day was missing, and start month/year was after or equal to the first administration of Afinitor®, then AE was considered as emergent.
- If start day and start month were missing, and start year was prior to the first administration of Afinitor®, then AE was considered as non-emergent.
- If start day and start month were missing, and start year was after or equal to the first administration of Afinitor®, then AE was considered as emergent.
- If start day, month and year were missing, then AE was considered as emergent.

If the seriousness or the relation of causality in AE page was missing, the worst case was considered (serious and/or suspected).

Other missing data were not replaced.

9.9.4 Sensitivity analyses

As mentioned in **Section 9.8.3.7**, 2 analyses were performed to estimate PFS: 1) a **main analysis** for which treatment collected after M12 (i.e. data reported in the last contact form) were excluded and 2) a **sensitivity analysis** including the whole dataset.

PFS time was defined as the time elapsed between the first dose of Afinitor® and tumour progression, death from any cause or follow-up discontinuation. Tumour progression (evaluated using RECIST 1.1 criteria) and patient status (dead or alive) were assessed at M1, M2−3, M6, M9, and M12 for all patients. For patients whose treatment was not interrupted at M12, only the status (dead or alive) and date of possible progression were collected via the last contact form. As the same level of information was not collected between patients who discontinued prematurely the treatment and those who continued the treatment after M12, the main analysis was restricted to the first 12 months of follow-up. The sensitivity analysis, including the whole dataset, was performed to support results from the main analysis.

9.9.5 Changes in the planned analyses

9.9.5.1 Research objectives not addressed in this study

Due to inconsistencies in the database, missing pages and missing data in the CRF, the following study objectives could not be addressed:

- Treatment doses and main reasons for dose reduction (Afinitor® and/or exemestane)
- Reason for interruption / treatment discontinuation (Afinitor® and/or exemestane)
- The percentage of patients with dose reduction, temporary interruption or discontinuation of Afinitor® following an episode of stomatitis or non-infectious lung disease (as part of primary objective)

In addition, the clinical benefit rate (response or disease stabilisation) was not computed. The clinical benefit rate is often defined as the percentage of patients who have achieved complete response, partial response, and stable disease for at least 6 months of therapy. The best overall response was collected at D15, M1, M2−3, M6, M9, and M12 for all patients and post-M12 (via the last contact form) only for patients whose treatment was not interrupted at M12. As data were not collected similarly between patients who discontinued prematurely the treatment and those who continued the treatment after M12, the results could not be representative of the overall population.

9.9.5.2 Complementary analyses performed after the database lock

The original SAP − version 2.0 dated 30-Nov-2017 − was reviewed, approved, and signed by the Biostatistician and the Sponsor prior to the database lock (30-Nov-2017).

During presentation of final study results (meeting held on 23-Feb-2018), Scientific Committee members requested to perform several complementary analyses. Following this meeting, there were 2 updates of the original SAP. Version 3 of the SAP (which is provided in

Annex 2) was issued on 15-Mar-2018 and included the following key additions and modifications:

1. Calculation of the proportion of patients with stomatitis and with non-infectious lung disease within the subgroups of patients described in **Section 9.8.3.4.2**:

Parameters	**Subgroups**
Age	< 70 years *versus* ≥ 70 years < 75 years *versus* ≥ 75 years
Number of previous lines of treatment in metastatic setting	0, 1−2 *versus* ≥ 3 lines
Previous chemotherapy, **for stomatitis only**	Presence *versus* absence
Pulmonary metastases at inclusion, **for non-infectious lung disease only**	Presence *versus* absence
Dose of the first Afinitor® intake	5 mg *versus* 10 mg
Pulmonary or hepatic metastases at inclusion	Presence *versus* absence
Bone metastases at inclusion	Presence of bone-only metastases *versus* Presence of bone and non-bone metastases *versus* Absence of bone metastases

2. Calculation of the proportion of patients with non-infectious lung disease within the subgroups of patients listed below:
   - *Patients with pulmonary metastases at inclusion*, according to the administered dose of Afinitor®: 5 mg *versus* 10 mg
   - *Patients without pulmonary metastases at inclusion*, according to the administered dose of Afinitor®: 5 mg *versus* 10 mg
3. Calculation of the following time periods:
   - Time from initial diagnosis to metastatic diagnosis (months) in patients with localised or locally advanced breast cancer at initial diagnosis who experienced relapse
   - Time from metastatic diagnosis to inclusion into the study (months) in the overall population as well as in the subgroup of patients diagnosed with localised or locally advanced breast cancer and with *de novo* metastatic breast cancer
4. Edition of the Wald 95% two-tailed CI for the variables listed below:
   - Mean number of stomatitis and non-infectious lung disease
   - Mean time to first occurrence of stomatitis and non-infectious lung disease (days)
   - Frequencies of stomatitis and non-infectious lung disease according to severity grades
5. Description of cancer relapses according to the previous adjuvant hormonal treatment:
   - Frequency of *primary hormone-resistant patients*, i.e. frequency of patients who experienced relapse of their breast cancer during the first 2 years of the adjuvant hormonal treatment

- Frequency of *secondary hormone-resistant patients*, i.e. frequency of patients who experienced relapse of their breast cancer ≥ 2 years after the beginning of the adjuvant hormonal treatment and until one year after the end of the adjuvant hormonal treatment
- Frequency of *hormone-sensitive patients*, i.e. frequency of patients who experienced relapse of their breast cancer ≥ 1 year after the end of the adjuvant hormonal treatment

9.10 Quality control

Data were entered from the paper-form CRFs into a validated database. Keyrus Biopharma, the designated CRO, was in charge of ensuring management, quality control, data entry, and data analyses of this study. All operations were conducted in accordance with the GCP Guideline and the data validation plan.

CRO was in charge of ensuring database quality by reviewing the data entered on the CRF. In case of missing or inconsistent data, requests were sent to the physicians to have additional information/corrections.

In addition, an on-site quality control including 10% of active sites randomly selected was performed by the CRO 12 months after the end of the inclusion period. This quality control aimed at ensuring the good execution of the clinical operations (verification that information note was given to patients and consent form was signed) and checking the quality of the data (verification that clinically pertinent and major data were well reported on the CRF and were consistent with source documents such as patients' files). This on-site quality control did not reveal any major issues:

- All patients received study information before inclusion and signed the consent form.
- The rate of discordance with source documents was 3% for eligibility criteria, 7−8% for data on Afinitor® and exemestane treatment intake, and < 1% for data related to stomatitis, non-infectious lung disease and study discontinuation.

The mean percentage of data discrepancies between CRF and source data was 2.62%.

Based on the main results of the quality control, the Scientific Committee don't dispute the study results.

As specified in the protocol, a database quality control was performed at the end of the study, before the final database lock. A random sample of 13,704 data was checked and showed an error rate of 0.04% (6/13,704), which was below the acceptable threshold of 0.1% set for this study.

10 Results

Results presented hereafter are based on summary data tables/figures (Final version 4) dated 15-Mar-2018 and on listings (Final version 2) dated 12-Mar-2018. These documents are provided in **Annex 1**.

As of this section, the event 'non-infectious lung disease' was referred to as NIP (which stands for non-infectious pneumopathy) in an attempt to be consistent with statistical source tables.

10.1 Patients

10.1.1 Disposition of patients

Study dates, number of participating centres, and number of patients included in the analysis populations are provided in **Table 1.1.1** and **Table 1.1.2**. Reasons for non-inclusion in the analysis populations are summarised in **Table 1.1.3**.

First patient first visit occurred on 06-Nov-2014, last patient first visit occurred on 23-Mar-2016, and last patient last visit (excluding last contact forms) occurred on 28-Apr-2017.

The patient disposition is summarised in **Figure 10-1**.

A total of 645 patients were included into the study by 112 centres, with a median number of 4 patients (range: 1−28) by centre.

Six patients were excluded from the **analyzable included population**, leading to a total of 639 patients in this population. The reasons for exclusion were:

- Moving of the study physician for centre 102 (2/6 patients, 33.3%).
- Refusal of the study physician to pursue the study for centre 117 (4/6 patients, 66.7%).

A further 43 patients were excluded from the **safety population**, leading to a total of 596 patients in this population. The reasons for exclusion were:

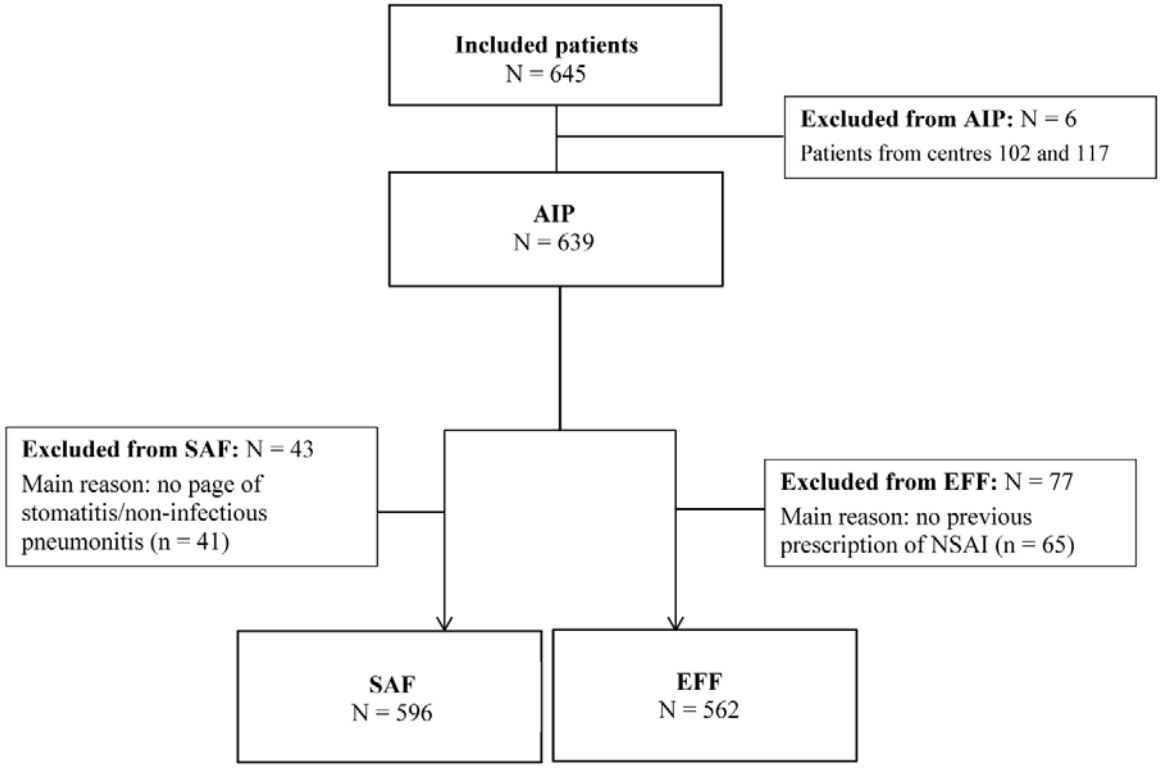
- Absence of CRF page of stomatitis/NIP or other AE (41/43 patients, 95.4%).
- Missing date of the first intake of treatment (6/43 patients, 14.0%).
- Date of the first intake of treatment more than 14 days before the date of inclusion into the study (2/43 patients, 4.7%).

Seventy-seven (77) patients were excluded from the **efficacy population**, leading to a total of 562 patients in this population. The reasons for exclusion were:

- Patients did not receive previous prescription of NSAI (65/77 patients, 84.4%).
- Patients were wrongly included with follow-up interrupted (12/77 patients, 15.6%).
- Date of the first intake of treatment was missing (6/77 patients, 7.8%).
- Interstitial pneumopathy at inclusion (2/77 patients, 2.6%).
- Patients received Herceptin® (2/77 patients, 2.6%).
- HER2 status was positive (2/77 patients, 2.6%).
- Date of the first intake of treatment more than 14 days before the date of the inclusion (2/77 patients, 2.6%).

Patients excluded from the analyzable included and safety populations are listed in **Listing 1** and those excluded from the analyzable included and efficacy populations are listed in **Listing 2**.

Figure 10-1. Patient disposition



AIP: Analyzable included population; EFF: Efficacy population; NSAI: Non-steroidal aromatase inhibitor; SAF: Safety population.
Source: **Tables 1.1.2** and **1.1.3**

10.1.2 Premature study withdrawal

Study completion, withdrawal, and total duration of exposure to Afinitor® and/or exemestane for each analysis population is summarised in **Table 1.1.5**, **Table 1.1.6**, and **Table 1.1.7**.

Among the 639 patients in the analyzable included population:

- 157 (24.6%) completed the end of the observation period of the study (M12).
- 463 (72.5%) withdrew from the study before the end.
- 19 (3.0%) did not have their end-of-study visit documented in the CRF.

Reasons for the premature study withdrawals for patients in all analysis populations are listed in in-text **Table 10-1**. The main reason for premature study withdrawal was a permanent discontinuation of Afinitor® + exemestane treatment.

Table 10-1. Incidence and reasons for premature study withdrawal

	Analyzable included population N = 639	Safety population N = 596	Efficacy population N = 562
Premature study withdrawal – *n (%)*			
Missing	19 (2.97%)	6 (1.01%)	11 (1.96%)
No	157 (24.57%)	149 (25.00%)	142 (25.27%)
Yes	463 (72.46%)	441 (73.99%)	409 (72.78%)
Reasons for withdrawals – *n (%)*			
Permanent discontinuation of Afinitor® and exemestane	407 (87.90%)	389 (88.21%)	371 (90.71%)
Patient death	31 (6.70%)	31 (7.03%)	28 (6.85%)
Lost to follow-up	7 (1.51%)	3 (0.68%)	6 (1.47%)
Patient's request to withdraw from study follow-up	5 (1.08%)	5 (1.13%)	4 (0.98%)
Other reasons[1]	13 (2.81%)	13 (2.95%)	0 (0.00%)

[1]Other reasons in the analyzable included and safety populations were wrong inclusion of patients into the study:
- 4/13 patients because they did not receive previous prescription of non-steroidal aromatase inhibitors.
- 2/13 patients because they were prescribed Afinitor® off-label.
- 1/13 patient because her HER2 status was positive
- 6/13 patients for whom the reason was not specified.

HER2: Human epidermal growth factor receptor 2.
Source: **Tables 1.1.5-7** and **Listing 4** (other reasons for premature study withdrawal)

10.1.3 Non-compliance to the protocol

The number (%) of patients with non-compliance to the protocol is provided in **Table 1.1.4** for the analysable included population and full details for each patient are presented in **Listing 3**. A summary is also provided in in-text **Table 10-2**.

Among the 639 patients in the analyzable included population, 284 (44.4%) had at least one non-compliance to the protocol:

- 263 (41.2%) did not fulfil inclusion criterion #2.
- 19 (3.0%) did not fulfil inclusion criterion #1.
- 2 (0.3%) fulfilled non-inclusion criterion #1.

Table 10-2. Summary of non-compliances to the protocol – Analyzable included population

	Number (%) of patients
Total	**639**
Patients with at least one non-compliance – n (%)	**284 (44.44%)**
Unfulfillment inclusion criteria	
Inclusion criterion 1	*19 (2.97%)*
HER2 status was positive.	2 (0.31%)
HER2 status was missing.	16 (2.50%)
The status of the hormonal receptors was missing.	1 (0.16%)
Patient received Herceptin®.	2 (0.31%)
Inclusion criterion 2	*263 (41.16%)*
The posology of Afinitor® was not 10 mg/day and the patient presented no hepatic insufficiency.	159 (24.88%)
The posology of Afinitor® was not 7.5 mg/day and the patient presented a mild hepatic insufficiency.	2 (0.31%)
The symptomatic character of the visceral disease was ticked 'Yes'.	84 (13.15%)
The symptomatic character of the visceral disease was missing.	6 (0.94%)
The patient had no previous prescription of NSAI.	65 (10.17%)
Interstitial pneumopathy at inclusion.	2 (0.31%)
Fulfillment non-inclusion criteria	
Non-inclusion criterion 1	*2 (0.31%)*
The date of the first intake of treatment was more than 14 days before the date of inclusion into the study.	2 (0.31%)

HER2: Human epidermal growth factor receptor 2; NSAI: Non-steroidal aromatase inhibitor.
Source: **Table 1.1.4**

10.2 Descriptive data

10.2.1 Physician characteristics and current practices

Physician characteristics are provided in **Table 1.2.1**.

The mean (SD) age of study physicians was 49.3 (9.1, N = 108) years and 59.1% (65/110) were male.

All physicians were either oncologists (79.1%, 87/110) or radiotherapist (21.8%, 24/110), except one (onco-haematologist; **Listing 5**). Study physicians worked either in public (43.6%, 48/110), private (54.5%, 60/110), or both public and private sectors (1.8%, 2/110). They worked for public hospitals (40.9%, 45/110), private hospitals (50.0%, 55/110), and/or cancer centres, generally known in France as 'Comprehensive Cancer Centres' (UNICANCER; 10.0%, 11/110).

Overall, study centres were distributed in 13 regions: 12 in metropolitan France and 1 in the region Outre-mer.The 3 main locations of the centres were: Ile-de-France (19.1%, 21/110), Grand-Est (14.6%, 16/110), and Nouvelle-Aquitaine (11.8%, 13/110).

Physician current practices are provided in **Table 1.2.2**.

Around 95.5% of physicians (105/110) took specific measures to treat stomatitis and 94.6% (104/110) took specific measures to treat NIP.

The 2 main measures to treat these AE consisted of reinforcing prevention messages (90.5% [95/105] for stomatitis and 83.7% [87/104] for NIP) and scheduling more frequent

appointments (61.9% [65/105] for stomatitis and 62.5% [65/104] for NIP). The third most common measure was more frequent testing for stomatitis (41.9%, 44/105) and referral to specialists (56.7%, 59/104) for NIP.

Details about combined measures taken by physicians are provided in **Table 1.2.2**.

10.2.2 Patient demographics and clinical characteristics at inclusion – Safety population

As indicated in **Section 9.8.3.3**, patient demographics and clinical characteristics at inclusion were described in the safety and efficacy populations. Overall, data at inclusion were comparable between the 2 populations. For the sake of clarity, it was decided to focus on results from the safety population as this population was used for the analysis of the primary outcome.

Data from the efficacy population are provided in **Tables 1.4.1** to **1.4.11** (**Annex 1**).

10.2.2.1 Age

Age data for patients included in the safety population are provided in **Table 1.3.1**. Additional data are also provided in **Table 1.1.8**. Summaries are presented in in-text **Table 10-3**.

Patient age ranged from 33 to 92 years (N = 596), with a mean (SD) of 65.1 (10.8) years. Few patients were less than 45 years old (17/596, 2.9%).

465/596 patients (78.0%) were aged < 75 years and 131/596 (22.0%) were aged 75 years or older.

Table 10-3. Age of patients – Safety population

Age (years)	Safety population (N = 596)
N	596
Mean (SD)	65.1 (10.8)
[Min ; Max]	[33 ; 92]
Age classes	
< 45 – *n (%)*	17 (2.85%)
[45 ; 60[– *n (%)*	161 (27.01%)
[60 ; 70[– *n (%)*	201 (33.72%)
≥ 70 – *n (%)*	217 (36.41%)
Other age classes	
< 75 – *n (%)*	465 (78.02%)
≥ 75 – *n (%)*	131 (21.98%)

Min & Max: Minimum and maximum; SD: Standard deviation.
Source: **Table 1.1.8** and **Table 1.3.1**

Age data for patients included in the efficacy population are presented in **Table 1.4.1** (and also in **Table 1.1.9**) and are similar to the ones described for the safety population.

10.2.2.2 Breast cancer history

Breast cancer histories are provided in **Table 1.3.2** for the safety population. Summaries are presented in in-text **Table 10-4**.

The median time since initial diagnosis was 7.5 years (range: 0.1−44.3; N = 596).

Ductal carcinoma was the most common histological type (462/596, 77.5%), followed by lobular carcinoma (113/596, 19.0%). 364/596 patients (61.1%) had a localised cancer at diagnosis in adjuvant setting, 145/596 (24.3%) were diagnosed with *de novo* metastatic breast cancer, and 87/596 (14.6%) were diagnosed with a locally advanced breast cancer.

368/596 patients (61.7%) had a SBR of grade II, 127/596 (21.3%) a SBR of a grade III, and 73/596 (12.3%) a SBR of grade I.

All patients had a HR+ breast cancer (595/596; HR status was missing in one patient).

578/596 patients (97.0%) were HER2-, whereas 2/596 patients (0.3%) were HER2+. The status was missing for 16/596 patients (2.7%).

Expression of Ki67 antigen, a marker for cellular proliferation, was collected on the CRF if available. Patients had a median Ki67 of 20% (range: 1−95). Nevertheless, these data should be interpreted with caution due to the high rate of missing data (64.6%, 385/596).

Table 10-4. History of breast cancer – Safety population

		Safety population (N = 596)
Time since initial diagnosis (years)		
N		596
Median [Q1 ; Q3]		7.50 [3.66 ; 13.26]
[Min ; Max]		[0.05 ; 44.29]
Histologic type		
N		596
Missing	n (%)	2 (0.34%)
Ductal carcinoma	n (%)	462 (77.52%)
Lobular carcinoma	n (%)	113 (18.96%)
Other	n (%)	19 (3.19%)
Stage at diagnosis		
N		596
Localised	n (%)	364 (61.07%)
Locally advanced	n (%)	87 (14.60%)
De novo metastatic	n (%)	145 (24.33%)
SBR score		
N		596
Missing	n (%)	28 (4.70%)
Grade I	n (%)	73 (12.25%)
Grade II	n (%)	368 (61.74%)
Grade III	n (%)	127 (21.31%)
Status of the hormonal receptors		
N		596
Missing	n (%)	1 (0.17%)
Positive	n (%)	595 (99.83%)
HER2 receptor status		
N		596
Missing	n (%)	16 (2.68%)
Negative	n (%)	578 (96.98%)
Positive	n (%)	2 (0.34%)
Ki67 (if available) (%)		
N		211
Missing		385
Median [Q1 ; Q3]		20 [10 ; 30]
[Min ; Max]		[1 ; 95]

Q1 & Q3: First and third quartiles; SBR: Scarff-Bloom-Richardson; SD: Standard deviation.
Source: **Table 1.3.2**

Breast cancer histories are presented in **Table 1.4.2** for the efficacy population and are similar to the ones described for the safety population.

10.2.2.3 Initial therapy: locoregional and adjuvant treatments

Locoregional treatments in patients diagnosed at the localised or locally advanced stage are described in **Table 1.3.3** for the safety population. Summaries are presented in in-text **Table 10-5**.

A total of 451/596 patients had a localised or locally advanced breast cancer at diagnosis. Almost all of them (441/451, 97.8%) had received at least one previous locoregional treatment. Most patients had undergone surgery (434/441, 98.4%) or had received radiotherapy (399/441, 90.5%). The median time since surgery was 8.3 years (range: 1 week−34.1 years).

Table 10-5. Initial therapy: Locoregional treatments − Patients diagnosed at the localised or locally advanced stage – Safety population

		Safety population (N = 451)
At least one locoregional treatment received?		
N		451
No	n (%)	10 (2.22%)
Yes	n (%)	441 (97.78%)
Surgery		
N		441
No	n (%)	7 (1.59%)
Yes	n (%)	434 (98.41%)
Time since surgery (years)		
N		385
Missing		49
Median [Q1 ; Q3]		8.34 [4.62 ; 14.28]
[Min ; Max]		[0.02 ; 34.13]
Radiotherapy		
	N	441
No	n (%)	42 (9.52%)
Yes	n (%)	399 (90.48%)

Min & Max: Minimum and maximum; Q1 & Q3: First and third quartiles.
Source: **Table 1.3.3**

Adjuvant treatments in patients diagnosed at the localised or locally advanced stage are described in **Table 1.3.4** for the safety population. Summaries are presented in in-text **Table 10-6**.

Of the 451 patients with localised or locally advanced breast cancer at diagnosis, 420 (93.1%) had received at least one adjuvant treatment as previous treatment for metastatic disease. The majority of them had received chemotherapy (336/420, 80.0%) or hormonotherapy (375/420, 89.3%).

The majority of patients previously on hormonotherapy had received one hormonal treatment (272/375, 72.5%). Non-steroidal aromatase inihibitors (231/375, 61.6%) were the most commonly prescribed hormonal agents, followed by antiestrogens (205/375, 54.7%) and steroidal aromatase inhibitors (39/375, 10.4%).

The median duration of hormonal treatment in adjuvant phase was 4.6 years (range: 1 week−21.8 years). The median interval to recurrence with respect to stop of adjuvant hormonal treatment was 33.8 months (range: 1 day−311 months).

Table 10-6. Initial therapy: Adjuvant treatments − Patients diagnosed at the localised or locally advanced stage − Safety population

		Safety population (N = 451)
At least one adjuvant treatment administered		
N		451
No	n (%)	31 (6.87%)
Yes	n (%)	420 (93.13%)
At least one chemotherapy		
N		420
No	n (%)	84 (20.00%)
Yes	n (%)	336 (80.00%)
At least one hormonotherapy		
N		420
No	n (%)	45 (10.71%)
Yes	n (%)	375 (89.29%)
Number of hormonal treatments		
N		375
1	n (%)	272 (72.53%)
2	n (%)	88 (23.47%)
3	n (%)	10 (2.67%)
4	n (%)	5 (1.33%)
Number of hormonal treatments		
N		375
At least one NSAI (letrozole, anastrozole)	n (%)	231 (61.60%)
At least one SAI (exemestane)	n (%)	39 (10.40%)
At least one anti-estrogen (tamoxifen)	n (%)	205 (54.67%)
Duration of hormonal treatment in adjuvant phase (years)		
N		367
Missing		8
Median [Q1 ; Q3]		4.63 [2.41 ; 5.09]
[Min ; Max]		[0.02 ; 21.80]
Interval to recurrence with respect to stop of adjuvant hormonal treatment (months)		
N		169
Missing		58
Median [Q1 ; Q3]		33.77 [9.49 ; 65.70]
[Min ; Max]		[0.03 ; 311.01]

Min & Max: Minimum and maximum; (N)SAI: (Non-)steroidal aromatase inhibitor; Q1 & Q3: First and third quartiles.
Source: **Table 1.3.4**

Results pertaining to locoregional and adjuvant treatments in patients diagnosed at the localised or locally advanced stage are presented in **Tables 1.4.3** and **1.4.4** for the efficacy population and are similar to the ones described for the safety population.

10.2.2.4 Relapses of breast cancer

Relapses of breast cancer are provided in **Table 1.3.5** for the safety population. Summaries are presented in in-text **Table 10-7**.

Overall, 449/596 patients (75.3%) experienced relapse of their breast cancer. Of them, 390/449 (86.7%) had metastatic relapse, 42/449 (9.4%) had locoregional relapse, and

17/449 (3.8%) had both metastatic and locoregional relapse. Patients experiencing relapse were all initially diagnosed with localised or locally advanced breast cancer.

A total of 407 patients with localised or locally advanced breast cancer at initial diagnosis experienced metastatic or locoregional/metastatic relapse of their breast cancer. In these patients, the median time from initial diagnosis to metastatic diagnosis was 74 months (range: 0−530).

In the overall population, the median time from metastatic diagnosis to inclusion into the study was 26 months (range: 0−284; N = 552). The median time from metastatic diagnosis to inclusion into the study was also evaluated separately in patients with localised or locally advanced breast cancer at diagnosis and in patients diagnosed with *de novo* metastatic breast cancer. Median times in these patients were 22 months (range: 0−236; N = 407) and 34 months (range: 1−284; N = 145), respectively.

Breast cancer relapses were also analysed according to the response to the previous adjuvant hormonal treatment (refer to **Section 9.9.5.2** for further details). Data were available for 375 patients, of them:

- 57 patients (15.2%) experienced relapse of their breast cancer during the first 2 years of the adjuvant hormonal treatment and were classified as *primary hormone-resistant patients*.
- 165 patients (44.0%) experienced relapse of their breast cancer ≥ 2 years after the beginning of the adjuvant hormonal treatment and until one year after the end of the adjuvant hormonal treatment and were classified as *secondary hormone-resistant patients*.
- 142 patients (37.9%) experienced relapse of their breast cancer ≥ 1 year after the end of the adjuvant hormonal treatment and were classified as *hormone-sensitive patients.*

Table 10-7. Relapses of breast cancer − Safety population

		Safety population (N = 596)
Had the patient relapsed?		
N		596
No	n (%)	147 (24.66%)
Yes	n (%)	449 (75.34%)
Type of relapse		
N		449
Locoregional relapse	n (%)	42 (9.35%)
Metastatic relapse	n (%)	390 (86.86%)
Locoregional and metastatic relapse	n (%)	17 (3.79%)
Time from initial diagnosis to metastatic diagnosis (months) – Patients with localised or locally advanced breast cancer at diagnosis		
N		407
Missing		0
Median [Q1 ; Q3]		74 [41 ; 128]
[Min ; Max]		[0 ; 530]
Time from metastatic diagnosis to inclusion into the study (months)		
Overall population		
N		552
Missing		44
Median [Q1 ; Q3]		26 [10 ; 53]
[Min ; Max]		[0 ; 284]
Patients with localised or locally advanced breast cancer at diagnosis		
N		407
Missing		0
Median [Q1 ; Q3]		22 [5 ; 48]
[Min ; Max]		[0 ; 236]
Patients with de novo metastatic breast cancer at diagnosis		
N		145
Missing		0
Median [Q1 ; Q3]		34 [19 ; 63]
[Min ; Max]		[1 ; 284]
Relapse of breast cancer according to the response to the previous adjuvant hormonal treatment		
N		375
Missing	n (%)	11 (2.93%)
Primary hormone-resistant patients[1]	n (%)	57 (15.20%)
Secondary hormone-resistant patients[1]	n (%)	165 (44.00%)
Hormone-sensitive patients[1]	n (%)	142 (37.87%)

[1] Primary hormone-resistant patients: patients experiencing relapse of their breast cancer during the first 2 years of the adjuvant hormonal treatment.
Secondary hormone-resistant patients: patients experiencing relapse of their breast cancer ≥ 2 years after the beginning of the adjuvant hormonal treatment and until one year after the end of the adjuvant hormonal treatment.
Hormone-sensitive patients: patients experiencing relapse of their breast cancer ≥ 1 year after the end of the adjuvant hormonal treatment.

Source: **Table 1.3.5**

Results pertaining to relapses of breast cancer are presented in **Table 1.4.5** for the efficacy population and are similar to the ones described for the safety population.

10.2.2.5 Presence and location of metastases at the time of study treatment prescription

Results pertaining to the presence and location of metastases at the time of study treatment prescription are provided in **Table 1.3.6** for the safety population. Additional results (e.g. bone metastases) are also provided in **Table 1.1.8**. Summaries are presented in in-text **Table 10-8**.

Overall, 591/596 patients (99.2%) had metastases at time of study treatment prescription, mainly to the bones (459/591, 77.7%). Other most common locations included, in decreasing order of frequency, liver (178/591, 30.1%), lungs (141/591, 23.9%), and lymph nodes (136/591, 23.0%).

Of the 459 patients with bone metastases, 199 (43.4%) had bone-only metastases and 260 (56.6%) had bone and non-bone metastases.

Metastases were also classified as ‘unique’, ‘mutiple’ or ‘unclassifiable’ visceral metastases (refer to footnote of in-text **Table 10-8** for definitions of visceral metastases). Overall, 172/591 patients (29.1%) had ‘unique’ visceral metastases, 61/591 (10.3%) had ‘multiple’ visceral metastases, 37/591 (6.3%) had ‘unclassifiable’ visceral metastases, and 270/591 (45.7%) had no visceral metastases.

80/591 patients (13.5%) had symptomatic visceral disease.

Table 10-8. Presence and location of metastases at time of study treatment prescription − Safety population

		Safety population (N = 596)
Metastases when prescribing Afinitor® + exemestane		
N		596
No	n (%)	5 (0.84%)
Yes	n (%)	591 (99.16%)
Metastasis location (several possible answers)		
N		591
Lung	n (%)	141 (23.86%)
Bone	n (%)	459 (77.66%)
Liver	n (%)	178 (30.12%)
Brain	n (%)	15 (2.54%)
Lymph nodes	n (%)	136 (23.01%)
Skin	n (%)	54 (9.14%)
Others	n (%)	101 (17.09%)
Classification of bone metastases		
N		459
Bone-only metastases	n (%)	199 (43.36%)
Bone and non-bone metastases	n (%)	260 (56.64%)
Classification of visceral metastases		
N		591
No visceral metastasis[1]	n (%)	270 (45.69%)
Unique visceral metastasis[1]	n (%)	172 (29.10%)
Multiple visceral metastasis[1]	n (%)	61 (10.32%)
Unclassifiable visceral metastases[1]	n (%)	37 (6.26%)
Symptomatic visceral disease?		
N		591
Missing	n (%)	91 (15.40%)
No	n (%)	406 (68.70%)
Yes	n (%)	80 (13.54%)
NA	n (%)	14 (2.37%)

[1] *No visceral metastases*: metastases located not in lungs, liver, brain or 'other'.
Unique visceral metastases: metastases located only in lungs, liver or brain.
Multiple visceral metastases: metastases located in at least 2 of the 3 following sites: lungs, liver or brain.
Unclassifiable visceral metastases: metastases located in lungs, liver and/or brain AND in 'other'. This applies to unique and multiple visceral metastases.
NA: Not applicable.
Source: **Table 1.1.8** and **Table 1.3.6**

Results pertaining to the presence and location of metastases at the time of study treatment prescription are provided in **Table 1.4.6** (and also in **Table 1.1.9**) for the efficacy population and are similar to the ones described for the safety population.

10.2.2.6 Previous treatments in metastatic phase

Lines of previous treatment in metastatic phase are provided in **Table 1.3.7** for the safety population. Summaries are presented in in-text **Table 10-9** and **Table 10-10**.

Overall, 113/596 patients (19.0%) had not received any line of previous treatment in metastatic phase, while 208/596 patients (34.9%) had received one single line, 126/596 (21.1%) had received 2 lines, and 63/596 (10.6%) had received 3 lines of previous

treatment. In patients with documented previous treatment, the median number of treatment lines was 2 (range: 1−8) (in-text **Table 10-9**).

Table 10-9. Number of lines of previous treatment by patient in metastatic phase – Safety population

	Safety population (N = 596)
Number (%[1]) of patients	
0 line	113 (18.96%)
1 line	208 (34.90%)
2 lines	126 (21.14%)
3 lines	63 (10.57%)
4 lines	43 (7.21%)
5 lines	24 (4.03%)
6 lines	10 (1.68%)
7 lines	7 (1.17%)
8 lines	2 (0.34%)
Number of lines of treatment in patients with at least one line	
N	483
Median [Q1 ; Q3]	2 [1 ; 3]
[Min ; Max]	[1 ; 8]

[1]Percentages were calculated on the total number of patients in the safety population (N = 596).
Min & Max: Minimum and maximum; Q1 & Q3: First and third quartiles.
Source: **Table 1.3.7**

The prescribed drugs, duration, interval to recurrence, and best overall response of the first 3 lines of previous treatment and of the last line is summarised in in-text **Table 10-10**.

The 3 most commonly prescribed drugs in first, second and third line were respectively:

- Letrozole (158/483 patients, 32.7%), anastrozole (69/483 patients, 14.3%), and fulvestrant (43/483 patients, 8.9%) − all known as hormonal agents − for the first line of previous treatment.
- Fulvestrant as well as chemotherapy ('others' and capecitabine) for the second line of previous treatment (84/275 [30.6%], 32/275 [11.6%], and 31/275 [11.3%] patients, respectively).
- For the third line of previous treatment, the same most common drugs were prescribed but in a different order (31/149 [20.8%], 20/149 [13.4%], and 18/149 [12.1%] patients were treated with chemotherapy [others], fulvestrant and capecitabine, respectively).

The median duration of previous treatments gradually decreased from the first (12.0 months, N = 473) to the third line of treatment (5.8 months, N = 149), while the median interval to recurrence remained stable over time (0.4−0.5 months).

Compared to first and second lines of treatment, the third line was associated:

- with a higher percentage of progression (63/149 [42.3%] patients for the third line *versus* 162/483 [33.5%] and 92/275 [33.5%] patients for the first and second lines, respectively) and a higher percentage of stable disease (58/149 [38.9%] patients for the third line *versus* 169/483 [35.0%] and 94/275 [34.2%] patients for the first and second lines, respectively).

- with a lower percentage of partial response (17/149 [11.4%] patients for the third line *versus* 98/483 [20.3%] and 63/275 [22.9%] patients for the first and second lines, respectively) and a lower percentage of complete response (3/149 [2.0%] patients for the third line *versus* 26/483 [5.4%] and 10/275 [3.6%] patients for the first and second lines, respectively).

Table 10-10. Prescribed drugs, duration, interval to recurrence, and best overall response of the first 3 lines of previous treatment and of the last line – Safety population

	Line 1	Line 2	Line 3	Last line
3 most common drugs				
N	483	275	149	483
Drug 1 – *n (%)*	Letrozole 158 (32.71%)	Fulvestrant 84 (30.55%)	Chemo – Other 31 (20.81%)	Letrozole 105 (21.74%)
Drug 2 – *n (%)*	Anastrozole 69 (14.29%)	Chemo – Other 32 (11.64%)	Fulvestrant 20 (13.42%)	Fulvestrant 94 (19.46%)
Drug 3 – *n (%)*	Fulvestrant 43 (8.90%)	Capecitabine 31 (11.27%)	Capecitabine 18 (12.08%)	Chemo – Other 60 (12.42%)
Duration (months)				
N	473	272	149	475
Missing	10	3	0	8
Median [Q1 ; Q3]	12.02 [5.19 ; 24.67]	7.47 [3.86 ; 15.06]	5.75 [3.22 ; 10.64]	7.85 [3.84 ; 16.92]
[Min ; Max]	[0.03 ; 147.27]	[0.72 ; 139.78]	[0.03 ; 60.45]	[0.03 ; 145.17]
Interval to recurrence (months)				
N	270	149	86	-
Missing	5	0	0	-
Median [Q1 ; Q3]	0.41 [0.03 ; 2.99]	0.43 [0.00 ; 2.00]	0.53 [0.16 ; 2.04]	-
[Min ; Max]	[0.00 ; 115.44]	[0.00 ; 74.80]	[0.00 ; 53.19]	-
Best overall response				
N	483	275	149	483
Missing – *n (%)*	4 (0.83%)	2 (0.73%)	0 (0.00%)	4 (0.83%)
Complete Response – *n (%)*	26 (5.38%)	10 (3.64%)	3 (2.01%)	23 (4.76%)
Partial Response – *n (%)*	98 (20.29%)	63 (22.91%)	17 (11.41%)	104 (21.53%)
Stable Disease – *n (%)*	169 (34.99%)	94 (34.18%)	58 (38.93%)	163 (33.75%)
Progression – *n (%)*	162 (33.54%)	92 (33.45%)	63 (42.28%)	156 (32.30%)
Not Assessable – *n (%)*	24 (4.97%)	14 (5.09%)	8 (5.37%)	33 (6.83%)

Chemo: Chemotherapy; Min & Max: Minimum and maximum; Q1 & Q3: First and third quartiles.
Source: **Table 1.3.7**

Results pertaining to lines of previous treatment in metastatic phase are presented in **Table 1.4.7** for the efficacy population and are similar to the ones described for the safety population.

10.2.2.7 Hepatic concomitant pathology

Incidence and severity of liver failure at inclusion are described in **Table 1.3.8** for the safety population. Summaries are presented in in-text **Table 10-11**.

Only 4/596 patients (0.7%) had liver failure, of mild intensity for 2 patients, moderate intensity for one patient, and severe intensity for another patient.

Table 10-11: Hepatic concomitant pathology – Safety population

		Safety population (N = 596)
Presence of liver failure		
N		596
No	n (%)	592 (99.33%)
Yes	n (%)	4 (0.67%)
Severity[1]		
N		4
Mild	n (%)	2 (50.00%)
Moderate	n (%)	1 (25.00%)
Severe	n (%)	1 (25.00%)

[1]Mild hepatic insufficiency: class A of Child-Pugh; moderate hepatic insufficiency: class B of Child-Pugh); severe hepatic insufficiency: class C of Child-Pugh).
Source: **Table 1.3.8**

Results pertaining to incidence and severity of liver failure at inclusion are presented in **Table 1.4.8** for the efficacy population and are similar to the ones described for the safety population.

10.2.2.8 ECOG-PS at time of study treatment prescription

The ECOG-PS at the time of study treatment prescription is described in **Table 1.3.9** for the safety population. Summaries are presented in in-text **Table 10-12**.

The ECOG-PS at the time of study treatment prescription was 0 for 242/596 patients (40.6%), 1 for 285/596 patients (47.8%), 2 for 47/596 patients (7.9%), 3 for 3/596 patients (0.5%) and 4 for 1/596 patients (0.2%).

Table 10-12. ECOG performance status at time of study treatment prescription − Safety population

		Safety population (N = 596)
ECOG performance status		
Missing	n (%)	18 (3.02%)
ECOG 0	n (%)	242 (40.60%)
ECOG 1	n (%)	285 (47.82%)
ECOG 2	n (%)	47 (7.89%)
ECOG 3	n (%)	3 (0.50%)
ECOG 4	n (%)	1 (0.17%)

ECOG: Eastern Cooperative Oncology Group.
Source: **Table 1.3.9**

Results pertaining to ECOG performance status at the time of study treatment prescription are presented in **Table 1.4.9** for the efficacy population and are similar to the ones described for the safety population.

10.2.2.9 Initial evaluation of oral cavity and preventive measures prescribed

Initial evaluation of the oral cavity and measures prescribed to prevent new stomatitis episodes are described in **Table 1.3.10** for the safety population. Summaries are presented in in-text **Table 10-13**.

Before initiation of Afinitor® + exemestane treatment, 114/596 patients (19.1%) visited a dentist. Stomatitis was diagnosed in 39/596 patients (6.5%). In the majority of these patients (33/39, 84.6%), stomatitis was induced by chemotherapy.

At the time of inclusion, the large majority of patients did not have stomatitis (593/596, 99.5%) or oral problems (539/596, 90.4%).

Table 10-13. Initial evaluation of oral cavity − Safety population

		Safety population (N = 596)
Visit to the dentist before Afinitor® + exemestane initiation		
N		596
No	n (%)	482 (80.87%)
Yes	n (%)	114 (19.13%)
Stomatitis before Afinitor® + exemestane initiation		
N		596
No	n (%)	557 (93.46%)
Yes	n (%)	39 (6.54%)
Type of previous stomatitis		
N		39
Chemotherapy-induced stomatitis	n (%)	33 (84.62%)
Non-chemotherapy-induced stomatitis	n (%)	6 (15.38%)
Current stomatitis at the time of the inclusion		
N		596
No	n (%)	593 (99.50%)
Yes	n (%)	3 (0.50%)
Type of current stomatitis at the inclusion		
N		3
Chemotherapy-induced stomatitis	n (%)	2 (66.67%)
Non-chemotherapy-induced stomatitis	n (%)	1 (33.33%)
Oral problems presented by the patients at inclusion		
N		596
No oral problem	n (%)	539 (90.44%)
Risk of site infection	n (%)	15 (2.52%)
Gingivitis/Periodontitis/Tooth loss	n (%)	11 (1.85%)
Mechanical irritation	n (%)	15 (2.52%)
Other problems	n (%)	25 (4.19%)

Source: **Table 1.3.10**

The measures taken to prevent new stomatitis episodes are described in **Table 1.3.10** for the safety population and are summarised in in-text **Table 10-14**.

Mouthwashes and hygiene advices were the 2 most common preventive measures (429/596 [72.0%] and 280/596 [47.0%], respectively), followed by dental care (37/596, 6.2%) and other actions (10/596, 1.7%). No preventive measure was taken for 145/596 patients (24.3%). The most common combination of preventive measures was ‘mouthwash/hygiene advice’, reported for 245/596 patients (41.1%). Further details about combined measures are provided in **Table 1.3.10**.

Table 10-14. Measures taken to prevent new stomatitis episodes − Safety population

		Safety population (N = 596)
Measures taken (several possible answers possible)		
N		596
No action	n (%)	145 (24.33%)
Dental care	n (%)	37 (6.21%)
Mouthwash	n (%)	429 (71.98%)
Hygiene advice	n (%)	280 (46.98%)
Other action	n (%)	10 (1.68%)
Measures taken (several possible answers possible)		
N		596
Mouthwash /Hygiene advice	n (%)	245 (41.11%)

Source: **Table 1.3.10**

Results pertaining to the initial evaluation of the oral cavity and measures prescribed to prevent new stomatitis episodes are presented in **Table 1.4.10** for the efficacy population and are similar to the ones described for the safety population.

10.2.2.10 Initial evaluation of the lungs

Results from initial evaluation of the lungs are described in **Table 1.3.11** for the safety population. A summary of pulmonary symptoms and results from imaging examinations is presented in in-text **Table 10-15** and **Table 10-16**, respectively.

At the time of inclusion, 52/596 patients (8.7%) had pulmonary symptoms. Of them, 33/52 (63.5%) presented dyspnoea and 22/52 (42.3%) presented cough.

Table 10-15: Pulmonary symptoms at inclusion − Safety population

		Safety population (N = 596)
At least one pulmonary symptom at the time of inclusion		
N		596
No	n (%)	544 (91.28%)
Yes	n (%)	52 (8.72%)
Details of the actual pulmonary symptom (several possible answers)		
N		52
Cough	n (%)	22 (42.31%)
Dyspnoea	n (%)	33 (63.46%)
Other	n (%)	10 (19.23%)

Source: **Table 1.3.11**

Overall, 564/596 (94.6%) patients did not consult a pulmonologist before initiation of Afinitor® + exemestane treatment. A pulmonary imaging examination was performed in 459/596 patients (77.0%). Chest scans, PET scans, and chest X-Ray were the most commonly performed examinations in these patients (255/459 [55.6%], 170/459 [37.0%], and 66/459 [14.4%], respectively). Results from these examinations indicated that lungs were normal in the majority of patients (269/459, 58.6%). Pulmonary metastases and pleural effusions were detected in 25.5% (117/459) and 14.8% (68/459) of patients, respectively, and pulmonary fibrosis in 1.1% of them (5/459).

Table 10-16. Imaging examinations performed and their results − Safety population

		Safety population (N = 596)
Pulmonology consultation before initiation?		
N		596
No	n (%)	564 (94.63%)
Yes	n (%)	32 (5.37%)
Pulmonary imaging assessment performed		
N		596
No	n (%)	137 (22.99%)
Yes	n (%)	459 (77.01%)
Type of pulmonary examination performed (several possible answers)		
N		459
Chest X-Ray	n (%)	66 (14.38%)
Chest scan	n (%)	255 (55.56%)
PET scan	n (%)	170 (37.04%)
Chest MRI	n (%)	3 (0.65%)
Other	n (%)	18 (3.92%)
Results of lung examination (several possible answers)		
N		459
Missing	n (%)	1 (0.22%)
Normal	n (%)	269 (58.61%)
Pulmonary metastases	n (%)	117 (25.49%)
Pleural effusion	n (%)	68 (14.81%)
Pulmonary fibrosis	n (%)	5 (1.09%)
Other	n (%)	54 (11.76%)

MRI: Magnetic resonance imaging; PET: positron emission tomography.
Source: **Table 1.3.11**

Results from initial evaluation of the lungs are presented in **Table 1.4.11** for the efficacy population and are similar to the ones described for the safety population.

10.3 Outcome data

The numbers of patients for each outcome, overall and by subgroup of interest, are detailed in **Sections 10.4−10.6**.

Tables 1.1.8 and **1.1.9** specifically present the number (%) of patients by subgroup of interest (refer to **Section 9.8.3** for more details) for the safety and efficacy populations, respectively.

10.4 Main results

10.4.1 Brief summary of adverse events, including stomatitis and NIP

An overview of AE (overall) and stomatitis/NIP events reported over the course of the study is presented in in-text **Table 10-17** for the safety population. This brief summary is also provided in **Table 2.1**.

In this section, AE referred to all AE reported during the study, including stomatitis and NIP.

The main results were as follows:

- A total of 559/596 patients (93.8%) experienced at least one AE over the course of the study. For 509/596 patients (85.4%), at least one AE was considered as related to Afinitor®.
- 167/596 patients (28.0%) experienced at least one SAE over the course of the study. For 90/596 patients (15.1%), at least one SAE was considered as related to Afinitor®.
- 48/596 patients (8.1%) experienced at least one AE leading to death over the course of the study. For 5/596 patients (0.8%), at least one fatal event was considered as related to Afinitor®.
- A total of 305/596 patients (51.2% [95% CI: 47.2−55.2]) experienced at least one stomatitis over the course of the study. For 301/596 patients (50.5% [95% CI: 46.5−54.5]), at least one stomatitis episode was considered as related to Afinitor®.
- 30/596 patients (5.0% [95% CI: 3.3−6.8]) experienced at least one serious stomatitis which was considered as related to Afinitor®.
- A total of 80/596 patients (13.4% [95% CI: 10.7−16.2]) experienced at least one NIP over the course of the study. For 73/596 patients (12.3 [95% CI: 9.6−14.9]), at least one NIP episode was considered as related to Afinitor®.
- 10/596 patients (1.7% [95% CI: 0.7−2.7]) experienced at least one serious NIP. For 9/596 patients (1.5% [95% CI: 0.5−2.5]), at least one serious NIP episode was considered as related to Afinitor®.

Table 10-17. Summary of AE – Safety population (N = 596)

Patients with:		Related or not to Afinitor®	Related to Afinitor®
≥ 1 AE[1]	n (%)	559 (93.79%)	509 (85.40%)
≥ 1 SAE[1]	n (%)	167 (28.02%)	90 (15.10%)
≥ 1 AE leading to death[1]	n (%)	48 (8.05%)	5 (0.84%)
≥ 1 stomatitis	n	305	301
	% [95% CI[2]]	51.17% [47.16 ; 55.19]	50.50% [46.49 ; 54.52]
≥ 1 serious stomatitis	n	30	30
	% [95% CI[2]]	5.03% [3.28 ; 6.79]	5.03% [3.28 ; 6.79]
≥ 1 NIP	n	80	73
	% [95% CI[2]]	13.42% [10.69 ; 16.16]	12.25% [9.62 ; 14.88]
≥ 1 serious NIP	n	10	9
	% [95% CI[2]]	1.68% [0.65 ; 2.71]	1.51% [0.53 ; 2.49]

[1]This included stomatitis, NIP, and other AE.
[2]95% CI were computed based on the Wald method.
95% CI: 95% confidence interval; NIP: Non-infectious pneumopathy; (S)AE: (Serious) adverse event.
Source: **Table 2.1**

Upon request from Scientific Committee members, the incidence of stomatitis and NIP was also evaluated by age group and according to several other clinical parameters.

Results from subgroup analyses are described in in-text **Table 10-18** for stomatitis and in in-text **Table 10-19** for NIP.

No clear associations were found between incidence of stomatitis on the one hand, and the age, Afinitor® dose, and presence of previous chemotherapy on the other hand. Interestingly, the percentage of patients who experienced ≥ 1 stomatitis tended to increase with the number of previous lines of treatment in metastatic setting (0 line: 38.1% [95% CI: 29.1−47.0%], 43/113; 1-2 lines: 51.8% [95% CI: 46.4−57.2], 173/334; ≥ 3 lines: 59.7% [95% CI: 51.9−67.6], 89/149).

Differences in the incidence of stomatitis according to the presence or absence of pulmonary/hepatic or bone metastases at inclusion should be interpreted with caution given that the 95% CI overlapped between metastasic subgroups. Therefore, no definite conclusion should be drawn at this stage (in-text **Table 10-18**).

Table 10-18. Incidence of stomatitis by subgroup of interest – Safety population (N = 596)

	Patients with ≥ 1 stomatitis		
Age	**< 70 years**		**≥ 70 years**
N	379		217
n	193		112
% [95% CI[1]]	50.92% [45.89 ; 55.96]		51.61% [44.96 ; 58.26]
Age	**< 75 years**		**≥ 75 years**
N	465		131
n	236		69
% [95% CI[1]]	50.75% [46.21 ; 55.30]		52.67% [44.12 ; 61.22]
Number of previous lines of treatment in metastatic setting	**0 line**	**1−2 lines**	**≥ 3 lines**
N	113	334	149
n	43	173	89
% [95% CI[1]]	38.05% [29.10 ; 47.00]	51.80% [46.44 ; 57.16]	59.73% [51.86 ; 67.61]
Previous chemotherapy	**Absence**		**Presence**
N	117		479
n	61		244
% [95% CI[1]]	52.14% [43.09 ; 61.19]		50.94% [46.46 ; 55.42]
Dose of the first Afinitor® intake	**5 mg**		**10 mg**
N	148		426
n	73		225
% [95% CI[1]]	49.32% [41.27 ; 57.38]		52.82% [48.08 ; 57.56]
Pulmonary or hepatic metastases at inclusion	**Absence**		**Presence**
N	330		266
n	182		123
% [95% CI[1]]	55.15% [49.79 ; 60.52]		46.24% [40.25 ; 52.23]
Bone metastases at inclusion	**Absence**	**Bone−only metastases**	**Bone/non−bone metastases**
N	137	199	260
n	79	102	124
% [95% CI[1]]	57.66% [49.39 ; 65.94]	51.26% [44.31 ; 58.20]	47.69% [41.62 ; 53.76]

[1]95% CI were computed based on the Wald method.
95% CI: 95% confidence interval.
Source: **Tables 2.2.4**, **2.2.7**, **2.2.10**, **2.2.13**, **2.2.16**, **2.2.19**, and **2.2.22**.

Overall, subgroup analyses did not reveal any notable differences between subgroups of interest with regards to NIP incidence (in-text **Table 10-19**). The relationship between NIP incidence and Afinitor® dose was evaluated in the overall population as well as in patients with or without pulmonary metastases at inclusion taken separately. No differences were found between the 5 mg/day dose regimen and the 10 mg/day dose regimen, whether or not patients had pulmonary metastases at inclusion:

- Patients without pulmonary metastases at inclusion: 12.7% [95% CI: 6.5−19.0] (14/110) for 5 mg/day dose regimen *versus* 12.5% [95% CI: 8.9−16.1] (41/328) for 10 mg/day dose regimen.
- Patients with pulmonary metastases at inclusion: 18.4% [95% CI: 6.1−30.8] (7/38) for 5 mg/day dose regimen *versus* 16.3% [95% CI: 9.0−23.6] (16/98) for 10 mg/day dose regimen.
- All patients, regardless of presence of pulmonary metastases at inclusion: 14.2% [95% CI: 8.6−19.8] (21/148) for 5 mg/day dose regimen *versus* 13.4% [95% CI: 10.2−16.6] (57/426) for 10 mg/day dose regimen.

Table 10-19. Incidence of NIP by subgroup of interest – Safety population (N = 596)

			Patients with ≥ 1 NIP
Age	**< 70 years**		**≥ 70 years**
N	379		217
n	55		25
% [95% CI[1]]	14.51% [10.97 ; 18.06]		11.52% [7.27 ; 15.77]
Age	**< 75 years**		**≥ 75 years**
N	465		131
n	69		11
% [95% CI[1]]	14.84% [11.61 ; 18.07]		8.40% [3.65 ; 13.15]
Number of previous lines of treatment in metastatic setting	**0 line**	**1−2 lines**	**≥ 3 lines**
N	113	334	149
n	16	47	17
% [95% CI[1]]	14.16% [7.73 ; 20.59]	14.07% [10.34 ; 17.80]	11.41% [6.30 ; 16.51]
Dose of the first Afinitor® intake	**5 mg**		**10 mg**
Overall population			
N	148		426
n	21		57
% [95% CI[1]]	14.19% [8.57 ; 19.81]		13.38% [10.15 ; 16.61]
Patients without pulmonary metastases at inclusion			
N	110		328
n	14		41
% [95% CI[1]]	12.73% [6.50 ; 18.96]		12.50% [8.92 ; 16.08]
Patients with pulmonary metastases at inclusion			
N	38		98
n	7		16
% [95% CI[1]]	18.42% [6.10 ; 30.75]		16.33% [9.01 ; 23.64]

	Patients with ≥ 1 NIP		
Pulmonary metastases at inclusion	**Absence**		**Presence**
N	455		141
n	57		23
% [95% CI[1]]	12.53% [9.49 ; 15.57]		16.31% [10.21 ; 22.41]
Pulmonary or hepatic metastases at inclusion	**Absence**		**Presence**
N	330		266
n	38		42
% [95% CI[1]]	11.52% [8.07 ; 14.96]		15.79% [11.41 ; 20.17]
Bone metastases at inclusion	**Absence**	**Bone−only metastases**	**Bone/non−bone metastases**
N	137	199	260
n	21	23	36
% [95% CI[1]]	15.33% [9.30 ; 21.36]	11.56% [7.12 ; 16.00]	13.85% [9.65 ; 18.04]

[1]95% CI were computed based on the Wald method.
95% CI: 95% confidence interval; NIP: Non-infectious pneumopathy.
Source: **Tables 2.2.28**, **2.2.31**, **2.2.34**, **2.2.37**, **2.2.40**, **2.2.43**, **2.2.46**, **2.2.49,** and **2.2.50**.

10.4.2 Therapeutic management of stomatitis and NIP – Primary objective

The **primary objective** of the study was to describe the therapeutic management of two specific AEs, stomatitis and NIP, in post-menopausal women with advanced HR+/HER2- breast cancer treated with Afinitor® + exemestane.

10.4.2.1 Therapeutic management of stomatitis

Therapeutic management of stomatitis are described in **Table 2.1.1** for the safety population. Summaries are presented in in-text **Table 10-20**.

A total of 305/596 patients (51.2%) experienced 400 episodes of stomatitis during the observation period. Of these 400 stomatitis episodes, 288 (72.0%) were grade > 1 in severity.

The 3 most common medications used to treat stomatitis episodes (irrespective of severity grade) were **mouthwashes** (309/400, 77.3%), **topical analgesics** (74/400, 18.5%), and **antifungals** (60/400, 15.0%).

Similar findings were observed for stomatitis of grade > 1, with **mouthwashes** (256/288, 88.9%), **topical analgesics** (72/288, 25.0%), and **antifungals** (58/288, 20.1%) reported as the commonly used medications.

Table 10-20. Therapeutic management of stomatitis – Safety population (N = 596)

	Irrespective of grade	Grade > 1
Patients with ≥ 1 stomatitis – *n (%[1])*	305 (51.17%)	-
Stomatitis episodes - *N*	400	288
Therapeutic management of stomatitis episodes		
Missing – *n (%[2])*	58 (14.50%)	3 (1.04%)
Mouthwashes – *n (%[2])*	309 (77.25%)	256 (88.89%)
Topical analgesics – *n (%[2])*	74 (18.50%)	72 (25.00%)
Antifungals – *n (%[2])*	60 (15.00%)	58 (20.14%)
Topical applications – *n (%[2])*	37 (9.25%)	33 (11.46%)
Others – *n (%[2])*	26 (6.50%)[3]	24 (8.33%)
Systemic analgesics – *n (%[2])*	22 (5.50%)	20 (6.94%)
Topical corticosteroids – *n (%[2])*	21 (5.25%)	20 (6.94%)
Dietary adjustments – *n (%[2])*	15 (3.75%)	15 (5.21%)
Antibiotics – *n (%[2])*	11 (2.75%)	11 (3.82%)
Antiulcer agents – *n (%[2])*	11 (2.75%)	10 (3.47%)
Systemic corticosteroids – *n (%[2])*	8 (2.00%)	7 (2.43%)
Analgesics dose level 3 – *n (%[2])*	5 (1.25%)	5 (1.74%)

[1]Percentages were calculated on the total number of patients in the safety population.
[2]Percentages were calculated on the total number of stomatitis episodes.
[3]Other therapeutic care for stomatitis included:
- Temporary interruption of Afinitor® for 10/26 patients
- Reduction of Afinitor® dose for 6/26 patients
- Laser for 3/26 patients
- Dentist for 1/26 patient
- Natural medicine for 1/26 patient
- Incomplete information for 5/26 patients

Source: **Table 2.1.1** and **Listing 8** (for other therapeutic care)

10.4.2.2 Therapeutic management of NIP

Therapeutic management of NIP are described in **Table 2.1.2** for the safety population. Summaries are presented in in-text **Table 10-21**.

A total of 80/596 patients (13.4%) experienced 88 episodes of NIP during the observation period. Of these 88 NIP episodes, 66 (75.0%) were grade > 1 in severity.

Overall and irrespective of severity grade, **corticosteroids** were the most common medications used to treat NIP episodes (35/88, 39.8%), followed in decreasing order of frequency by other treatments (22/88, 25.0%), antibiotic therapy (9/88, 10.2%), treatment by a pulmonologist (4/88, 4.6%), and oxygen therapy (1/88, 1.1%).

Medications used to treat NIP of grade > 1 showed a similar order of frequency: **corticosteroids** (33/66, 50.0%), other treatments (20/66, 30.3%), antibiotic therapy (8/66, 12.1%), treatment by a pulmonologist (4/66, 6.1%), and oxygen therapy (1/66, 1.5%). Percentages were slightly higher compared to all-grade NIP, which is probably explained by the absence of missing data (0/66 [0.0%] for NIP of grade > 1 *versus* 17/88 [19.3%] for all-grade NIP).

Table 10-21. Therapeutic management of NIP – Safety population (N = 596)

	Irrespective of grade	Grade > 1
Patients with ≥ 1 NIP – n (%[1])	80 (13.42%)	-
NIP episodes − *N*	88	66
Therapeutic management of NIP episodes		
Missing – *n (%[2])*	17 (19.32%)	0 (0.00%)
Corticosteroids – *n (%[2])*	35 (39.77%)	33 (50.00%)
Other – *n (%[2])*	22 (25.00%)	20 (30.30%)
Antibiotic therapy – *n (%[2])*	9 (10.23%)	8 (12.12%)
Treated by a pulmonologist – *n (%[2])*	4 (4.55%)	4 (6.06%)
Oxygen therapy – *n (%[2])*	1 (1.14%)	1 (1.52%)

[1]Percentages were calculated on the total number of patients in the safety population.
[2]Percentages were calculated on the total number of stomatitis episodes.
NIP: Non-infectious pneumopathy.
Source: **Table 2.1.2**

10.4.3 Characteristics of stomatitis and NIP

The secondary objectives included, among others, the description of stomatitis and NIP in clinical practice (incidence, time to first occurrence, duration, outcome, severity).

10.4.3.1 Characteristics of stomatitis

10.4.3.1.1 Overall analysis

Table 2.2.1 shows characteristics of stomatitis, in terms of incidence, time to first occurrence, duration, and outcome.

As mentioned in **Section 10.4.2.1**, 305/596 patients presented at least one stomatitis episode during the observation period. The same number of patients presented at least one stomatitis episode, when only events occurring in patients on Afinitor® treatment were taken into account. The number of stomatitis episodes by patient ranged from 1 to 7, with a median

value of 1, whether calculated on all patients or only on those being treated with Afinitor® (in text **Table 10-22**). Details about the number of stomatitis by patient by severity grade (1−5) can be found in **Table 2.2.1**.

At the time of SAP writing, it was decided to estimate the time to first stomatitis occurrence, and the duration and outcome of stomatitis episodes in patients being treated with Afinitor® (as monotherapy or in combination with exemestane). Those only treated with exemestane or who had discontinued both drugs were not considered in the analysis.

The time to first occurrence of stomatitis was defined as the time elapsed between the first Afinitor® intake and the occurrence of the first stomatitis episode. It ranged from 1 to 333 days (~11 months), with a median value of 16 days when missing data are not substituted (N = 260) or 21 days when missing data are imputed by mean substitution (N = 305) (in-text **Table 10-22**).

The duration and outcome of stomatitis episodes were described for the first 3 episodes experienced by patients. The median duration of stomatitis tended to decrease as the number of episodes increased. The median (range) duration was 24 (1−407) days for episode 1 (N = 234), 20 (0−187) days for episode 2 (N = 54), and 10 (1−116) days for episode 3 (N = 11). However, these results need to be interpreted with caution due the low number of available data for episode 3. Complete resolution was observed for the majority of patients, with percentages varying from 87.2% (266/305) for episode 1 to 84.9% (62/73) for episode 2 and 70.6% for episode 3 (12/17). Stomatitis had worsened for a minority of patients, as indicated by the following numbers: 3.6% (11/305), 2.7% (2/73), and 5.9% (1/17) for episode 1,2, and 3, respectively. No deaths related to stomatitis were reported for the first 3 stomatitis episodes (in-text **Table 10-23**).

Table 10-22. Number of stomatitis by patient and time to first occurrence of stomatitis – Safety population

Variables	Safety population (N = 305, patients with ≥ 1 stomatitis)
Number of stomatitis by patient	
N	305
Median [Q1 ; Q3]	1 [1 ; 1]
[Min ; Max]	[1 ; 7]
Number of stomatitis on Afinitor® treatment by patient	
N	305
Median [Q1 ; Q3]	1 [1 ; 1]
[Min ; Max]	[1 ; 7]
Time to first occurrence of stomatitis (days)[1]	
N	260
Missing	45
Median [Q1 ; Q3]	16 [10 ; 34]
[Min ; Max]	[1 ; 333]
Time to first occurrence of stomatitis (days)[1] [mean imputation][2]	
N	305
Median [Q1 ; Q3]	21 [11 ; 32]
[Min ; Max]	[1 ; 333]

[1]Time elapsed between the first Afinitor® intake and the occurrence of the first stomatitis episode in patients still on treatment.
[2]Missing data were imputed by mean substitution.
Min & Max: Minimum and maximum; Q1 & Q3: First and third quartiles.
Source: **Table 2.2.1**

Table 10-23. Duration and outcome of the first 3 stomatitis episodes – Safety population (N = 596)

	Episode 1	Episode 2	Episode 3
Duration of stomatitis (days)[1]			
N	234	54	11
Missing	36	11	2
Median [Q1 ; Q3]	24 [13 ; 49]	20 [11 ; 32]	10 [8 ; 29]
[Min ; Max]	[1 ; 407]	[0 ; 187][2]	[1 ; 116]
Outcome of stomatitis			
N	305	73	17
Missing – *n (%[3])*	1 (0.33%)	0 (0.00%)	0 (0.00%)
Complete resolution – *n (%[3])*	266 (87.21%)	62 (84.93%)	12 (70.59%)
Resolution with sequelae – *n (%[3])*	4 (1.31%)	3 (4.11%)	1 (5.88%)
Improvement – n (%[3])	11 (3.61%)	2 (2.74%)	2 (11.76%)
Condition unchanged – *n (%[3])*	12 (3.93%)	4 (5.48%)	1 (5.88%)
Worsening – *n (%[3])*	11 (3.61%)	2 (2.74%)	1 (5.88%)
Fatal – *n (%[3])*	0 (0.00%)	0 (0.00%)	0 (0.00%)

[1]Duration was calculated for completed episodes only. If outcome was 'improvement/condition unchanged/worsening', the episode was not considered as completed.
[2]If stomatitis resolved before first Afinitor® intake or started after last Afinitor® intake, the duration of stomatitis episode was imputed to 0.
[3]Percentages were calculated on the total number of stomatitis by episode.
Min & Max: Minimum and maximum; Q1 & Q3: First and third quartiles.
Source: **Table 2.2.1**

Table 2.2.2 shows the percentage of patients for whom the most severe stomatitis episode was classified as grade 1, 2, 3, 4 and 5 and **Table 2.2.3** shows similar results when severity grades

are grouped (grades 1−2, grade 3, grades 4−5). Results are presented for stomatitis episodes related or not to Afinitor® and for related events only.

The most severe stomatitis episode was reported grade 1 or 2 for 86.9% [95% CI: 83.1−90.7] of patients (265/305), grade 3 for 12.8% [95% CI: 9.0−16.5] of patients (39/305), and grade 4 for one single patient (0.3% [95% CI: 0.0−1.0]). Causal relationship with Afinitor® was suspected for 98.5% (261/265) of grades 1−2 most severe stomatitis episodes. Grade 3 and grade 4 most severe stomatitis episodes were all considered as related to Afinitor® (**Table 10-24**).

Brief narrative for the patient with grade 4 stomatitis event (Patient 115-0069):

This 80-year-old female patient started the study treatment for her metastatic breast cancer at a dose of 10 mg daily for Afinitor® and 25 mg daily for exemestane. She experienced a first episode of **grade 3 stomatitis** that started 6 days after study treatment initiation and developed one week later moderate mucosal inflammation characterised by skin pruritus, macular-papular rash, and skin lesions (sparing the face). Afinitor® treatment was temporary interrupted due to these events. She was hospitalised and received enteral feeding because oral feeding was impossible. She was also treated with mouthwashes, topical and systemic analgesics, morphinics, antiulcer agents, and her diet was adjusted or stopped (not specified). She completely recovered from this first episode of stomatitis (23 days after its onset) and restarted Afinitor® treatment at a dose of 5 mg daily. A few days after Afinitor® treatment was restarted, she experienced a second episode of **grade 4 stomatitis** and also developed erythematous skin eruption. Afinitor® treatment was temporary interrupted due to these events. This second episode of stomatitis was treated with mouthwashes and topical and systemic analgesics, and completely resolved 25 days after its onset. The events stomatitis (both episodes), mucosal inflammation, pruritus, macular-papular rash and skin lesions were all considered as related to Afinitor® by the physician and the Sponsor (**Listings 9 and 12**, and full narratives from the Pharmacovigilance database in **Annex 1**).

Table 10-24. Most severe stomatitis episode experienced by patients sorted by severity grade – Safety population (N = 305, patients with ≥ 1 stomatitis)

	Grades 1−2	Grade 3	Grades 4−5
Most severe stomatitis episode			
n (%[1])	265	39	1[2]
% [95% CI[3]]	86.89% [83.10 ; 90.67]	12.79% [9.04 ; 16.53]	0.33% [0.00 ; 0.97]
Most severe related stomatitis episode			
n (%[1])	261	39	1[2]
% [95% CI[3]]	85.57% [81.63 ; 89.52]	12.79% [9.04 ; 16.53]	0.33% [0.00 ; 0.97]

[1]Percentage of patients for whom the most severe stomatitis episode was classified as grades 1−2, grade 3, and grades 4−5. Percentages were calculated on the total number of patients with at least one stomatitis episode.
[2]Actually, the most severe stomatitis episode in this patient was classified as grade 4.
[3]95% CI were computed based on the Wald method.
Source: **Tables 2.2.2−3**

10.4.3.1.2 Subgroup analyses

Characteristics of stomatitis were also described by age group and according to several other clinical parameters as depicted below:

Parameters	Subgroups	Tables
Age	< 70 years *versus* ≥ 70 years < 75 years *versus* ≥ 75 years	**Tables 2.2.4−6** **Tables 2.2.7−9**
Number of previous lines of treatment in metastatic setting	0, 1−2 *versus* ≥ 3 lines	**Tables 2.2.10−12**
Previous chemotherapy	Presence *versus* absence	**Tables 2.2.13−15**
Dose of the first Afinitor® intake	5 mg *versus* 10 mg	**Tables 2.2.16−18**
Pulmonary or hepatic metastases at inclusion	Presence *versus* absence	**Tables 2.2.19−21**
Bone metastases at inclusion	Presence of bone-only metastases *versus* Presence of bone and non-bone metastases *versus* Absence of bone metastases	**Tables 2.2.22−24**

Overall, subgroup analyses did not reveal any notable differences between subgroups of interest.

Interestingly though, the percentage of patients for whom the most severe stomatitis episode was classified as grade 1 or 2 tended to decrease with the number of previous lines of treatment in metastatic setting (0 line: 90.7% [95% CI: 82.0−99.4], 39/43; 1-2 lines: 87.3% [95% CI: 82.3−92.3], 151/173; ≥ 3 lines: 84.3% [95% CI: 76.7−91.8], 75/89). Conversely, the percentage of patients for whom the most severe stomatitis episode was classified as grade 3 tended to increase (0 line: 9.3% [95% CI: 0.6−18.0], 4/43; 1-2 lines: 12.1% [95% CI: 7.3−17.0], 21/173; ≥ 3 lines: 15.7% [95% CI: 8.2−23.3], 14/89). As the number of available data is not balanced between subgroups, these trends need to be interpreted with caution.

Note: For some variables (e.g. duration and outcome of stomatitis episode 3), the number of available data was very low, making result interpretation extremely difficult.

10.4.3.2 Characteristics of NIP

10.4.3.2.1 Overall analysis

Table 2.2.25 shows characteristics of NIP, in terms of incidence, time to first occurrence, duration, and outcome.

As mentioned in **Section 10.4.2.2**, 80/596 patients presented at least one NIP episode during the observation period. Of these patients, 78 were still being treated with Afinitor® when these events were diagnosed. The number of NIP episodes by patient (still on Afinitor® or not) ranged from 1 to 2, with a median value of 1. The same results were found when only NIP occurring on Afinitor® treatment were taken into account (in text **Table 10-25**). Details about the number of NIP by patient by severity grade (1−5) can be found in **Table 2.2.25**.

At the time of SAP writing, it was decided to estimate the time to first NIP occurrence, and the duration and outcome of NIP episodes in patients being treated with Afinitor® (as monotherapy or in combination with exemestane). Those only treated with exemestane or who had discontinued both drugs were not considered in the analysis.

The time to first occurrence of NIP was defined as the time elapsed between the first Afinitor® intake and the occurrence of the first NIP episode. It ranged from 1 to 396 days (~13 months), with a median value of 94 days when missing data are not substituted (N = 71) or 104 days when missing data are imputed by mean substitution (N = 80) (in text **Table 10-25**).

The median (range) duration of NIP was 19 (0−142) days for the first episode (N = 63) and 10 (0−245) days for the second episode (N = 6). Complete resolution was observed for the majority of patients, with percentages of 82.5% (66/80) for the first episode and 87.5% (7/8) for the second episode. NIP had worsened for one patient and led to death for another patient. These cases were reported as first NIP episode for both patients (in-text **Table 10-26**).

The NIP fatal case was considered as related to Afinitor® and is described in a narrative format in **Section 10.6.6**.

Brief narrative for the patient with NIP worsening case (Patient 077-0895):

This 69-year-old female patient started Afinitor® for her breast cancer at a dose of 5 mg daily, increased to 10 mg daily 72 days later. Afinitor® was discontinued 240 days after initiation because of pruritus. Thirty-five days after Afinitor® discontinuation, the patient developed NIP. NIP was initially diagnosed because of clinical signs of dyspnoea and was at that time considered as grade 2 in severity. One week after the onset of NIP, a chest scan showed that the patient had signs of pleural effusion with atelectasis. The NIP event was therefore upgraded as grade 3 in severity and was considered as a second episode of NIP. Two weeks after the onset of NIP, the patient underwent pleural puncture and received oxygen therapy, and was hospitalised 3 weeks later to treat her pleural effusion with talc pleurodyesis. Post-operative evolution was good. Almost one year (348 days) after Afinitor® initiation, the patient died from metastatic progression of breast cancer and general physical health deterioration. Both episodes of NIP were considered as serious and related to Afinitor® by the investigator (**Listings 12, 14 and 19**, and full narratives from the Pharmacovigilance database in **Annex 1**).

Table 10-25. Number of NIP by patient and time to first occurrence of NIP – Safety population

Variables	Safety population (N = 80, patients with ≥ 1 NIP)
Number of NIP by patient	
N	80
Median [Q1 ; Q3]	1 [1 ; 1]
[Min ; Max]	[1 ;2]
Number of NIP on Afinitor® treatment by patient	
N	78
Median [Q1 ; Q3]	1 [1 ; 1]
[Min ; Max]	[1 ;2]
Time to first occurrence of NIP (days)[1]	
N	71
Missing	9
Median [Q1 ; Q3]	94 [44 ; 137]
[Min ; Max]	[1 ; 396]
Time to first occurrence of NIP (days)[1] [mean imputation][2]	
N	80
Median [Q1 ; Q3]	104 [54 ; 128]
[Min ; Max]	[1 ; 396]

[1]Time elapsed between the first Afinitor® intake and the occurrence of the first NIP episode in patients still on treatment.
[2]Missing data were imputed by mean substitution.
Min & Max: Minimum and maximum; NIP: Non-infectious pneumopathy; Q1 & Q3: First and third quartiles.
Source: **Table 2.2.25**

Table 10-26. Duration and outcome of the NIP episodes – Safety population (N = 596)

	Episode 1	Episode 2
Duration of NIP (days)[1]		
N	63	6
Missing	7	1
Median [Q1 ; Q3]	19 [2 ; 41]	10 [1 ; 71]
[Min ; Max]	[0 ; 142][2]	[0 ; 245][2]
Outcome of NIP		
N	80	8
Missing – *n (%[3])*	0 (0.00%)	0 (0.00%)
Complete resolution – *n (%[3])*	66 (82.50%)	7 (87.50%)
Resolution with sequelae – *n (%[3])*	3 (3.75%)	0 (0.00%)
Improvement – n (%[3])	3 (3.75%)	0 (0.00%)
Condition unchanged – *n (%[3])*	6 (7.50%)	1 (12.50%)
Worsening – *n (%[3])*	1 (1.25%)	0 (0.00%)
Fatal – *n (%[3])*	1 (1.25%)	0 (0.00%)

[1]Duration was calculated for completed episodes only. If outcome was 'improvement/condition unchanged/worsening', the episode was not considered as completed.
[2]If NIP resolved before first Afinitor® intake or started after last Afinitor® intake, the duration of NIP episode was imputed to 0.
[3]Percentages were calculated on the total number of NIP by episode.
Min & Max: Minimum and maximum; NIP: Non-infectious pneumopathy; Q1 & Q3: First and third quartiles.
Source: **Table 2.2.25**

Table 2.2.26 shows the percentage of patients for whom the most severe NIP episode was classified as grade 1, 2, 3, 4 and 5 and **Table 2.2.27** shows similar results when severity grades are grouped (grades 1−2, grade 3, grades 4−5). Results are presented for NIP episodes related or not to Afinitor® and for related events only.

The most severe NIP episode was reported grade 1 or 2 for 91.3% [95% CI: 85.1−97.4] of patients (73/80), grade 3 for 7.5% [95% CI: 1.7−13.3] of patients (6/80), and grade 5 for one single patient (1.3% [95% CI: 0.0−3.7]). Causal relationship with Afinitor® was suspected for 91.8% (67/73) of grades 1−2 most severe NIP episodes. All grade 3 most severe NIP episodes except one (5/6, 83.3%) were considered as related to Afinitor®, as was the single grade 5 episode (**Table 10-27**).

One NIP event resulted in death and was therefore graded 5 in severity as per CTCAE grading criteria. As mentioned above, this NIP fatal case is described in a narrative format in **Section 10.6.6**.

Table 10-27. Most severe NIP episode experienced by patients sorted by severity grade – Safety population (N = 80, patients with ≥ 1 NIP)

	Grades 1−2	Grade 3	Grades 4−5
Most severe NIP episode			
n (%[1])	73	6	1[2]
% [95% CI[3]]	91.25% [85.06 ; 97.44]	7.50% [1.73 ; 13.27]	1.25% [0.00 ; 3.68]
Most severe related NIP episode			
n (%[1])	67	5	1[2]
% [95% CI[3]]	83.75% [75.67 ; 91.83]	6.25% [0.95 ; 11.55]	1.25% [0.00 ; 3.68]

[1]Percentage of patients for whom the most severe NIP episode was classified as grades 1−2, grade 3, and grades 4−5. Percentages were calculated on the total number of patients with at least one NIP episode.
[2]Actually, the most severe NIP episode in this patient was classified as grade 5.
[3]95% CI were computed based on the Wald method.
NIP: Non-infectious pneumopathy.
Source: **Tables 2.2.26−7**

10.4.3.2.2 Subgroup analyses

Characteristics of NIP were also described by age group and according to several other clinical parameters as depicted below:

Parameters	Subgroups	Tables
Age	< 70 years *versus* ≥ 70 years < 75 years *versus* ≥ 75 years	**Tables 2.2.28−30** **Tables 2.2.31−33**
Number of previous lines of treatment in metastatic setting	0, 1−2 *versus* ≥ 3 lines	**Tables 2.2.34−36**
Pulmonary metastases at inclusion	Presence *versus* absence	**Tables 2.2.37−39**
Dose of the first Afinitor® intake	5 mg *versus* 10 mg	**Tables 2.2.40−42**
Pulmonary or hepatic metastases at inclusion	Presence *versus* absence	**Tables 2.2.43−45**
Bone metastases at inclusion	Presence of bone-only metastases *versus* Presence of bone and non-bone metastases *versus* Absence of bone metastases	**Tables 2.2.46−48**

Given the relatively low number of patients in subgroups, no clear associations were found between NIP characteristics on the one hand, and the age, Afinitor® dose, presence of metastases, or number of previous lines of treatment on the other hand.

10.4.4 Description of study treatment

10.4.4.1 Initiation of Afinitor® treatment

Data pertaining to Afinitor® treatment initiation are presented in **Table 3.1** for the efficacy population. Summaries are presented in in-text **Table 10-28**.

The dose of Afinitor® prescribed at inclusion ranged from 2.5 to 10 mg/day, with a mean (SD) value of 8.7 (2.2) mg/day. The majority of patients (74.7%, 420/562) were prescribed a starting dose of 10 mg/day, as recommended in the Summary of Product Characteristics (SmPC dated 13-Sep-2017), and a quarter of them (25.1%, 141/562) were prescribed a reduced dose of 5 mg/day. One patient was prescribed 5 mg of Afinitor® every other day and was therefore assigned to the 2.5 mg/day dose regimen.

The first dose of Afinitor® actually taken by patients ranged from 0 to 10 mg/day, with a mean (SD) value of 8.7 (2.3) mg/day. The majority of patients (71.2%, 400/562) started Afinitor® treatment at the recommended dose of 10 mg/day, a quarter of them (23.1%, 130/562) at a reduced dose of 5 mg/day and a few of them (0.9%, 5/562) at a reduced dose of 2.5 mg/day. Of the 5 patients whose first documented dose was 2.5 mg/day, 4 had actually been prescribed a higher dose regimen at inclusion. The remaining one was the patient who was prescribed 5 mg of Afinitor® every other day. The first dose of Afinitor® actually taken was not documented for 26/562 (4.6%) patients. As shown in **Table 5.1**, the log treatment page of the CRF had not been completed by the study physician for 24/562 patients (4.3%).

Table 10-28. Prescribed dose of Afinitor® and first dose actually taken – Efficacy population (N = 562)

	Prescribed dose of Afinitor® at inclusion	First dose of Afinitor® actually taken
N	562	536
Missing	0	26
Mean (SD) – mg/day	8.7 (2.2)	8.7 (2.3)
Median [Q1 ; Q3] – mg/day	10 [5 ; 10]	10 [5 ; 10]
[Min ; Max] – mg/day	[2.5 ; 10]	[0 ; 10]
Dose regimen		
N	562	562
Missing – *n (%)*	0 (0.00%)	26 (4.63%)
0 mg/day – *n (%)*	-	1 (0.18%)[3]
2.5 mg/day – *n (%)*	1 (0.18%)[1]	5 (0.89%)[2]
5 mg/day – *n (%)*	141 (25.09%)	130 (23.13%)
10 mg/day – *n (%)*	420 (74.73%)	400 (71.17%)

[1]One patient was prescribed 5 mg of Afinitor® every other day at inclusion and was therefore assigned to the 2.5 mg/day dose regimen.
[2]Including the patient who was prescribed 5 mg of Afinitor® every other day at inclusion.
[3]Results pertaining to the first dose of Afinitor® actually taken were calculated using information reported in the study treatment page of the CRF. For one patient (#114-0386), the only information reported in the study treatment page was 0 mg of Afinitor® with start date on 05-Jul-2016 and end date on 15-Jul-2016. However, for this patient, Afinitor® was prescribed at a dose of 10 mg/kg as reported in the inclusion page of the CRF and the date of first intake was 20-Jul-2015 as reported in the visit D15 page. Taken together, this explains why this patient was part of the efficacy population but was assingned to the 0 mg/day category for the first dose actually taken.
CRF: Case Report Form; Min & Max: Minimum and maximum; Q1 & Q3: First and third quartiles; SD: Standard deviation.
Source: **Table 3.1**

10.4.4.2 Duration of exposure to Afinitor® + exemestane combination

As mentioned in **Section 9.8.3.5**, the duration of exposure to Afinitor® + exemestane combination (months) was defined as the time from the first dose of treatment until documented treatment discontinuation (at least one drug discontinued) or end of observation period. It was computed using Kaplan-Meier method.

10.4.4.2.1 Overall analysis

Duration of exposure to Afinitor® + exemestane combination is described in **Table 3.2** and is graphically displayed in **Figure 3.1**. Summaries are presented in in-text **Table 10-29**.

In the efficacy population (N = 562), the duration of exposure to Afinitor® + exemestane combination ranged from one day to 26.5 months. The median duration of exposure (i.e. time after which 50% of patients were still on combination therapy) was 5.3 months (95% CI: 4.8−6.0). Treatment rates (i.e. proportions of patients still on combination therapy at different time points) gradually decreased over time and were 72.0%, 45.8%, 31.6%, and 22.7% at 3, 6, 9, and 12 months, respectively.

A sensitivity analysis was conducted by excluding treatment data collected after M12, i.e. data reported in the last contact form. These results are described in **Table 3.3** and are graphically displayed in **Figure 3.2**. Overall, results from the sensitivity analysis confirmed those from the main analysis. As post-M12 data were excluded from the sensitivity analysis, the maximum duration of exposure was lower when calculated with the sensitivity analysis compared to the main analysis (22.0 months *versus* 26.5 months) (in-text **Table 10-29**).

Table 10-29. Duration of exposure to Afinitor® + exemestane combination: Kaplan-Meier estimates – Efficacy population (N = 562)

	Main analysis	Sensitivity analysis (post-M12 data excluded)
N	562	562
Missing	48 (8.54%)	48 (8.54%)
Number of events	435 (77.40%)	396 (70.46%)
Number of censored data	79 (14.06%)	118 (21.00%)
[Min ; Max]	[0.03 ; 26.45]	[0.03 ; 22.01]
75% [95% CI]	2.8 [2.3−3.1]	2.8 [2.3−3.1]
50% (Median) [95% CI]	5.3 [4.8−6.0]	5.3 [4.8−6.0]
25% [95% CI]	11.7 [9.6−12.6]	11.7 [9.6−12.4]
Treatment rate at 3 months – *n (%)*	365 (72.0%)	365 (72.0%)
Treatment rate at 6 months – *n (%)*	230 (45.8%)	230 (45.8%)
Treatment rate at 9 months – *n (%)*	159 (31.6%)	159 (31.6%)
Treatment rate at 12 months – *n (%)*	96 (22.7%)	64 (22.5%)

95% CI: 95% confidence interval; M: Month; Min & Max: Minimum and maximum.
Source: **Tables 3.2** and **3.3**

10.4.4.2.2 Subgroup analyses

Duration of exposure to Afinitor® + exemestane combination was also described by age group and according to several other clinical parameters as depicted below:

Parameters	Subgroups	Tables/Figures
Age	< 70 years *versus* ≥ 70 years < 75 years *versus* ≥ 75 years	**Table 3.4/Figure 3.3** **Table 3.5/Figure 3.4**
Number of previous lines of treatment in metastatic setting	0, 1−2 *versus* ≥ 3 lines 0, 1, 2, 3 *versus* > 3 lines	**Table 3.6/Figure 3.5** **Table 3.7/Figure 3.6**
Visceral metastases at inclusion	Presence *versus* absence	**Table 3.8/Figure 3.7**
Type of previous hormonal therapy	≥1 SAI *versus* ≥ 1 antioestrogen	**Table 3.9/Figure 3.8**
Interval to recurrence with respect to stop of adjuvant hormonal treatment	0 month,]0−12 months] *versus* > 12 months	**Table 3.10/Figure 3.9**
Duration of response to previous hormonal therapy	≤ 6 months *versus* > 6 months	**Table 3.11/Figure 3.10**
Dose of the first Afinitor® intake	5 mg *versus* 10 mg	**Table 3.12/Figure 3.11**
Pulmonary or hepatic metastases at inclusion	Presence *versus* absence	**Table 3.13/Figure 3.12**
Bone metastases at inclusion	Presence of bone-only metastases *versus* Presence of bone and non-bone metastases *versus* Absence of bone metastases	**Table 3.14/Figure 3.13**

SAI: Steroidal aromatase inhibitor.

Among Kaplan-Meier estimates, we selected the median duration of exposure to compare subgroups of interest. The main findings can be summarised as follows:

- The median [95% CI] duration of exposure tended to be lower in older patients (4.1 [3.4−5.3] months in ≥ 70-year age group, N = 207 and 3.9 [3.1−5.0] months in ≥ 75-year age group, N = 125) than in younger ones (5.9 [5.0−6.7] months in < 70-year age group, N = 355 and 5.8 [4.9−6.6] months in < 75-year age group, N = 437) (in text **Table 10-30**).
- The median [95% CI] duration of exposure tended to be lower in patients with visceral metastases at inclusion (4.7 [4.1−5.8] months, N = 269) than in those without visceral metastases (5.8 [4.8−6.6] months, N = 259). A similar association was found with pulmonary/hepatic metastases; the median [95% CI] duration of exposure tended to be lower in patients with pulmonary or hepatic metastases (4.6 [4.0−5.7] months, N = 244) than in those without metastases (5.9 [4.9−6.7] months, N = 318). In contrast, no notable differences were observed between patients with bone metastases (5.2 [4.3−6.6] months for bone-only metastases, N = 184 and 5.3 [4.1−6.2] months for bone and non-bone metastases, N = 250) and patients without bone metastases (5.6 [4.2−7.2] months, N = 128) (in-text **Table 10-31**).
- The median [95% CI] duration of exposure tended to be lower in patients who had received ≥ 3 previous lines of treatment in metastatic setting (4.8 [4.0−5.9] months, N = 143) *versus* those who had received 0 (5.7 [3.9−7.1] months, N = 94) or 1−2 (5.7 [4.8−6.4] months, N = 325) previous lines of treatment. When previous lines of

treatment were classified into 5 categories (0, 1, 2, 3 *versus* > 3 lines), results were more variable, with no real trend being obvious (in-text **Table 10-32**).

- The median [95% CI] duration of exposure seemed to be associated with the duration of response to previous hormonal therapy (≤ 6 months *versus* > 6 months); patients with shorter duration of response had shorter exposure to study treatment (4.4 [3.0−6.4] months, N = 77) than patients with longer duration of response (5.7 [4.8−6.5] months, N = 328) (in-text **Table 10-33**).
- Trends described above should be interpreted with caution because the 95% CI associated with the median duration of exposure overlapped between subgroups. Whether or not age, presence of visceral metastases or pulmonary/hepatic metastases, number of previous lines of treatment, or duration of response to previous hormonal therapy actually influenced the duration of exposure to study treatment remains uncertain at this stage.
- No differences between subgroups were found with other parameters, in particular Afinitor® dose, type of previous hormonal therapy, and interval to recurrence with respect to stop of adjuvant hormonal treatment.

Table 10-30. Duration of exposure to Afinitor® + exemestane combination by age: Kaplan-Meier estimates – Efficacy population (N = 562)

	< 70 years	**≥ 70 years**
N	355	207
Missing	27 (7.61%)	21 (10.14%)
Number of events	280 (78.87%)	155 (74.88%)
Number of censored data	48 (13.52%)	31 (14.98%)
75% [95% CI]	3.0 [2.7−3.5]	2.3 [2.1−2.8]
50% (Median) [95% CI]	5.9 [5.0−6.7]	4.1 [3.4−5.3]
25% [95% CI]	12.0 [9.9−14.1]	9.5 [7.6−12.6]
	< 75 years	**≥ 75 years**
N	437	125
Missing	34 (7.78%)	14 (11.20%)
Number of events	338 (77.35%)	97 (77.60%)
Number of censored data	65 (14.87%)	14 (11.20%)
75% [95% CI]	3.0 [2.6−3.2]	2.2 [1.9−2.8]
50% (Median) [95% CI]	5.8 [4.9−6.6]	3.9 [3.1−5.0]
25% [95% CI]	12.0 [10.2−14.1]	7.8 [6.1−10.5]

95% CI: 95% confidence interval.
Source: **Tables 3.4** and **3.5**

Table 10-31. Duration of exposure to Afinitor® + exemestane combination according to the presence of metastases: Kaplan-Meier estimates – Efficacy population (N = 562)

	Absence of visceral metastases	Presence of visceral metastases
N	259	269
Missing	26 (10.04%)	21 (7.81%)
Number of events	190 (73.36%)	217 (80.67%)
Number of censored data	43 (16.60%)	31 (11.52%)
75% [95% CI]	2.7 [2.2−3.1]	2.8 [2.2−3.1]
50% (Median) [95% CI]	5.8 [4.8−6.6]	4.7 [4.1−5.8]
25% [95% CI]	12.3 [10.2−14.9]	9.5 [8.4−11.9]
	Absence of pulmonary and hepatic metastases	**Presence of pulmonary or hepatic metastases**
N	318	244
Missing	29 (9.12%)	19 (7.79%)
Number of events	239 (75.16%)	196 (80.33%)
Number of censored data	50 (15.72%)	29 (11.89%)
75% [95% CI]	2.9 [2.3−3.2]	2.7 [2.2−3.1]
50% (Median) [95% CI]	5.9 [4.9−6.7]	4.6 [4.0−5.7]
25% [95% CI]	12.0 [10.2−14.1]	9.5 [8.3−12.5]

	Absence of bone metastases	Presence of bone-only metastases	Presence of bone and non-bone metastases
N	128	184	250
Missing	9 (7.03%)	17 (9.24%)	22 (8.80%)
Number of events	103 (80.47%)	133 (72.28%)	199 (79.60%)
Number of censored data	16 (12.50%)	34 (18.48%)	29 (11.60%)
75% [95% CI]	3.1 [2.3−3.4]	2.7 [2.1−3.2]	2.6 [2.2−3.1]
50% (Median) [95% CI]	5.6 [4.2−7.2]	5.2 [4.3−6.6]	5.3 [4.1−6.2]
25% [95% CI]	10.5 [8.8−13.4]	13.6 [10.2−17.2]	9.9 [8.7−12.5]

95% CI: 95% confidence interval.
Source: **Tables 3.8**, **3.13** and **3.14**

Table 10-32. Duration of exposure to Afinitor® + exemestane combination according to the number of previous lines of treatment in metastatic setting: Kaplan-Meier estimates – Efficacy population (N = 562)

	0 line	1−2 lines	≥ 3 lines
N	94	325	143
Missing	4 (4.26%)	31 (9.54%)	13 (9.09%)
Number of events	73 (77.66%)	243 (74.77%)	119 (83.22%)
Number of censored data	17 (18.09%)	51 (15.69%)	11 (7.69%)
75% [95% CI]	3.0 [2.4−3.5]	2.8 [2.2−3.1]	2.6 [2.1−3.2]
50% (Median) [95% CI]	5.7 [3.9−7.1]	5.7 [4.8−6.4]	4.8 [4.0−5.9]
25% [95% CI]	12.5 [9.2−14.9]	11.8 [9.2−14.2]	9.9 [7.5−12.3]

	0 line	1 line	2 lines	3 lines	> 3 lines
N	94	200	125	58	85
Missing	4 (4.26%)	24 (12.00%)	7 (5.60%)	4 (6.90%)	9 (10.59%)
Number of events	73 (77.66%)	146 (73.00%)	97 (77.60%)	47 (81.03%)	72 (84.71%)
Number of censored data	17 (18.09%)	30 (15.00%)	21 (16.80%)	7 (12.07%)	4 (4.71%)
75% [95% CI]	3.0 [2.4−3.5]	2.6 [2.1−3.1]	3.0 [2.2−3.4]	2.9 [1.8−4.1]	2.2 [1.9−3.1]
50% (Median) [95% CI]	5.7 [3.9−7.1]	5.9 [4.6−6.9]	4.9 [4.1−6.9]	7.0 [4.1−9.9]	4.1 [3.3−5.0]
25% [95% CI]	12.5 [9.2−14.9]	11.7 [9.2−15.1]	11.8 [8.2−16.2]	12.6 [9.9−15.7]	7.5 [5.2−10.5]

95% CI: 95% confidence interval.
Source: **Tables 3.6** and **3.7**

Table 10-33. Duration of exposure to Afinitor® + exemestane combination according to the duration of response to previous hormonal therapy: Kaplan-Meier estimates – Efficacy population (N = 562)

	Duration of response to previous hormonal therapy	
	≤ 6 months	> 6 months
N	77	328
Missing	8 (10.39%)	28 (8.54%)
Number of events	58 (75.32%)	255 (77.74%)
Number of censored data	11 (14.29%)	45 (13.72%)
75% [95% CI]	2.3 [1.8−2.9]	2.8 [2.2−3.2]
50% (Median) [95% CI]	4.4 [3.0−6.4]	5.7 [4.8−6.5]
25% [95% CI]	9.9 [7.0−15.9]	12.0 [9.9−13.9]

95% CI: 95% confidence interval.
Source: **Table 3.11**

10.4.4.3 Other treatment characteristics

As mentioned in **Section 9.9.5.1**, the following study objectives could not be addressed:

- Treatment doses and main reasons for dose reduction (Afinitor® and/or exemestane). Only the prescribed dose of Afinitor® and the first dose actually taken are described in the present report (see **Section 10.4.4.1**).
- Reason for interruption / treatment discontinuation (Afinitor® and/or exemestane).

10.4.5 Anticancer therapies prescribed after discontinuation of study treatment (Afinitor®, exemestane or their combination)

Anticancer therapies prescribed after discontinuation of study treatment (Afinitor®, exemestane or their combination) are described in **Table 3.15** for the efficacy population, only in patients for whom the date of last intake of Afinitor® and/or exemestane was confirmed. Full details for each patient are presented in **Listing 21**.

Results are summarised in in-text **Table 10-34** and are presented separately for patients who prematurely discontinued Afinitor® alone, exemestane alone, or the combination of both drugs.

The date of last Afinitor® intake was confirmed for 445 patients from the efficacy population. Of these 445 patients, 91 (20.5%) prematurely discontinued Afinitor® treatment alone. The majority of these patients (61/91, 67.0%) were prescribed other anticancer treatments after Afinitor® discontinuation. Continuation of exesmestane in monotherapy (50/61 participants, 82.0%) was reported as the most commonly prescribed anticancer treatment, followed by chemotherapy (7/61 patients, 11.5%), other treatments (5/61 patients, 8.2%), and hormone treatments excluding exemestane (1/61 patients, 1.6%). Other treatments included palbociclib for 3/5 patients (60%), bevacizumab for 1/5 patient (20%), and radiotherapy for 1/5 patient (20%) (**Listing 21**). Only 2 patients were prescribed combined anticancer therapy, consisting of ‘exemestane + other treatment’ in one patient and ‘chemotherapy + other treatment’ in the other patient. Full details about the number (%) of patients on monotherapy or combination therapy can be found in **Table 3.15**.

The date of last exemestane intake was confirmed for 411 patients from the efficacy population. Of these 411 patients, 57 (13.9%) prematurely discontinued exemestane treatment

alone. The majority of these patients (46/57, 80.7%) were prescribed other anticancer treatments after exemestane discontinuation. Initiation of other hormone treatments (26/46 patients, 56.5%) was reported as the most commonly prescribed anticancer treatment, followed by chemotherapy (19/46 patients, 41.3%), and other treatments (10/46 patients, 21.7%). Other treatments included palbociclib for 7/10 patients (70%), fulvestrant for 4/10 patients (40%), and bevacizumab for 1/10 patient (10%) (**Listing 21**). Nine patients were prescribed combined anticancer therapy, among whom, 6 received 'other hormone treatment + other treatment', 2 received 'other hormone treatment + chemotherapy', and one received 'chemotherapy + other treatment'. Full details about the number (%) of patients on monotherapy or combination therapy can be found in **Table 3.15**.

For 437 patients from the efficacy population, the date of last Afinitor® and exemestane intake was confirmed, as was the date of discontinuation of at least one of these treatments. Of these 437 patients, 347 (79.4%) prematurely discontinued the Afinitor® + exemestane combination. The majority of these patients (279/347, 80.4%) were subsequently prescribed other anticancer treatments, with chemotherapy (197/279, 70.6%) reported as the most common prescription, followed by hormone treatments excluding exemestane (71/279 patients, 25.5%), and other treatments (54/279 patients, 19.4%). Palbociclib (30/54 patients, 55.6%), fulvestrant (12/54 patients, 22.2%), targeted therapy (5/54 patients, 9.3%), bevacizumab (4/54 patients, 7.4%) and radiotherapy (4/54 patients, 7.4%) were the most commonly prescribed other treatments (**Listing 21**). Forty-three patients were prescribed combined anticancer therapy, with the majority of them (28/43) receiving the combination 'other hormone treatment + other treatment'. Full details about the number (%) of patients on monotherapy or combination therapy can be found in **Table 3.15**.

Table 10-34. Anticancer therapies prescribed after discontinuation of study treatment (Afinitor®, exemestane or their combination) – Efficacy population

Patients for whom the date of last Afinitor® intake was confirmed (N = 445)	
Premature discontinuation of Afinitor®	
N	445
Missing – *n (%[1])*	6 (1.35%)
No – *n (%[1])*	348 (78.20%)
Yes – *n (%[1])*	91 (20.45%)
If premature discontinuation, other anticancer treatment(s)	
N	91
No – *n (%)*	30 (32.97%)
Yes – *n (%)*	61 (67.03%)
If other anticancer treatment(s), therapeutic classe(s)[2]	
N	61
Continuation of exemestane alone – *n (%)*	50 (81.97%)
Other hormone treatments– *n (%)*	1 (1.64%)
Chemotherapy– *n (%)*	7 (11.48%)
Other treamtents – *n (%)*	5 (8.20%)
Patients for whom the date of last exemestane intake was confirmed (N = 411)	
Premature discontinuation of exemestane	
N	411
Missing – *n (%)*	6 (1.46%)
No – *n (%)*	348 (84.67%)
Yes – *n (%)*	57 (13.87%)
If premature discontinuation, other anticancer treatment(s)	
N	57
No – *n (%)*	11 (19.30%)
Yes – *n (%)*	46 (80.70%)
If other anticancer treatment(s), therapeutic classe(s)[1]	
N	46
Other hormone treatments – *n (%)*	26 (56.52%)
Chemotherapy – *n (%)*	19 (41.30%)
Other treamtents – *n (%)*	10 (21.74%)
Patients for whom the date of last Afinitor® and exemestane intake was confirmed, as was the date of discontinuation of at least one of these treatments (N = 437)	
Premature discontinuation of Afinitor® + exemestane combination	
N	437
Missing – *n (%)*	6 (1.37%)
No – *n (%)*	84 (19.22%)
Yes – *n (%)*	347 (79.41%)
If premature discontinuation, other anticancer treatment(s)	
N	347
Missing – *n (%)*	3 (0.86%)
No – *n (%)*	65 (18.73%)
Yes – *n (%)*	279 (80.40%)
If other anticancer treatment(s), therapeutic classe(s)[1]	
N	279
Missing – *n (%)*	2 (0.72%)
Other hormone treatments – *n (%)*	71 (25.45%)
Chemotherapy – *n (%)*	197 (70.61%)
Other treamtents – *n (%)*	54 (19.35%)

[1]Patients could have more than one other anticancer treatment; therefore the sum of the number of patients with each anticancer treatment can exceed the overall number of patients with at least one other anticancer treatment.
Source: **Table 3.15**

10.4.6 Efficacy

10.4.6.1 Tumour evaluation including best overall response

10.4.6.1.1 Overall analysis

Results from tumour evaluation performed during treatment with Afinitor® + exemestane combination are described in **Table 4.1** for the efficacy population. Summaries are presented in in-text **Table 10-35**.

Regarding best overall response (assessed using RECIST 1.1 criteria), 12/562 patients (2.1%) had a complete response, 98/562 patients (17.4%) had a partial response, 165/562 patients (29.4%) showed stable disease, and 125/562 patients (22.2%) showed progressive disease during treatment with Afinitor® + exemestane combination. The distribution of patients in the 4 RECIST categories should be treated with caution due to the high proportion of missing data (27.6%).

A total of 222 episodes of disease progression were reported during treatment with Afinitor® + exemestane combination. Of these 222 episodes, 138 (62.2%) were associated with development of new metastases. New metastases were mainly located in the liver (38.4%, 53/138) and bones (32.6%, 45/138). Other locations included, in decreasing order of frequency, other metastitic sites (18.8%, 26/138), lungs (18.1%, 25/138), lymph nodes (13.0%, 18/138), brain (7.3%, 10/138), and skin (3.6%, 5/138). At the time of study treatment prescription, bone metastases (459/591, 77.7%) predominated over all other metastatic sites, including the liver (178/591, 30.1%), lungs (141/591, 23.9%), and lymph nodes (136/591, 23.0%) (in-text **Table 10-8**).

New metastases were also classified as ‘unclassifiable’, ‘unique’ or ‘mutiple’ visceral metastases (refer to footnote of in-text **Table 10-35** for definitions of visceral metastases). Around 42.0% of metastases (58/138) were considered as ‘unique’ visceral metastases, 9.4% (13/138) as ‘multiple’ visceral metastases, and 16.7% (23/138) as ‘unclassifiable’ visceral metastases. The remainder (31.9%, 44/138) did not meet the definition of visceral metastases.

Table 10-35. Tumour evaluation during treatment with Afinitor® + exemestane combination – Efficacy population (N = 562)

Best overall response (assessed using RECIST 1.1 criteria)	
N	562
Missing – *n (%[1])*	155 (27.58%)
Complete Response – *n (%[1])*	12 (2.14%)
Partial Response – *n (%[1])*	98 (17.44%)
Stable Disease – *n (%[1])*	165 (29.36%)
Progressive Disease – *n (%[1])*	125 (22.24%)
Not Assessable – *n (%[1])*	7 (1.25%)
Episodes of disease progression and metastases	
Number of episodes of disease progression	222
If progression, apparition of new metastases	
Missing – *n (%[1])*	1 (0.45%)
No – *n (%[1])*	83 (37.39%)
Yes – *n (%[1])*	138 (62.16%)
Location of new metastases	
N	138
Lung (At least one) – *n (%)*	25 (18.12%)
Bone (At least one) – *n (%)*	45 (32.61%)
Liver (At least one) – *n (%)*	53 (38.41%)
Brain (At least one) – *n (%)*	10 (7.25%)
Lymph nodes (At least one) – *n (%)*	18 (13.04%)
Cutaneous (At least one) – *n (%)*	5 (3.62%)
Other (At least one) – *n (%)*	26 (18.84%)
Classification of visceral metastases	
N	138
No visceral metastases – *n (%)*	44 (31.88%)
Unique visceral metastases– *n (%)*	58 (42.03%)
Multiple visceral metastases– *n (%)*	13 (9.42%)
Unclassifiable visceral metastases– *n (%)*	23 (16.67%)

[1]Missing data were included in the calculation of percentages.
[2] *No visceral metastases*: metastases not located in lungs, liver, brain or 'other'.
Unique visceral metastases: metastases located only in lungs, liver or brain.
Multiple visceral metastases: metastases located in at least 2 of the 3 following sites: lungs, liver or brain.
Unclassifiable visceral metastases: metastases located in lungs, liver and/or brain AND in 'other'. This applies to unique and multiple visceral metastases.
RECIST: Response Evaluation Criteria In Solid Tumors.
Source: **Table 4.1**

10.4.6.1.2 Subgroup analyses

Tumour evaluation including best overall response was also described by age group and according to several other risk factors as depicted below:

Risk factors	Subgroups	Tables/Figures
Age	< 70 years *versus* ≥ 70 years < 75 years *versus* ≥ 75 years	**Table 4.2** **Table 4.3**
Number of previous lines of treatment in metastatic setting	0, 1−2 *versus* ≥ 3 lines 0, 1, 2, 3 *versus* > 3 lines	**Table 4.4** **Table 4.5**
Visceral metastases at inclusion	Presence *versus* absence	**Table 4.6**
Type of previous hormonal therapy	≥1 SAI *versus* ≥ 1 antioestrogen	**Table 4.7**
Interval to recurrence with respect to stop of adjuvant hormonal treatment	0 month,]0−12 months] *versus* > 12 months	**Table 4.8**
Duration of response to previous hormonal therapy	≤ 6 months *versus* > 6 months	**Table 4.9**
Pulmonary or hepatic metastases at inclusion	Presence *versus* absence	**Table 4.10**
Bone metastases at inclusion	Presence of bone-only metastases *versus* Presence of bone and non-bone metastases *versus* Absence of bone metastases	**Table 4.11**

SAI: Steroidal aromatase inhibitor.

Subgroup analyses performed on the the best overall response were also largely influenced by the proportion of missing data. Also, for several subgroup analyses (age, number of previous lines of treatment, duration of reponse to previous hormonal therapy, presence or absence of bone metastases), the proportion of missing data was not balanced between subgroups of interest, making comparisons unconclusive. Overall, no clear associations were found between overall response rates and risk factors evaluated in the study.

Special attention was given to development and location of new metastases in patients (in case of disease progression) with or without visceral, pulmonary/hepatic, or bone metastases at inclusion. The incidence of new metastases was found to be higher in patients without visceral metastases (65.2% [60/92] *versus* 59.5% [69/116]) or without pulmonary/hepatic metastases (65.8% [79/120] *versus* 57.8% [59/102]) at inclusion. This trend, however, was not confirmed by the subgroup analysis on bone metastases; incidence of new metastases was 67.7% (46/68) in patients with bone-only metastases, 61.4% (62/101) in patients with bone and non-bone metastases, and 56.6% (30/53) in patients without bone metastases.

For location of new metastases, only patients who progressed during treatment with Afinitor® + exemestane combination were considered in the analysis. The percentage of new metastases located in the liver, lungs, and brain was higher in the subgroup of patients with visceral metastases at inclusion (46.4% [32/69], 21.7% [15/69], and 10.1% [7/69], respectively) compared with the subgroup without visceral metastases (31.7% [19/60], 15.0% [9/60], and 5.0% [3/60], respectively). Similarly, the percentage of new metastases located in the liver and the lungs was higher in the subgroup of patients with pulmonary/hepatic metastases at inclusion (50.9% [30/59] and 22.0% [13/59], respectively) compared with the subgroup without pulmonary/hepatic metastases (29.1% [23/79] and 15.2% [12/79], respectively). Finally, the percentage of new metastases located in the bones was higher in the subgroups of patients with bones metastases at inclusion (47.8% [22/46] for

bone-only metastases and 29.0% [18/62] for bone and non-bone metastases) compared with the subgroup without bone metastases (16.7% [5/30]).

10.4.6.2 Progression-free survival

As mentioned in **Section 9.8.3.7**, the PFS time (months) was defined as the time elapsed between the first dose of Afinitor® and tumour progression, death from any cause or follow-up discontinuation, whichever came first.

10.4.6.2.1 Overall analysis

The main analysis was performed by excluding data collected after M12, i.e. data reported in the last contact form. PFS results based on the main analysis are described in **Table 4.12** and are graphically displayed in **Figure 4.1**. Summaries are presented in in-text **Table 10-36**.

In the efficacy population (N = 562), 377 patients (67.1%) experienced disease progression or death during the 12-month follow-up period, with disease progression reported for 351 patients (93.1%) and death for 26 patients (6.9%). The PFS time ranged from 0.4 to 15.1 months, with a median value (i.e. time after which 50% of patients had progressed or died) of 6.9 months (95% CI: 6.2−7.8). PFS rates (i.e. proportions of patients without progression or death at different time points) gradually decreased over time and were 80.2%, 55.8%, 40.1%, and 27.6% at 3, 6, 9, and 12 months, respectively.

A sensitivity analysis was conducted on all available data, including those collected after M12 via the last contact form. These results are described in **Table 4.13** and are graphically displayed in **Figure 3.2**. Overall, results from the sensivity analysis confirmed those from the main analysis. As all available data were included in the sensitivity analysis, the number of patients experiencing disease progression or death was higher (414/562, 73.7%), as was the maximum PFS time (27.8 months). No other differences were found between the main analysis and the sensitivity analysis as shown in in-text **Table 10-36**.

Table 10-36. PFS: Kaplan-Meier estimates – Efficacy population (N = 562)

	Main analysis (post-M12 data excluded)	Sensitivity analysis (all available data)
N	562	562
Missing	1 (0.18%)	1 (0.18%)
Number of events	377 (67.08%)	414 (73.67%)
Progression	351 (93.10%)	387 (93.48%)
Death	26 (6.90%)	27 (6.52%)
Number of censored data	184 (32.74%)	147 (26.16%)
[Min ; Max]	[0.36 ; 15.14]	[0.36 ; 27.76]
75% [95% CI]	3.4 [3.2−3.9]	3.4 [3.2−3.9]
50% (Median) [95% CI]	6.9 [6.2−7.8]	6.9 [6.2−7.8]
25% [95% CI]	12.5 [11.8−12.9]	12.7 [11.9−14.5]
PFS rate at 3 months – *n (%)*	418 (80.2%)	420 (80.2%)
PFS rate at 6 months – *n (%)*	274 (55.8%)	275 (55.9%)
PFS rate at 9 months – *n (%)*	191 (40.1%)	192 (40.2%)
PFS rate at 12 months – *n (%)*	74 (27.6%)	115 (28.5%)

95% CI: 95% confidence interval; M: Month; Min & Max: Minimum and maximum; PFS: Progression-free survival.
Source: **Tables 4.12** and **4.13**

10.4.6.2.2 Subgroup analyses

PFS times and rates were also described by age group and according to several other risk factors as depicted below:

Risk factors	Subgroups	Tables/Figures
Age	< 70 years *versus* ≥ 70 years < 75 years *versus* ≥ 75 years	**Table 4.14/Figure 4.3** **Table 4.15/Figure 4.4**
Number of previous lines of treatment in metastatic setting	0, 1−2 *versus* ≥ 3 lines 0, 1, 2, 3 *versus* > 3 lines	**Table 4.16/Figure 4.5** **Table 4.17/Figure 4.6**
Visceral metastases at inclusion	Presence *versus* absence	**Table 4.18/Figure 4.7**
Type of previous hormonal therapy	≥1 SAI *versus* ≥ 1 antioestrogen	**Table 4.19/Figure 4.8**
Interval to recurrence with respect to stop of adjuvant hormonal treatment	0 month,]0−12 months] *versus* > 12 months	**Table 4.20/Figure 4.9**
Duration of response to previous hormonal therapy	≤ 6 months *versus* > 6 months	**Table 4.21/Figure 4.10**
Dose of the first Afinitor® intake	5 mg *versus* 10 mg	**Table 4.22/Figure 4.11**
Pulmonary or hepatic metastases at inclusion	Presence *versus* absence	**Table 4.23/Figure 4.12**
Bone metastases at inclusion	Presence of bone-only metastases *versus* Presence of bone and non-bone metastases *versus* Absence of bone metastases	**Table 4.24/Figure 4.13**

SAI: Steroidal aromatase inhibitor.

Only data collected until M12 visit were considered in these subgroup analyses.

Among Kaplan-Meier estimates, we selected the median PFS time to compare subgroups of interest. The main findings can be summarised as follows:

- The median [95% CI] PFS time tended to be lower in patients aged ≥ 70 years (6.7 [5.4−7.8] months, N = 207) than in those aged < 70 years (7.3 [6.3−8.3] months, N = 355). Differences between subgroups were even higher when the threshold for age was 75 years (5.7 [4.3−7.4] months in ≥ 75-year age group [N = 125] and 7.4 [6.4−8.6] months in < 75-year age group [N = 437]) (in-text **Table 10-37**).
- The median [95% CI] PFS time tended to be lower in patients with visceral metastases at inclusion (5.7 [5.0−6.7] months, N = 269) than in those without visceral metastases (8.6 [6.9−9.5] months, N = 259). A similar association was found with pulmonary/hepatic metastases; the median [95% CI] PFS time tended to be lower in patients with pulmonary or hepatic metastases (5.7 [5.0−6.7] months, N = 244) than in those without metastases (8.1 [6.9−9.1] months, N = 318). In contrast, presence of bone-only metastases did not seem to be associated with lower PFS values (7.7 [6.3−9.3] months, N = 184 *versus* 7.8 [5.9−9.2] months in the absence of bone metastases, N = 128) (in-text **Table 10-38**).
- The median [95% CI] PFS time tended to decrease with the number of previous lines of treatment in metastatic setting (8.1 [5.9−10.2] [N = 94], 7.5 [6.6−8.7] [N = 325], and 5.4 [4.4−6.6] [N = 143] months for 0, 1-2, ≥ 3 previous lines of treatment, respectively) (in-text **Table 10-39**).

- The median [95% CI] PFS time seemed to be associated with the type of previous hormonal therapy (≥ 1 SAI *versus* ≥ 1 antioestrogen), the duration of response to previous hormonal therapy (≤ 6 months *versus* > 6 months), and the interval to recurrence with respect to stop of adjuvant hormonal therapy (0 month,]0−12 months] *versus* > 12 months). Patients with at least one SAI had shorter PFS time (5.9 [4.8−7.0] months, N = 105) than patients with at least one antiestrogen (7.0 [6.0−8.1] months, N = 354). Similarly, patients with shorter duration of response to previous hormonal therapy had shorter PFS time (5.0 [3.4−7.1] months, N = 77) than patients with longer duration of response (7.5 [6.2−8.8] months, N = 328). Finally, patients who experienced recurrence more than 12 months after discontinuation of adjuvant hormonal therapy had longer PFS time (8.3 [6.6−9.5] months, N = 114) than those who experienced recurrence at time of discontinuation (6.6 [5.7−8.1] months, N = 137) or within 12 months after discontinuation (6.2 [4.8−8.6] months, N = 45) (in-text **Table 10-40**).
- Trends described above should be interpreted with caution because the 95% CI associated with the median PFS time overlapped between subgroups. The only exceptions were subgroup analyses on visceral metastases and pulmonary/hepatic metastases (where 95% CI did not overlap).
- No differences were found between patients who started Afinitor® treatment at a dose of 5 mg/day and those treated at a dose of 10 mg/day (7.0 [5.2−8.6] months and 6.7 [5.9−7.8] months, respectively).

Table 10-37. PFS by age (until M12): Kaplan-Meier estimates – Efficacy population (N = 562)

	< 70 years	**≥ 70 years**
N	355	207
Missing	0 (0.00%)	1 (0.48%)
Number of events	234 (65.92%)	143 (69.08%)
Number of censored data	121 (34.08%)	63 (30.43%)
75% [95% CI]	3.7 [3.1−4.3]	3.4 [2.9−3.9]
50% (Median) [95% CI]	7.3 [6.3−8.3]	6.7 [5.4−7.8]
25% [95% CI]	12.7 [12.0− .]	11.8 [9.5−12.7]
	< 75 years	**≥ 75 years**
N	437	125
Missing	0 (0.00%)	1 (0.80%)
Number of events	286 (65.45%)	91 (72.80%)
Number of censored data	151 (34.55%)	33 (26.40%)
75% [95% CI]	3.8 [3.3−4.2]	3.1 [2.7−3.4]
50% (Median) [95% CI]	7.4 [6.4−8.6]	5.7 [4.3−7.4]
25% [95% CI]	12.7 [12.1−15.1]	10.2 [8.6−12.3]

95% CI: 95% confidence interval; M: Month; PFS: Progression-free survival.
Source: **Tables 4.14** and **4.15**

Table 10-38. PFS according to the presence of metastases (until M12): Kaplan-Meier estimates – Efficacy population (N = 562)

	Absence of visceral metastases	Presence of visceral metastases
N	259	269
Missing	0 (0.00%)	1 (0.37%)
Number of events	155 (59.85%)	199 (73.98%)
Number of censored data	104 (40.15%)	69 (25.65%)
75% [95% CI]	3.9 [3.2−4.8]	3.2 [2.8−3.5]
50% (Median) [95% CI]	8.6 [6.9−9.5]	5.7 [5.0−6.7]
25% [95% CI]	13.8 [12.3−15.1]	11.0 [9.3−12.6]
	Absence of pulmonary and hepatic metastases	**Presence of pulmonary or hepatic metastases**
N	318	244
Missing	0 (0.00%)	1 (0.41%)
Number of events	199 (62.58%)	178 (72.95%)
Number of censored data	119 (37.42%)	65 (26.64%)
75% [95% CI]	4.0 [3.4−4.7]	3.2 [2.6−3.5]
50% (Median) [95% CI]	8.1 [6.9−9.1]	5.7 [5.0−6.7]
25% [95% CI]	13.8 [12.1−15.1]	11.6 [9.3−12.7]

	Absence of bone metastases	Presence of bone−only metastases	Presence of bone and non−bone metastases
N	128	184	250
Missing	1 (0.78%)	0 (0.00%)	0 (0.00%)
Number of events	86 (67.19%)	112 (60.87%)	179 (71.60%)
Number of censored data	41 (32.03%)	72 (39.13%)	71 (28.40%)
75% [95% CI]	3.9 [3.2−4.7]	3.6 [3.0−4.5]	3.3 [2.8−3.7]
50% (Median) [95% CI]	7.8 [5.9−9.2]	7.7 [6.3−9.3]	6.0 [5.2−6.9]
25% [95% CI]	12.6 [11.8− .]	15.1 [12.2−15.1]	11.6 [9.5−12.7]

95% CI: 95% confidence interval; M: Month; PFS: Progression-free survival.
Source: **Tables 4.18**, **4.23** and **4.24**

Table 10-39. PFS time according to the number of previous lines of treatment in metastatic setting (until M12): Kaplan-Meier estimates – Efficacy population (N = 562)

	0 line	1−2 lines	≥ 3 lines
N	94	325	143
Missing	1 (1.06%)	0 (0.00%)	0 (0.00%)
Number of events	54 (57.45%)	216 (66.46%)	107 (74.83%)
Number of censored data	39 (41.49%)	109 (33.54%)	36 (25.17%)
75% [95% CI]	4.1 [3.4−5.3]	3.8 [3.2−4.4]	2.8 [2.2−3.3]
50% (Median) [95% CI]	8.1 [5.9−10.2]	7.5 [6.6−8.7]	5.4 [4.4−6.6]
25% [95% CI]	NR [12.3− .]	12.6 [11.8−12.9]	11.0 [9.1−14.2]

	0 line	1 line	2 lines	3 lines	> 3 lines
N	94	200	125	58	85
Missing	1 (1.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Number of events	54 (57.45%)	135 (67.50%)	81 (64.80%)	39 (67.24%)	68 (80.00%)
Number of censored data	39 (41.49%)	65 (32.50%)	44 (35.20%)	19 (32.76%)	17 (20.00%)
75% [95% CI]	4.1 [3.4−5.3]	3.7 [2.8−4.4]	4.0 [3.0−4.8]	3.2 [2.2−5.6]	2.6 [1.5−3.2]
50% (Median) [95% CI]	8.1 [5.9−10.2]	7.7 [6.4−9.2]	7.5 [6.2−8.3]	7.6 [5.6−11.0]	4.3 [3.4−5.2]
25% [95% CI]	NR [12.3− .]	12.5 [11.7−15.1]	12.6 [10.1− .]	13.8 [10.1−14.2]	9.1 [5.5−11.4]

95% CI: 95% confidence interval; M: Month; NR: Not reached; PFS: Progression-free survival.
Source: **Tables 4.16** and **4.17**

Table 10-40. PFS according to the type of previous hormonal therapy, duration of response to previous hormonal therapy, and interval to recurrence with respect to stop of adjuvant hormonal therapy (until M12): Kaplan-Meier estimates – Efficacy population

	Type of previous hormonal therapy	
	≥ 1 SAI	≥ 1 antioestrogen
N	105	354
Missing	0 (0.00%)	1 (0.28%)
Number of events	82 (78.10%)	244 (68.93%)
Number of censored data	23 (21.90%)	109 (30.79%)
75% [95% CI]	3.2 [2.2−3.9]	3.4 [3.0−4.1]
50% (Median) [95% CI]	5.9 [4.8−7.0]	7.0 [6.0−8.1]
25% [95% CI]	10.2 [9.0−11.9]	12.2 [11.4−12.7]
	Duration of response to previous hormonal therapy	
	≤ 6 months	**> 6 months**
N	77	328
Missing	0 (0.00%)	0 (0.00%)
Number of events	58 (75.32%)	216 (65.85%)
Number of censored data	19 (24.68%)	112 (34.15%)
75% [95% CI]	2.6 [1.8−3.3]	3.8 [3.2−4.3]
50% (Median) [95% CI]	5.0 [3.4−7.1]	7.5 [6.2−8.8]
25% [95% CI]	11.6 [8.8− .]	12.6 [11.9−14.2]
	Interval to recurrence with respect to stop of adjuvant hormonal therapy		
	0 month,	**]0−12 months]**	**> 12 months**
N	137	45	114
Missing	0 (0.00%)	0 (0.00%)	1 (0.88%)
Number of events	89 (64.96%)	37 (82.22%)	74 (64.91%)
Number of censored data	48 (35.04%)	8 (17.78%)	39 (34.21%)
75% [95% CI]	3.4 [2.8−4.0]	4.3 [2.8−5.1]	3.9 [2.9−4.8]
50% (Median) [95% CI]	6.6 [5.7−8.1]	6.2 [4.8−8.6]	8.3 [6.6−9.5]
25% [95% CI]	12.6 [9.3− .]	10.1 [7.5−15.1]	12.7 [11.2−14.2]

95% CI: 95% confidence interval; M: Month. PFS: Progression-free survival; SAI: Steroidal aromatase inhibitor.
Source: **Tables 4.19−21**

10.4.6.3 Overall survival

As mentioned in **Section 9.8.3.7**, the OS time (months) was defined as the time elapsed between the first dose of Afinitor® and death from any cause or follow-up discontinuation, whichever came first.

10.4.6.3.1 Overall analysis

OS results are described in **Table 4.25** and are graphically displayed in **Figure 4.14**. Summaries are presented in in-text **Table 10-41**.

In the efficacy population (N = 562), 46 patients (8.2%) died during the observation period. OS time ranged from 0.4 to 27.8 months. As more than 75% of patients remained alive at the end of the observation period, the 75th quartile, median, and 25th quartile OS times could not be determined. OS rates (i.e. proportions of patients still alive at different time points) gradually decreased over time from 97.5% at Month 3 to 88.2% at Month 12.

Table 10-41. OS: Kaplan-Meier estimates – Efficacy population (N = 562)

	Kaplan Meier estimates
N	562
Missing	1 (0.18%)
Number of events	46 (8.19%)
Number of censored data	515 (91.64%)
[Min ; Max]	[0.36 ; 27.76]
75% [95% CI]	NR [22.7− .]
50% (Median) [95% CI]	NR [.− .]
25% [95% CI]	NR [.− .]
OS rate at 3 months – *n (%)*	452 (97.5%)
OS rate at 6 months – *n (%)*	317 (93.8%)
OS rate at 9 months – *n (%)*	233 (91.8%)
OS rate at 12 months – *n (%)*	146 (88.2%)

95% CI: 95% confidence interval; Min & Max: Minimum and maximum; NR: Not reached; OS: Overall survival.
Source: **Tables 4.25**

10.4.6.3.2 Subgroup analyses

OS times and rates were also described by age group and according to several other risk factors as depicted below:

Risk factors	Subgroups	Tables/Figures
Age	< 70 years *versus* ≥ 70 years	**Table 4.26/Figure 4.15**
	< 75 years *versus* ≥ 75 years	**Table 4.27/Figure 4.16**
Number of previous lines of treatment in metastatic setting	0, 1−2 *versus* ≥ 3 lines	**Table 4.28/Figure 4.17**
	0, 1, 2, 3 *versus* > 3 lines	**Table 4.29/Figure 4.18**
Visceral metastases at inclusion	Presence *versus* absence	**Table 4.30/Figure 4.19**
Type of previous hormonal therapy	≥1 SAI *versus* ≥ 1 antioestrogen	**Table 4.31/Figure 4.20**
Interval to recurrence with respect to stop of adjuvant hormonal treatment	0 month,]0−12 months] *versus* > 12 months	**Table 4.32/Figure 4.21**
Duration of response to previous hormonal therapy	≤ 6 months *versus* > 6 months	**Table 4.33/Figure 4.22**
Dose of the first Afinitor® intake	5 mg *versus* 10 mg	**Table 4.34/Figure 4.23**
Pulmonary or hepatic metastases at inclusion	Presence *versus* absence	**Table 4.35/Figure 4.24**
Bone metastases at inclusion	Presence of bone-only metastases *versus* Presence of bone and non-bone metastases *versus* Absence of bone metastases	**Table 4.36/Figure 4.25**

SAI: Steroidal aromatase inhibitor.

More than 75% of patients remained alive in most subgroups of interest, thereby precluding calculation of 75th quartile, median, and 25th quartile OS times. In addition, the number of patients who died during the observation period was very low, making description of results by subgroup not very informative.

10.4.6.4 ECOG-PS

The maximum ECOG-PS value reported by the patients during the observation period is described in **Table 4.37** for the efficacy population. The maximum ECOG-PS value was 0 for 81/562 patients (14.4%), 1 for 292/562 patients (52.0%), 2 for 132/562 patients (23.5%), 3 for 37/562 patients (6.6%) and 4 for 5/562 patients (0.9%).

A shift table for ECOG (ECOG class at inclusion versus highest ECOG class during follow-up) is provided in **Table 4.38** for the efficacy population.

10.5 Other analyses

Not applicable.

10.6 Adverse events excluding stomatitis and NIP

10.6.1 Duration of exposure to Afinitor®

The total duration of exposure to Afinitor® was calculated on patients for whom the discontinuation of Afinitor® treatment was documented and confirmed. These results are provided in **Table 1.1.6** for the safety population.

The duration of exposure to Afinitor® ranged from 1 day to 23.1 months, with a median value of 4.3 months (N = 471). Similar analyses were repeated by excluding data collected after M12, i.e. data reported in the last contact form. As expected, the median duration of exposure to Afinitor® was slightly lower in this case and was 3.9 months (range: 1 day−13.9 months; N = 429). As mentioned above, these data were collected on a subset of patients, i.e. patients for whom the discontinuation of Afinitor® treatment was confirmed. Therefore, they are not representative of the whole study population and need to be interpreted with caution.

10.6.2 Brief summary of adverse events

An overview of **all AE** reported over the course of the study is provided in **Section 10.4.1**. Main results are summarised herebelow:

- A total of 559/596 patients (93.8%) experienced at least one AE over the course of the study. For 509/596 patients (85.4%), at least one AE was considered as related to Afinitor®.
- 167/596 patients (28.0%) experienced at least one SAE over the course of the study. For 90/596 patients (15.1%), at least one SAE was considered as related to Afinitor®.
- 48/596 patients (8.1%) experienced at least one AE leading to death over the course of the study. For 5/596 patients (0.8%), at least one fatal event was considered as related to Afinitor®.

In the present section, focus is given to **all AE excluding stomatitis and NIP** reported over the course of the study. A brief summary of these events is presented in in-text **Table 10-42** for the safety population.

The main results were as follows:

- A total of 503/596 patients (84.4%) experienced at least one AE (excluding stomatitis and NIP) over the course of the study. For 418/596 patients (70.1%), at least one AE was considered as related to Afinitor®.
- 136/596 patients (22.8%) experienced at least one SAE (excluding stomatitis and NIP) over the course of the study. For 55/596 patients (9.2%), at least one SAE was considered as related to Afinitor®.

- 48/596 patients (8.1%) experienced at least one AE leading to death over the course of the study. For 5/596 patients (0.8%), at least one fatal event was considered as related to Afinitor®.
- 160/596 patients (26.9%) experienced at least one AE leading to dose reduction or temporary interruption of Afinitor® over the course of the study. For 140/596 patients (23.5%), at least one of these events was considered as related to Afinitor®.
- 102/596 patients (17.1%) experienced at least one AE leading to permanent discontinuation of Afinitor® over the course of the study. For 78/596 patients (13.1%), at least one of these events was considered as related to Afinitor®.

Table 10-42. Summary of AE excluding stomatitis and NIP – Safety population (N = 596)

Number (%[1]) of patients with:	Related or not to Afinitor®	Related to Afinitor®
≥ 1 AE	503 (84.40%)	418 (70.13%)
≥ 1 SAE	136 (22.82%)	55 (9.23%)
≥ 1 AE leading to death	48 (8.05%)	5 (0.84%)
≥ 1 AE leading to a dose reduction or temporary interruption of Afinitor®	160 (26.85%)	140 (23.49%)
≥ 1 AE leading to permanent discontinuation of Afinitor®	102 (17.11%)	78 (13.09%)

[1]Percentages were calculated on the total number of patients in the safety population (N = 596).
(S)AE: (Serious) adverse event.
Source: **Table 2.3.1**

10.6.3 Adverse events by system organ class (SOC) and preferred term (PT)

AE (excluding stomatitis and NIP) observed in ≥ 10% of patients are summarised by SOC/PT in in-text **Table 10-43**.

Overall, 503/596 patients (84.4%) experienced at least one AE over the course of the study; for 418/596 patients (70.1%), at least one AE was considered as related to Afinitor®.

The most common AE (incidence ≥ 10%) were in decreasing order of frequency:

- *Asthenia* (general disorders and administration site conditions SOC): 140/596 patients (23.5%) including 111/596 (18.6%) for whom this event was considered as related to Afinitor®.
- *Diarrhoea* (gastrointestinal disorders SOC): 86/596 patients (14.4%) including 67/596 (11.2%) for whom this event was considered as related to Afinitor®.
- *Rash* (skin and subcutaneous tissue disorders SOC): 67/596 patients (11.2%) including 61/596 (10.2%) for whom this event was considered as related to Afinitor®.

More summary information on AE is provided in **Table 2.3.2** and full details for each patient are presented in **Listing 15**.

Table 10-43. AE excluding stomatitis and NIP observed in ≥ 10%[1] of patients by SOC and PT – Safety population (N = 596)

SOC *PT*	Number (%[2]) of patients with AE **related or not** to Afinitor®	Number (%[2]) of patients with AE **related** to Afinitor®
Total[3]	503 (84.4%)	418 (70.1%)
General disorders and administration site conditions	261 (43.8%)	191 (32.0%)
Asthenia	*140 (23.5%)*	*111 (18.6%)*
Gastrointestinal disorders	185 (31.0%)	137 (23.0%)
Diarrhoea	*86 (14.4%)*	*67 (11.2%)*
Skin and subcutaneous tissue disorders	171 (28.7%)	151 (25.3%)
Rash	*67 (11.2%)*	*61 (10.2%)*

[1]Only PT observed in ≥ 10% of patients are presented. The selection was performed on all AE (related or not to Afinitor®).
[2]Number (%) of patients with at least one AE. Percentages were calculated on the total number of patients in the safety population (N = 596).
[3]Patients could have more than one event; therefore, the sum of the number of patients with each event can exceed the overall number of patients with at least one event.
AE: Adverse event; NIP: Non-infectious pneumopathy; PT: Preferred term; SOC: System organ class.
Source: **Table 2.3.2**

10.6.4 Adverse events by SOC/PT and severity grade

Overall, incidence of AE decreased with severity grade; the majority of AE were grade 1 or 2 and a small proportion of them were grade 4 or 5.

AE (excluding stomatitis and NIP) observed in ≥ 10% of patients are summarised by SOC/PT and severity grade (grades 1−2, grade 3, grades 4−5) in in-text **Table 10-44**.

As reported in **Section 10.6.3**, *asthenia* (general disorders and administration site conditions SOC), *diarrhoea* (gastrointestinal disorders SOC), and *rash* (skin and subcutaneous tissue disorders SOC) were the most common AE. These events were mainly grade 1 or 2 in severity:

- *Asthenia*: the most severe episode was grade 1 or 2 for 126/596 patients (21.1%), grade 3 for 12/596 patients (2.0%), and grade 4 or 5 for 1/596 patients (0.2%).
- *Diarrhoea*: the most severe episode was grade 1 or 2 for 81/596 patients (13.6%), grade 3 for 3/596 patients (0.5%), and grade 4 or 5 for 1/596 patients (0.2%).
- *Rash*: the most severe episode was grade 1 or 2 for 66/596 patients (11.1%) and grade 3 for 1/596 patients (0.2%).

Asthenia, *diarrhea*, and *rash* related to Afinitor® were also mainly recorded in the lowest severity category (grades 1−2). It should be noted that none were grade 4 or 5 in severity.

More summary information on AE by severity grade is provided in **Table 2.3.8** and full details for each patient are presented in **Listing 15**.

Table 10-44. AE excluding stomatitis and NIP observed in ≥ 10%[1] of patients by SOC/PT and severity grade (most severe[2]) – Safety population (N = 596)

SOC *PT*	Number (%[3]) of patients with AE **related or not** to Afinitor®			Number (%[3]) of patients with AE **related** to Afinitor®		
	Grades 1−2	Grade 3	Grades 4−5	Grades 1−2	Grade 3	Grades 4−5
General disorders and administration site conditions	208 (34.9%)	23 (3.9%)	30 (5.0%)	168 (28.2%)	19 (3.2%)	3 (0.5%)
Asthenia	*126 (21.1%)*	*12 (2.0%)*	*1 (0.2%)*	*100 (16.8%)*	*10 (1.7%)*	*0 (0.0%)*
Gastrointestinal disorders	169 (28.4%)	10 (1.7%)	5 (0.8%)	131 (22.0%)	5 (0.8%)	0 (0.0%)
Diarrhoea	*81 (13.6%)*	*3 (0.5%)*	*1 (0.2%)*	*64 (10.7%)*	*2 (0.3%)*	*0 (0.0%)*
Skin and subcutaneous tissue disorders	165 (27.7%)	6 (1.0%)	0 (0.0%)	146 (24.5%)	5 (0.8%)	0 (0.0%)
Rash	*66 (11.1%)*	*1 (0.2%)*	*0 (0.0%)*	*60 (10.1%)*	*1 (0.2%)*	*0 (0.0%)*

[1]Only PT observed in ≥ 10% of patients are presented. The selection was performed on all AE (related or not to Afinitor®).
[2]If a patient experienced several episodes of the same event, only the highest severity grade was counted in the corresponding PT. Similarly, if a patient experienced several events from the same SOC, only the highest severity grade was counted in this SOC.
[3]Number (%) of patients with at least one AE in each severity grade. Percentages were calculated on the total number of patients in the safety population (N = 596).
AE: Adverse event; NIP: Non-infectious pneumopathy; PT: Preferred term; SOC: System organ class.
Source: **Table 2.3.8**

In addition to NIP, hypersensitivity reactions (anaphylactic reactions) have been identified in the Risk Management Plan for Afinitor® as important, identified and potential risks that need close monitoring.

In the safety population, 1/596 patient (0.2%) experienced grade 2 (moderate) *drug hypersensitivy* (immune system disorders SOC) considered as related to Afinitor® by the physician (**Tables 2.3.2** and **2.3.8**).

Several AE included in the skin and subcutaneous tissue disorders SOC can be considered as clinical manifestations of hypersensitivity reactions. Therefore, results of this SOC are more throroughly described hereafter.

A total of 171/596 patients (28.7%) experienced at least one AE included in the skin and subcutaneous tissue disorders SOC; for 151/596 patients (25.3%), at least one of these events was considered as related to Afinitor® (**Table 2.3.2**).

As shown in **Table 2.3.8**, AE included in the skin and subcutaneous tissue disorders SOC and considered as related to Afinitor® were mainly grade 1 or 2 in severity:

- The most severe event was rated grade 1 or 2 in severity for 146/596 patients (24.5%) and grade 3 for 5/596 patients (0.8%).
- No patient reported grade 4 or 5 events.

10.6.5 Serious adverse events by SOC and PT

SAE (excluding stomatitis and NIP) observed in ≥ 1% of patients are summarised by SOC/PT in in-text **Table 10-45**.

Overall, 136/596 patients (22.8%) experienced at least one SAE (excluding stomatitis and NIP) over the course of the study; for 55/596 patients (9.2%), at least one SAE was considered as related to Afinitor®.

The most common SAE (incidence ≥ 1%), regardless of causal relationship with Afinitor®, were:

- *General physical health deterioration, disease progression* and *asthenia* (all classified in the general disorders and administration site conditions SOC): 18/596 patients (3.0%), 15/596 patients (2.5%), and 12/596 patients (2.0%), respectively.
- *Anaemia* (blood and lymphatic system disorders SOC): 9/596 patients (1.5%).
- *Decreased appetite* (metabolism and nutrition disorders SOC): 8/596 patients (1.3%).
- *Dyspnoea* (respiratory, thoracic and mediastinal disorders SOC): 8/596 patients (1.3%).
- *Renal failure* (renal and urinary disorders SOC): 6/596 patients (1.0%).

Note:

*As indicated in **Section 9.4.3.1**, disease progressions were to be exempted from AE reporting except for those with a fatal outcome. All 15 cases of disease progression reported here led to*

*death and were graded 5 in severity as per CTCAE grading criteria (**Table 2.3.7, Listings 17 and 20**).*

The most common SAE related to Afinitor® (incidence ≥ 1%) was *asthenia*, which was reported by 9/596 patients (1.5%).

More summary information on SAE is provided in **Table 2.3.4** and full details for each patient are presented in **Listing 17**. Full narratives of SAE related to Afinitor®, extracted from the Pharmacovigilance database, are provided in **Annex 1**. Finally, SAE by SOC/PT observed in ≥ 2% of patients are presented in **Table 2.3.3**.

Table 10-45. SAE excluding stomatitis and NIP observed in ≥ 1% of patients[1] by SOC and PT – Safety population (N = 596)

SOC *PT*	Number (%[2]) of patients with SAE **related or not** to Afinitor®	Number (%[2]) of patients with SAE **related** to Afinitor®
Total[3]	136 (22.8%)	55 (9.2%)
General disorders and administration site conditions	46 (7.7%)	16 (2.7%)
General physical health deterioration	*18 (3.0%)*	*2 (0.3%)*
Disease progression	*15 (2.5%)*	*0 (0.0%)*
Asthenia	*12 (2.0%)*	*9 (1.5%)*
Blood and lymphatic system disorders	17 (2.9%)	9 (1.5%)
Anaemia	*9 (1.5%)*	*5 (0.8%)*
Metabolism and nutrition disorders	20 (3.4%)	10 (1.7%)
Decreased appetite	*8 (1.3%)*	*5 (0.8%)*
Respiratory, thoracic and mediastinal disorders	25 (4.2%)	9 (1.5%)
Dyspnoea	*8 (1.3%)*	*0 (0.0%)*
Renal and urinary disorders	8 (1.3%)	5 (0.8%)
Renal failure	*6 (1.0%)*	*4 (0.7%)*

[1]Only PT observed in ≥ 1% of patients are presented. The selection was performed on all SAE (related or not to Afinitor®).
[2]Number (%) of patients with at least one SAE. Percentages were calculated on the total number of patients in the safety population (N = 596).
[3]Patients could have more than one event; therefore, the sum of the number of patients with each event can exceed the overall number of patients with at least one event.
NIP: Non-infectious pneumopathy; PT: Preferred term ; SAE: Serious adverse event; SOC: System organ class.
Source: **Table 2.3.4**

10.6.6 Adverse events leading to death by SOC and PT

Table 2.3.7 presents the number of patients with at least one AE leading to death by SOC/PT. These AE are listed per patient in **Listing 20**.

Overall, 48/596 patients (8.1%) experienced at least one AE leading to death over the course of the study; for 5/596 patients (0.8%), at least one fatal event was considered as related to Afinitor®.

Five patients experienced a total of 6 fatal AE considered as related to Afinitor®: *general physical health deterioration*, *multiple organ dysfunction syndrome* (general disorders and administration site conditions SOC, one patient each), *epistaxis*, *interstitial lung disease* (respiratory, thoracic and mediastinal disorders SOC, one patient each), *metastases to pleura*

(neoplasms benign, malignant and unspecified [incl cysts and polyps] SOC, one patient), and *disorientation* (psychiatric disorders SOC, one patient).

Brief narratives of treatment-related AE leading to death are provided herebelow and are mainly based on tables and listings, and when appropriate, on full narratives from the Pharmacovigilance database (see **Annex 1**).

Narratives of treatment-related AE leading to death:

1) Patient 013-0209: *epistaxis*

This 75-year-old female patient started Afinitor® for her breast cancer at a dose of 5 mg daily and developed in the same month grade 3 (severe) **epistaxis** (exact time to event occurrence not known). Twenty-six days after Afinitor® initiation, she presented malignant neoplasm progression (disease progression). Afinitor® treatment was discontinued on the same day. Thirty-two days after Afinitor® initiation, she died due to both epistaxis and malignant neoplasm progression. The event 'epistaxis' was upgraded as grade 5 in severity and was considered as related to Afinitor® treatment by the physician and the Sponsor.

2) Patient 021-0271: *interstitial lung disease*

This 83-year-old female patient started Afinitor® for her metastatic breast cancer at a dose of 5 mg daily. Thirty-seven days after Afinitor® initiation, she developed a grade 4 (life-threatening) **interstitial lung disease**. Chest X-ray and scan revealed findings compatible with interstitial lung disease of possible infectious origin. Nevertheless, blood culture and cytobacteriological examination of the urine were negative, as were antigenaemia and detection of bacterial antigens in the urine. Afinitor® treatment was discontinued and an antibiotherapy was initiated. The patient ended up dying as a result of her interstitial lung disease (67 days after onset of this event). No autopsy was performed. The event 'interstitial lung disease' was upgraded as grade 5 in severity and was considered as related to Afinitor® treatment by the physician and the Sponsor.

3) Patient 077-0203: *multiple organ dysfunction syndrome* and *lung disorder*

This 64-year-old female patient started Afinitor® for her metastatic breast cancer at a dose of 5 mg daily. Nine months (265 days) after Afinitor® initiation, she was hospitalised for renal failure and severe dyspnoae, and Afinitor® treatment was discontinued. On the day after admission, chest CT-scan revealed bilateral pleural effusion and grade 2 **lung disorder** (non-infectious lung disease), which were treated with corticosteroids. Seven days after hospital admission, she developed peritonitis, peripheral oedema (lower limb oedema), and **multiple organ dysfunction syndrome** characterised by grade 3 (severe) renal failure and grade 4 (life-threatening) hepatic failure. She was also diagnosed with suspicion of septic shock as shown by biological work-up and signs of cholestasis. In addition, chest X-ray showed increased pleural effusion. Despite numerous treatment interventions (oxygen 2 L/min, methylprednisolone, vitamin K, Augmentin® [amoxicillin, clavulanic acid], Lasilix® [furosemide], insulin glucose, hydration), her condition worsened. Eleven days after hospital admission, she developed acute pulmonary oedema and ended up dying on that same day. Death was attributed to multiple organ dysfunction syndrome and lung disorder (non-infectious lung disease). Both fatal events were considered as related to Afinitor® treatment by the physician. According to the Sponsor, reduced immunity due to underlying

advanced malignancy with multiple metastases could better explain multiple organ dysfunction syndrome.

4) Patient 101-0481: *general physical health deterioration* and *disorientation*

This 87-year-old female patient started Afinitor® for her breast cancer at a dose of 5 mg daily. Sixty-two days after Afinitor® initiation, she was hospitalised for grade 3 (severe) mucosal inflammation and grade 3 (severe) **general physical health deterioration**. At hospital admission, temporospatial **disorientation** was also noted. Afinitor® treatment was discontinued on the day of admission. The patient died due to general physical health deterioration and temporospatial disorientation (24 days after onset of these events). These fatal events were all considered as related to Afinitor® treatment by the physician. However, according to the Sponsor, the events 'general physical health deterioration' and 'disorientation' were more likely complications of patient's underlying advanced breast cancer; hence they were assessed by the Sponsor as not related to Afinitor®. The causality for the event 'mucosal inflammation' could not be properly assessed by the Sponsor.

5) Patient 114-0387: *metastases to pleura*

This 75-year-old female patient started Afinitor® for her metastatic breast cancer at a dose of 10 mg daily. She presented malignant neoplasm progression (disease progression) after 2.7 months (81 days) of treatment with Afinitor®. Later on, after 4 months (121 days) of treatment, she experienced pleural effusion with grade 3 (severe) dyspnoae, and Afinitor® treatment was discontinued. On the same day, radiography and scan were performed, revealing **metastases to pleura** (metastatic pleurisy). Two weeks after hospital admission, she ended up dying due to metastases to pleura, pleural effusion, dyspnoea, and malignant neoplasm progression. No autopsy was performed. The events 'metastases to pleura' and 'pleural effusion' were considered as related to Afinitor® treatment by the physician.

10.6.7 Adverse events leading to dose reduction or temporary interruption of Afinitor® by SOC and PT

Overall, 160/596 patients (26.9%) experienced at least one AE leading to dose reduction or temporary interruption of Afinitor® over the course of the study; for 140/596 patients (23.5%), at least one of these events was considered as related to Afinitor®.

The first most common AE leading to dose reduction or temporary interruption of Afinitor® were (with equal incidence) *asthenia* (general disorders and administration site conditions SOC) and *rash* (skin and subcutaneous tissue disorders SOC), which were reported in 17/596 patients each (2.9%).

The second most common AE leading to dose reduction or temporary interruption of Afinitor® was *decreased appetite* (metabolism and nutrition disorders SOC), which was reported in 16/596 patients (2.7%).

The third most common AE leading to dose reduction or temporary interruption of Afinitor® was *diarrhoea* (gastrointestinal disorders SOC), which was reported in 13/596 patients (2.2%).

Other AE leading to dose reduction or temporary interruption of Afinitor® occurred in ≤ 2% of patients.

Results presented above are based on all AE, whether or not related to Afinitor® treatment.

More summary information on AE leading to dose reduction or temporary interruption of Afinitor® is provided in **Table 2.3.5** and full details for each patient are presented in **Listing 18**.

10.6.8 Adverse events leading to permanent discontinuation of Afinitor® by SOC and PT

Overall, 102/596 patients (17.1%) experienced at least one AE leading to permanent discontinuation of Afinitor® over the course of the study; for 78/596 patients (13.1%), at least one of these events was considered as related to Afinitor®.

The first most common AE leading to permanent discontinuation of Afinitor® was *asthenia* (general disorders and administration site conditions SOC), which was reported in 14/596 patients (2.3%).

The second most common AE leading to permanent discontinuation of Afinitor® was *diarrhoea* (gastrointestinal disorders SOC), which was reported in 9/596 patients (1.5%).

The third most common AE leading to permanent discontinuation of Afinitor® was *rash* (skin and subcutaneous tissue disorders SOC), which was reported in 7/596 patients (1.2%).

Other AE leading to permanent discontinuation of Afinitor® occurred in ≤ 1% of patients.

Results presented above are based on all AE, whether or not related to Afinitor® treatment.

More summary information on AE leading to permanent discontinuation of Afinitor® is provided in **Table 2.3.6** and full details for each patient are presented in **Listing 19**.

11 Discussion

11.1 Key results and interpretation

In the pivotal phase III BOLERO-2 trial, the combination everolimus + exemestane more than doubled the PFS − as assessed by local radiological review – compared to exemestane + placebo in post-menopausal women with HR+ advanced breast cancer progressing after NSAI therapy (7.8 months *versus* 3.2 months, respectively; hazard ratio = 0.45; *P*-value < 0.0001). These results were confirmed by central radiological assessment (11.0 months *versus* 4.1 months, respectively; hazard ratio = 0.38; *P*-value < 0.0001). In the BOLERO-2 trial, stomatitis and NIP were the most frequent AE leading to dose reduction or treatment discontinuation. Their overall incidence was 59% and 16%, respectively.

TANGO is a French observational prospective study that aimed to confirm in a real-life setting the safety and the efficacy of Afinitor® + exemestane in the treatment of post-menopausal women with advanced HR+/HER2- breast cancer. The primary objective of this non-interventional study was to describe the management of 2 specific AE − stomatitis and NIP – occurring in these patients. Secondary objectives included, among others, evaluation of the overall safety of Afinitor®, duration of exposure to Afinitor® + exemestane combination, and PFS (as part of efficacy measurement).

TANGO baseline patient characteristics:

A total of 596 patients were included in the safety population. The mean (SD) patient age was 65.1 (10.8) years, with 465/596 patients (78.0%) aged < 75 years and 131/596 (22.0%) aged ≥ 75 years. The median time since primary diagnosis of breast cancer was 7.5 years (range: 0.1−44.3). At the time of study treatment prescription, almost all patients had metastases (591/596 patients [99.2%]), mainly to the bones (459/591, 77.7%), liver (178/591, 30.1%), lungs (141/591, 23.9%), and lymph nodes (136/591, 23.0%). The ECOG-PS at the time of study treatment prescription was 0 or 1 for most patients (242/596 patients [40.6%] and 285/596 patients [47.8%], respectively). The majority of patients had received 1 or 2 previous lines of treatment in metastatic settings (208/596 patients [34.9%] and 126/596 patients [21.1%], respectively) and 113/596 patients (19.0%) had no prior therapy. The safety population in TANGO was comparable to the population of another non-interventional study (BRAWO) including patients from Germany treated with the combination Afinitor® + exemestane (Fasching et al, 2014). Both real-world studies represent a broader population than the BOLERO-2 trial (Baselga et al, 2012) with no limitations on the number of previous lines of treatment, prior exemestane therapy, or time of recurrence or progression after NSAI therapy, and are expected to be more representative of the population of patients treated with Afinitor® + exemestane in routine clinical practice.

The BOLERO-2 trial supports the indication of Afinitor® in the treatment of post-menopausal women with hormone-resistant advanced breast cancer, i.e. women who had recurred or progressed after previous therapy with a non-steroidal aromatase inhibitor (letrozole or anastrozole). In TANGO study, 222/375 relapsed patients (59.2%) had hormone-resistant breast cancer and 142/375 (37.9%) had hormone-sensitive breast cancer.

Incidence and severity of stomatitis and NIP:

A total of 305/596 patients (51.2%) experienced 400 episodes of stomatitis over the course of the study; for 301/596 patients (50.5%), at least one stomatitis episode was considered as related to Afinitor®. Similarly, a total of 80/596 patients (13.4%) experienced 88 episodes of NIP during the observation period; for 73/596 patients (12.3%), at least one NIP episode was considered as related to Afinitor®. These results were consistent with those reported in other studies evaluating the combination Afinitor® + exemestane (BALLET, BOLERO-2, BRAWO, STEPAUT, 4EVER). In these studies, between 39.8% and 59.0% of patients experienced stomatitis and between 7.8% and 16.0% of patients experienced NIP (Yardley et al, 2013; Jerusalem et al, 2016; Lousberg and Jerusalem, 2016). Several factors may account for differences in incidence among studies, including the duration of patient follow-up, the duration of exposure to Afinitor® treatment and the use of prophylactic measures to prevent stomatitis and NIP. The median duration of follow-up was shorter in BALLET study than in BOLERO-2 study (4.6 months *versus* 17.7 months), as was the incidence of stomatitis and NIP (46.0% *versus* 59.0% and 9.5% *versus* 16.0%, respectively). The median duration of treatment with Afinitor® was longer in BOLERO-2 study (~6 months) than in TANGO (~5 months, calculated for the combination) and BALLET (~4 months) studies. The longer the duration of treatment, the higher the incidence of stomatitis (59.0%, 51.2%, 46.0% for BOLERO-2, TANGO, and BALLET respectively) and NIP (16.0%, 13.4%, and 9.5%, respectively). Finally, a higher percentage of patients received prophylactic treatment for

stomatitis in BRAWO compared to TANGO study (86.8% *versus* 75.7%), which could partly explain the lower incidence of stomatitis reported in BRAWO (39.8% *versus* 51.2%).

In BALLET study (Neven et al, 2015), the incidence of stomatitis (all grades) was found to be slightly higher in elderly (70−90 years) than in non-elderly (55.5% *versus* 51.9%), as was the incidence of NIP (11.2% *versus* 8.9%). In TANGO, subgroup analyses did not reveal any notable differences between age groups. Whether older age has an impact on occurrence of stomatitis/NIP in patients treated with Afinitor® need further investigation.

The mechanism by which mTOR inhibitors such as Afinitor® induce NIP is not understood. In our subgroup analyses, there is no evidence that the presence of pulmonary metastases is a predisposing factor for the development of NIP in patients treated with Afinitor®. Our results also suggest an absence of dose-effect; we did not find any differences in NIP incidence between the 5 mg/day and 10 mg/day dose regimens, whether or not patients had pulmonary metastases at inclusion.

In TANGO study, the most severe stomatitis episode was reported grade 1 or 2 for 265/305 patients (86.9%), grade 3 for 39/305 patients (12.8%), and grade 4 for one single patient (0.3%). A similar trend was observed for NIP; the most severe episode was reported grade 1 or 2 for 73/80 patients (91.3%), grade 3 for 6/80 patients (7.5%), and grade 5 for one single patient (1.3%). Although our results focus on the most severe episode (thereby omitting those observed in the lowest severity categories), they tend to indicate that the majority of stomatitis and NIP were grade 1 (mild) or grade 2 (moderate) in severity. Grade 3 (severe) events were less frequently reported, which is in line with other studies evaluating the combination of Afinitor® + exemestane. In BOLERO-2, the percentage of patients with grade 3 stomatis was 8% (*versus* 29% and 22% for grade 1 and 2, respectively) and the percentage of patients with grade 3 NIP was 3% (*versus* 7% and 6% for grade 1 and 2, respectively) (Yardley et al, 2013). In BRAWO, the percentage of patients with grade 3 stomatis was 3.4% (*versus* 23.2% and 17.0% for grade 1 and 2, respectively) (Fasching et al, 2014). In BALLET, 9.3% of patients experienced grade 3 stomatitis (*versus* 52.8% for all grades) and 1.6% experienced grade 3 NIP (*versus* 9.5% for all grades) (Jerusalem et al, 2016). Whether in TANGO or other studies, grade 4 stomatitis and NIP were only encountered in a few patients. Finally, direct comparisons with other studies need to be treated with caution due to differences in methods used to calculate incidence of stomatis/NIP by severity grade.

In TANGO, the median time to first occurrence of stomatitis and NIP was 21 days (range: 1−333) and 104 days (range: 1−396), respectively. Similar results were found in BALLET study where the median time to onset for stomatitis events and NIP events was 29 days (range: 1–396) and 87 days (range: 1–231), respectively (Jerusalem et al, 2016). Median duration of NIP was also found to be similar between both studies (19 days).

Management of stomatitis and NIP:

In TANGO, different measures were taken to treat stomatitis and NIP episodes. The 3 most common medications used to treat stomatitis episodes (all grades; grade > 1) were mouthwashes (309/400, 77.3%; 256/288, 88.9%), topical analgesics (74/400, 18.5%; 72/288, 25.0%), and antifungals (60/400, 15.0%; 58/288, 20.1%), in agreement with recommendations found in the review of Aapro et al (2014) and in the Afinitor® prescribing information (Afinitor [everolimus] prescribing information, Novartis, Revised 2017). Interestingly, in

another non-interventional study (BRAWO; Fasching et al, 2014), the most common therapeutic measure for grade 1 stomatitis was non-drug mouthwash solution (54.5%), followed by cooling and systemic drugs (18.2% each). For grade 2 stomatitis, the most common therapeutic measures included non-drug mouthwash solution (51.1%), temporary treatment interruption (41.1%), and cooling (37.8%). Measures taken for grade 3 stomatitis were mainly systemic drugs, temporary treatment interruption (58.8% each) and topical drugs (47.1%). It should be noted that direct comparisons between both TANGO and BRAWO studies need to be considered carefully due to different methods of calculation for treatment incidence (regardless of severity grade in TANGO *versus* by severity grade in BRAWO).

Management of stomatitis has been updated and new recommendations have been published after TANGO study was completed. These new recommendations are based on results from the single-arm phase II SWISH trial that tested prophylactic use of alcohol-free dexamethasone oral solution in post-menopausal women with breast cancer treated with Afinitor® plus exemestane. This trial showed that dexamethasone oral solution, used as mouthwash during the first 8 weeks of treatment, substantially decreased incidence and severity of stomatitis in these patients (Rugo et al, 2017).

NIP episodes (all grades; grade > 1) were mainly treated with corticosteroids (35/88, 39.8%; 33/66, 50.0%) and to a lesser extent with antibiotic therapy (9/88, 10.2%; 8/66, 12.1%) and oxygen therapy (1/88, 1.1%; 1/66, 1.5%). These results are also in agreement with the Afinitor® prescribing information (Afinitor [everolimus] prescribing information, Novartis, Revised 2017), advising the use of corticosteroids in case of NIP, and with recommendations found in the review of Aapro et al (2014). Importantly, the majority of stomatitis and NIP episodes (> 80%) completely resolved during the study, suggesting that French physicians were well informed about the risks of Afinitor® and properly implemented general management recommendations for these adverse reactions.

Dose reduction or discontinuation is also recommended in the management of grade ≥ 2 stomatitis and NIP. Nevertheless,the proportion of patients with stomatitis and NIP who reduced or discontinued the treatment was not addressed in this study.

Duration of exposure to Afinitor® + exemestane combination:

The duration of exposure to Afinitor® + exemestane combination was defined as the time from the first dose of treatment until documented treatment discontinuation (at least one drug discontinued) or end of observation period. In the efficacy population (N = 562), the median duration of exposure to Afinitor® + exemestane combination was 5.3 months (95% CI: 4.8−6.0). We also found that the median [95% CI] duration of exposure to Afinitor® + exemestane tended to be lower in older patients (4.1 [3.4−5.3] months in ≥ 70-year age group, N = 207) than in younger ones (5.9 [5.0−6.7] months in < 70-year age group, N = 355). This is in line with results obtained in BALLET study where median duration of exposure to Afinitor® was 3.8 months in elderly (70−90 years) *versus* 5.2 months in non-elderly (Neven et al, 2015). However, the comparison between both studies should be taken with caution, as the duration of exposure in TANGO is calculated for the combination of everolimus + exemestane and not for everolimus alone.

PFS as measurement of treatment efficacy:

The PFS time was defined as the time elapsed between the first dose of Afinitor® and tumour progression, death from any cause or follow-up discontinuation, whichever came first. In TANGO, a total of 377/562 patients (67.1%) experienced disease progression or death during the 12-month follow-up period, with disease progression reported for 351 patients (93.1%) and death for 26 patients (6.9%). In the efficacy population, the median PFS time was 6.9 months (95% CI: 6.2−7.8), which was similar to the median PFS time observed in BOLERO-2 (7.8 months [Yardley et al, 2013]) and BRAWO (8 months, 95% CI: 6.7-9.1 [Fasching et al, 2014]). The PFS in TANGO slightly differs from that obtained in the Phase IIIb study 4EVER (5.6 months, 95% CI: 5.4-6.0 [Lousberg and Jerusalem, 2016]). This difference could be explained by the fact that patients included in 4EVER were more heavily pretreated. Around 50% of them had received ≥ 3 previous lines of treatment, suggesting they were suffering from more advanced and/or refractory disease. In TANGO, the median [95% CI] PFS time tended to decrease with the number of previous lines of treatment in metastatic setting (8.1 [5.9−10.2], 7.5 [6.6−8.7] and 5.4 [4.4−6.6] months for 0, 1-2, ≥ 3 previous lines of treatment, respectively), as shown by subgroup analyses.

A multivariate analysis performed on BRAWO dataset support the evidence that predictive factors, such as the Body Mass Index (*P*-value: < 0.001), therapeutic line for Afinitor® (1^{st} *versus* $2^{nd} + 3^{rd}$ *versus* $\geq 4^{th}$; *P*-value: 0.013), presence of visceral metastases (*P* -value: < 0.001) and ECOG (*P* -value: < 0.001) status at the beginning of the therapy correlated significantly with the PFS. Such correlation was not found with Afinitor® starting dose (5 mg *versus* 10 mg) (Fasching et al, 2017). Similar findings were observed in TANGO study. The PFS tended to decrease in patients more heavily pretreated (8.1 [5.9−10.2], 7.5 [6.6−8.7] and 5.4 [4.4−6.6] months for 0, 1-2, ≥ 3 previous lines of treatment, respectively) and in those with visceral metastases at inclusion (5.7 [5.0−6.7] months *versus* 8.6 [6.9−9.5] months when no visceral metastases were present). No differences were found between patients who started Afinitor® treatment at a dose of 5 mg/day and those treated at a dose of 10 mg/day (7.0 [5.2−8.6] months and 6.7 [5.9−7.8] months, respectively).

Overall safety of Afinitor®:

In TANGO, when all AE are taken into account (including stomatitis and NIP), 559/596 patients (93.8%) experienced at least one AE over the course of the study, including 509 patients (85.4%), for whom at least one AE was considered as related to Afinitor®. A total of 167/596 patients (28.0%) experienced at least one SAE over the course of the study, including 90 patients (15.1%) for whom at least one SAE was considered as related to Afinitor®. Similar percentages for AE and SAE were reported in BOLERO-2 and BALLET studies (Baselga et al, 2012; Yardley et al, 2013; Jerusalem et al, 2016).

The majority of AE were grade 1 or 2 in severity and a small proportion of them were grade 4 or 5. Irrespective of grade and causal relationship with Afinitor®, the most frequent AE (excluding stomatitis and NIP) were *asthenia* (140/596 patients, 23.5%), *diarrhoea* (86/596 patients, 14.4%) and *rash* (67/596, 11.2%). Hence, AE observed in TANGO were consistent with those reported in other studies − in particular BOLERO-2 (Baselga et al, 2012; Yardley et al, 2013), BALLET (Jerusalem et al, 2016), and BRAWO (Fasching et al, 2014) − and in

the Afinitor® prescribing information (Afinitor [everolimus] prescribing information, Novartis, Revised 2017).

A total of 48/596 patients (8.1%) experienced at least one AE leading to death. AE leading to death considered as related to Afinitor® were reported in 5 patients and included *general physical health deterioration*, *multiple organ dysfunction syndrome*, *epistaxis*, *interstitial lung disease*, *metastases to pleura* and *disorientation* (one patient each). This is in line with results from BALLET study where only a few patients (4/2131) died because of AE suspected to be related to Afinitor® (*cardiorespiratory arrest* in one patient. *general physical health deterioration* in one patient, *NIP* in 2 patients) (Jerusalem et al, 2016).

11.2 Limitations

Several limitations have to be considered when interpreting the results of this study:

- This is an exploratory, descriptive study for which no formal hypothesis was tested. The study was not designed to demonstrate significant differences between subgroups of interest for safety or efficacy parameters.
- The database has been locked with a high proportion of patients with unsolved queries (173/639 [27.1%] in the analyzable included population, 161/596 [27.0%] in the safety population, and 157/562 [27.9%] in the efficacy population, **Table 5.1**). Moreover, some CRF pages were not systematically completed by physicians in particular the log treatment page and the end-of-study page. In the 3 populations of the study, the proportion of patients lacking a log treatment page varied between 2.5% and 5.2% and the proportion of patients lacking an end-of-study page varied between 1.0% and 3.0% (**Table 5.1**). Inconsistencies in the database and missing pages led to a high proportion of missing data, precluding evaluation of several objectives (treatment doses and main reasons for dose reduction, reason for interruption / treatment discontinuation).
- Due to missing data, an algorithm was defined to determine the last administration date for each treatment and dates were considered as confirmed if at least 2 informations in the database validated treatment discontinuation (see Section 4.6 of the SAP version 3 and **Table 5.2**). It is important to remember that this algrorithm only provided estimates of the 'true' date of last treatment administration.

11.3 Generalizability

Although missing data might have caused some bias, results from this study can be extrapolated to the overall population of breast cancer patients in France treated with Afinitor®.

12 Other information

None.

13 Conclusion

Safety and efficacy results provided by TANGO were consistent with those obtained in the pivotal BOLERO-2 trial and in real-life observational studies such as BALLET or BRAWO. TANGO results reinforce the known safety profile of Afinitor® and complement existing data on the management of stomatitis and NIP occurring during Afinitor® treatment in a real-life setting.

Most stomatitis and NIP episodes completely resolved during TANGO. Thus, the management of stomatitis and NIP is essential to optimise the duration of exposure to Afinitor® and, subsequently, to achieve a better clinical benefit. The main challenge is to continue educating physicians and patients to identify AE related to Afinitor® and manage them properly.

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Appendices

Annex 1 – List of stand-alone documents

Annex 1 is provided in a separate file and includes the following documents:

Annex 1.1	Tables, figures and listings
Annex 1.2	Narratives of deaths and serious adverse events related to Afinitor®
Annex 1.2.1	Narratives of deaths
Annex 1.2.2	Narratives of serious adverse events related to Afinitor®

Annex 2 – Additional information

Annex 2 is provided in a separate file and includes the following documents:

Annex 2.1	Study information
Annex 2.2	Protocol and protocol amendments
Annex 2.3	Sample case report form
Annex 2.3.1	General case report form – All patients
Annex 2.3.2	Last contact form – Patients continuing treatment after Month 12
Annex 2.4	Regulatory approvals
Annex 2.4.1	Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé / French Committee on Information Processing in Material Research in the Field of Health (CCTIRS)
Annex 2.4.2	Commission Nationale de l'Informatique et des Libertés / French National Commission on Informatics and Liberty (CNIL)
Annex 2.4.2.1	Protocol version 01: email dated 08-Jul-2014
Annex 2.4.2.2	Protocol version 02: formal authorisation from the CNIL dated 13-Aug-2014
Annex 2.4.3	Conseil National de l'Ordre des Médecins / French National Medical Council (CNOM)
Annex 2.5	List and description of active centres
Annex 2.6	Documentation of statistical methods
Annex 2.6.1	Validated statistical analysis plan
Annex 2.6.2	Plan of tables, listings and graphs
Annex 2.7	Important publications referenced in the report