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Department
BU Oncology, CPO Germany

Afinitor®/Everolimus

Non-interventional Study/Final Report
CRAD001JDE53

Breast Cancer Treatment with Afinitor® (Everolimus) and Exemestane for HR+ Women (BRAWO)

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Country of study	Germany
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1 Abstract

The abstract is provided separately.

2 List of abbreviations

ADR	Adverse drug reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired immune deficiency syndrome
AKT	Protein kinase B
AMG	Drug law (German “Arzneimittelgesetz”)
ATC	Anatomical Therapeutic Chemical
BfArM	Federal institute for drugs and medical devices (German “Bundesinstitut für Arzneimittel und Medizinprodukte“)
BOR	Best overall response
CCI	Charlson comorbidity index
CNS	Central nervous system
CRO	Contract Research Organization
CT	Computed tomography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
ER	Estrogen receptor
FAS	Full analysis set
FSA	Voluntary self-control of pharmaceutical industry (German “freiwillige Selbstkontrolle der Arzneimittelindustrie”)
HER2-	Human epidermal growth factor receptor 2-negative
HER2/neu	Human epidermal growth factor receptor 2/neu
HR+	Hormone receptor-positive
IA	Interim analysis
IEC	Independent Ethics Committee
KAS	Physical activity score (German “Körperliche Aktivitäts-Skalen”)
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	Mammalian target of rapamycin
MRI	Magnetic resonance imaging
NIS	Non-Interventional Study
nsADR	Non-serious Adverse Drug Reaction
nsAEnr	Non-serious Adverse Event not-related
NSAI	Non-steroidal aromatase inhibitors
PASS	Post-Authorization Safety Study
PEI	Paul-Ehrlich-Institute
PET	Positron emission tomography
PFS	Progression free survival
PgR	Progesterone receptor
PI3K	phosphoinositide 3-kinase
PSOC	Primary system organ class (based on MedDRA)
PT	Preferred term (MedDRA)
PT-Table	Post text-table
QLQ	Quality of Life Questionnaire
QLQ-BR23	Breast cancer specific QLQ

QLQ-C30	QLQ core questionnaire
QoL	Quality of Life
RMP	Risk management plan
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAEnr	Serious Adverse Event not-related
SAP	Statistical Analysis Plan
SDV	Source data verification
SOC	System organ class (MedDRA)
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
TTP	Time to progression
VFA	German “Verband forschender Arzneimittelhersteller”
WHO	World Health Organisation
WLTAS	Weekly leisure-time activity score

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A detailed list of all investigators and of all collaborating institutions may be available upon request.

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date
Start of observation period Last patient included Last patient last visit End of observation period	October 2012 December 2016 December 2017 December 2017	05 October 2012 29 December 2016 29 December 2017 31 December 2017
End of data collection eCRF	31 March 2018	31 March 2018
Interim analysis IA1	approximately 6 months after inclusion of 500 patients	17 January 2014 (data cut-off)
Interim analysis IA2	approximately 12 months after inclusion of 500 patients	08 July 2014 (data cut-off)
Interim analysis IA3	approximately 18 months after inclusion of 500 patients	08 January 2015 (data cut-off)
Final report of study results	December 2018	November 2018
Any other important milestone applicable to the study Protocol approval by independent ethics committee (IEC) Protocol Amendment 1 approval by independent ethics committee (IEC)	 27 September 2012 05 September 2013	 27 September 2012 05 September 2013

Milestone	Planned date	Actual date
Protocol Amendment 2 approval by independent ethics committee (IEC)	05 September 2013	05 September 2013
Protocol Amendment 3 approval by independent ethics committee (IEC)	26 June 2014	26 June 2014
Protocol Amendment 4 approval by independent ethics committee (IEC)	-[a]	-[a]
Protocol Amendment 5 approval by independent ethics committee (IEC)	07 October 2015	07 October 2015
Protocol Amendment 6 approval by independent ethics committee (IEC)	-[a]	-[a]

[a] non-substantial amendment

6 Rationale and background

Breast cancer is the most common type of cancer in women. In Europe, 13% of all new cancer diagnoses are breast cancer, which cause 130,000 deaths per year (Boyle et al. 2005).

About 40% of newly diagnosed patients with breast cancer develop metastases. The treatment of metastatic breast cancer is palliative and concentrates on reduction of tumor size, decrease of disease progression and the reduction of complications associated with this disease e.g. fatigue, bone fractures, and hypercalcemia. The average life expectancy for women with metastatic breast cancer is usually between 24 and 30 months [World Health Organization (WHO) Facts and Figures].

Endocrine therapies are fundamental in treatment of women with hormone receptor-positive (HR+) progressed breast cancer. Non-steroidal aromatase inhibitors (NSAI, e.g. letrozole and anastrozole) are state of the art in first-line therapy in post-menopausal patients (AGO-guidelines 2012). However, not all patients respond to an endocrine first-line therapy (primary or *de novo* resistance) or develop a resistance to these agents during therapy (Johnston et al. 2010).

It is known, that this resistance to endocrine therapy in breast cancer is often associated with an over-activation of the intracellular phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signal pathway. This signal pathway plays a crucial role in proliferation, survival, angiogenesis, and metabolism of cells. Furthermore, a close interaction between the PI3K/AKT/mTOR and the estrogen signal pathway could be shown (Di Cosimo S and Baselga, 2010). Therefore, the parallel inhibition of both signal pathways is a promising therapy concept to overcome resistances to endocrine therapies. Afinitor® (everolimus) is an orally available inhibitor of mTOR, a serine-threonine-kinase, which is a central part of the PI3K/AKT/mTOR signal pathway (Baselga et al. 2011).

The efficacy of a combination of mTOR inhibitor with endocrine therapy has been proven in several clinical studies. In a randomized phase 2 study to compare everolimus plus letrozole with letrozole as monotherapy in neoadjuvant treatment of patients with estrogen receptor positive (ER+) breast cancer, the response rate under combination therapy was significantly higher than under letrozole monotherapy (Baselga et al. 2009).

These data were recently confirmed by the results of the BOLERO 2-study, an international placebo controlled phase 3 study relevant for approval. BOLERO 2 investigated the efficacy and safety of Afinitor® in combination with exemestane in comparison to exemestane monotherapy in patients with recurrent relapse or progression under or after letrozole or anastrozole therapy.

In the final analysis after a median follow-up of 18 months, the combination therapy led to a significant increase in progression free survival (PFS) from 3.2 to 7.8 months in local radiological evaluation and decreased the risk for a disease progression by 55%. These results were confirmed by independent central radiological evaluation (PFS 4.1 vs. 11.0 months, decrease of risk by 62%). In all subgroups evaluated, a remarkable effect in favor of Everolimus was seen. The time until deterioration of quality of life, assessed by patient questionnaires, was significantly longer under combination therapy. After a follow-up of 18 months and 200

documented events, a numerical favor of the combination therapy compared to the placebo arm was seen with regard to total survival (32.2% vs. 25.4%). The final analysis of the total survival was planned to take place when 398 deaths were documented (Piccard et al. 2012).

Based on the results of the BOLERO 2-study, Afinitor® was approved in combination with exemestane for treatment of postmenopausal patients with progressed HR+, human epidermal growth factor receptor 2 (HER2)/neu-negative breast cancer without symptomatic visceral metastases, following relapse or progression after NSAI.

There were no data available regarding efficacy of Afinitor® therapy within this indication in routine praxis outside of clinical studies. The approval of the medication for this indication was made in July 2012. In the context of the approval, patients who could not be included in the approval study due to their previous therapy or their health status, were also allowed to be treated with Afinitor®. This included, amongst others, patients with metastases in late chemotherapy lines. Therefore, it was of absolute relevance to evaluate data for efficacy of Afinitor® in routine treatment, i.e. outside of controlled clinical studies with given in- and exclusion criteria. These data allowed an estimation if the efficacy proven in the clinical approval study is also seen in routine treatment.

An important goal in palliative treatment of cancer patients is to provide good quality of life (QoL) for as long as possible. For this reason, this non-interventional study (NIS) investigated if QoL changed during treatment with Afinitor®. The respective questionnaires were planned to be filled in by the patients in the 1st and 3rd month after start of therapy and thereafter in a 3-monthly rhythm.

Kind and extent of physical activity could influence the efficacy and/or the QoL of patients with metastatic breast cancer. Such an influence was shown for prevention as well as for the adjuvant setting (Friedensreich 2011). There are hints that a positive effect of physical activity in women with HR+ breast cancer might be more pronounced than in other types of breast cancer (Carmichael et al. 2010). However, the body of evidence for the metastatic setting is limited. One objective of this NIS was therefore to determine kind and extent of physical activity by patient questionnaires, and to evaluate a possible correlation with efficiency and QoL. In this context, it should also be evaluated if fatigue, present under many therapies, can be reduced by physical activity.

Stomatitis is a very common side effect of therapy with Afinitor® and exemestane, often develops very early after therapy start and often subsides during therapy (Porta et al. 2011). In the acute phase, various possibilities for the patients' relief are available to the treating physician. Kind and duration of treatment depends on grade of stomatitis and individual decision criteria of each physician. Based on the yet unclear data, no explicit recommendation for one or the other treatment of stomatitis under Afinitor® could be given. Nevertheless, it could be shown that stomatitis under mTOR inhibitors is distinct from stomatitis that occurs under certain chemotherapies. For this reason, measures of prophylaxis and stomatitis treatments and their results were investigated in this NIS.

For the treatment of post-menopausal women with metastatic breast cancer, various treatment options were available. These included endocrine therapies as well as chemotherapies (guidelines of AGO-commission Mamma 2012). The decision for the respective therapy was

made by the treating physician in agreement with the patient and with regard to her individual situation. During this NIS previous therapies and the therapy following Afinitor® and exemestane were documented. The objective was to determine therapy sequences used in routinely practice for the combined therapy with Afinitor® and exemestane.

The use of Afinitor® and exemestane was based on the respective summary of product characteristic (SmPC) and exclusively adhered to the medical-therapeutical necessities.

7 Research question and objectives

The objective of this NIS was to gain knowledge from routine care

- about the effect of physical care on effectiveness and quality of life,
- about prophylaxis and handling of stomatitis in clinical practice,
- about therapy sequence

in the treatment of patients with progressive or metastatic HR+ breast cancer following approval with Afinitor® and exemestane.

Primary objective

Primary objective was the evaluation of effectiveness (PFS) of a combination therapy with Afinitor® and exemestane in daily practice in relation to extent of physical exercise. For subgroup analyses, the courses of therapy in patients with increased activity were to be compared to that in patients with low activity. For the evaluation of effectiveness, PFS under treatment with Afinitor® and exemestane according to the investigator's assessment had to be documented.

Secondary objectives/parameters

Quality of life and physical activity

- To evaluate the QoL of patients during treatment with Afinitor® [patient questionnaire: European Organization for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire C30 (QLQ-C30/BR23)] and the impact of physical activity on the QoL. Kind and extent of physical activity were evaluated by the "Godin Leisure-Time Exercise Questionnaire" and the "Körperliche Aktivitäts-Skalen" (KAS, physical activity score).

Drug utilization and therapy sequence

- Duration of therapy with Afinitor® and exemestane in practice routine.
- Extended knowledge on routine therapy of breast cancer and suitable therapy algorithms. Prior therapies and direct follow-up therapy were documented as well as kind, duration and reason for termination of prior therapy.
- Number of patients with modified, interrupted or terminated treatment including kind of dose modification, duration and reason for interruption.

Stomatitis management

- Prophylaxis and treatment of stomatitis as adverse event (AE) under routine use with Afinitor® in combination with exemestane and used concomitant medication, start and end date.

Documentation of AEs.

8 Amendments and updates to the protocol

Version number of study protocol	Date	Section of study protocol	Amendment or update	Reason
1.0	08 August 2012	Throughout protocol		
Amended version 1.1	27 May 2013	Throughout protocol	Amendment 1	Section on adverse events was completely changed: Definition of adverse events (AEs) Reporting frame of AEs Reporting frame of serious AEs (SAEs) Events of special interest
Amended version 1.2	25 July 2013	Throughout protocol	Amendment 2	Introduction of the 2-weeks visit and adaption of observation parameter Update causal relationship AE/SAE and reporting frame (only within 30 days after end of therapy)
Amended version 1.3	05 June 2014	Throughout protocol	Amendment 3	Additional patient questionnaire regarding stomatitis was introduced Complementation of inclusion criteria Study extended to Dec 2015, Dec 2016, respectively Dose adjustment in case of AEs according to SmPC Adjustment of monitoring 3rd interim analysis with focus on stomatitis
Amended version 1.4	12 August 2014	Throughout protocol	Amendment 4	Minor changes (patient information and informed consent)
Amended version 1.5	03 September 2015	Throughout protocol	Amendment 5	Introduction of the progression free survival visit Update AE/SAE reporting frame Study extended to Dec 2016, Dec 2017, respectively
Amended version 1.6	10 November 2015	Throughout protocol	Amendment 6	Formal Changes

9 Research methods

9.1 Study design

This was a retro- and prospective, non-controlled, non-interventional, open-label, multicenter study according to § 4 section 23 subsection 3 of the German drug law (German "Arzneimittelgesetz, AMG") and in accordance with the voluntary self-control of pharmaceutical industry (German: freiwillige Selbstkontrolle der Arzneimittelindustrie, FSA codex) and respective common guidelines of the Federal Institute for Drugs and Medical Devices (German "Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM") and the Paul-Ehrlich-Institut (PEI) for planning, conduct, and evaluation of NIS and the German association of researching drug companies (German "Verband Forschender Arzneimittelhersteller, VFA") recommendations for an improvement in quality and transparency of NIS.

A NIS intends to observe routine clinical practice and the study therefore only has a few in- and exclusion criteria and no specified interventions. This was suitable for the described objectives, as no specifications regarding kind and extent of physical activity were made, as well as few recommendations on prophylaxis and handling of stomatitis. Moreover, the clinical routine and the daily activity situation of patients were to be documented by evaluating the data of a relatively large number of patients. Additionally, therapy sequence for patients treated with Afinitor® in routine clinical practice outside of clinical trials was documented.

Study centers and patients

This multicenter NIS was planned to be conducted in up to 400 gynecological and oncological practices/hospitals. The participating physicians were informed about objectives and modalities of the NIS by the medical leader. The employed field staff of Novartis GmbH was appointed for administrative cause during the course of the NIS and distributed the relevant documents to the participating centers.

Information on indication of Afinitor® and exemestane as well as contraindications and possible side effects were provided in the appended SmPC. The therapy was not allowed to be performed for the purpose of inclusion into the NIS but was solely based on medical-therapeutic necessity.

Duration of observation

The approval study for Afinitor® demonstrated a statistically significant clinical benefit of Afinitor® in combination with exemestane compared to placebo plus exemestane, which was confirmed by an increase in PFS from 3.2 to 7.8 months according to local radiological assessment. The risk for a progression of the cancer disease decreased by 55%. These results were confirmed by the independent central radiological assessment (4.1 vs. 11.0 months, decrease of risk by 62%). The observation period finished on 31 December 2017. The last patient was observed for 12 months at a maximum. If therapy with Afinitor® was discontinued prior to disease progression, documentation was continued until progressive disease or death. If a patient did not start the indicated therapy with Afinitor® and exemestane for any reason, she was not documented within this NIS. Interruptions in therapy were documented about the

whole observation period. In case the therapy with Afinitor® was discontinued permanently for any reason, the date of the last intake and the main reason for discontinuation was documented.

Time flow:

Start of observation period	October 2012
First interim analysis	March 2014
Second interim analysis	Data-cut 08 July 2014
Third interim analysis	Data-cut 08 January 2015
Last patient inclusion	December 2016
End of observation period	December 2017
Last data collection eCRF	March 2018
Final report	November 2018

Only data, entered by web-application into the NIS-data base until 31 March 2018, or questionnaires sent to the CRO [redacted] until 24 March 2018, were considered for statistical evaluation and reimbursement (confirmation necessary).

Data management

All measures during data management regarding quality assurance were defined in a data management plan and specified of all phases of data management:

- Automatic plausibility control during data entry
- Data validation plan with questions that could lead to queries at a study center
- Implementation of an audit trail according to the food and drug administration (FDA) CFR21 Part 11 standard
- Assurance of data integrity by documented data base closure
- Data handling report for the handling of continued data inconsistencies relevant for analysis after data base closure. The data handling report was an integrated part of the statistical analysis plan (SAP).

All data management processes are based on the study operating procedures of the CRO [redacted]

9.2 Setting

During the observation period, data were documented at various study visits. Suggested timing of these documentations and details on all assessments are shown in Figure 9-1.

Figure 9-1 Flow chart

Assessment	Baseline	After approx. 2 weeks	After approx. 1 month	After approx. 3, 6, 12 etc. months (3-monthly intervals)	End of treatment with Afinitor® and exemestane
Patient characteristics	X				
Demography and vital signs	X		X	X	
Medical history, disease characteristics	X				
Prior treatment	X				
Tumor anamnesis	X				
Concomitant diseases	X				
Patient questionnaires on QoL and KAS	X		X	X	
Patient questionnaire on stomatitis prophylaxis		X	X	X	
Afinitor® and exemestane prescription	X		X	X	X
Prophylactic measures and stomatitis treatment	X	X	X	X	
Antiresorptive treatment	X				
Distribution of calendar diagram	X				
AEs/SAEs		X	X	X	X
Current tumor treatment with Afinitor® (dose, dose reduction, interruption of treatment, reason for dose changes)	X	X	X	X	X
Reason for termination of documentation					X
Reason for termination of treatment					X
Treatment response				X	X
Follow-up treatment					X

AE = Adverse event, KAS= Physical activity score, QoL=Quality of life, SAE = Serious AEs

9.3 Patients

It was planned to document prospectively the treatment courses of a total of 3,000 patients who were treated with Afinitor® in combination with exemestane according to routine practice and the respective SmPC. The planned observation time per patients corresponded to the duration of treatment with Afinitor® in combination with exemestane, but ended at the end of the observation phase at the latest. This meant that the last patient was observed at a maximum of 12 months, if recruitment of 3,000 patients was not finished earlier. The observation intervals were not defined by the observational plan, but followed clinical routine and clinical symptoms of the respective patient, e.g. about 2 weeks, 1 and 3 months, and thereafter in a 3-monthly interval (6, 9, 12, etc.) after start of treatment with Afinitor® and exemestane. The end of treatment should have been documented independently from the aspired interval, if the treatment was finished before the next regular treatment control.

The following patients were suitable for inclusion in this NIS:

- Patients treated with Afinitor® in combination with exemestane according to label and the SmPC, or respective patients, for whom a treatment with Afinitor® and exemestane was indicated.
- Postmenopausal women with advanced HR-positive, HER2/neu-negative breast cancer without symptomatic visceral metastases.
- Relapse or progression after treatment with non-steroidal aromatase inhibitor (e.g. anastrozole, letrozole).
- Age ≥18 years.
- Patients who were informed about the NIS and signed the consent form.

There were no exclusion criteria, except for the contraindications described in the SmPC. Participating patients were not allowed to take part in a controlled clinical study, as this is not common practice and is, therefore, in contrary to the objectives of a NIS according to § 4 section 23 subsection 3 of AMG.

9.4 Variables

9.4.1 Primary variable

The primary variable was PFS under a combination therapy with Afinitor® and exemestane in relation to extent of physical exercise.

9.4.2 Secondary variables

- Quality of life and physical exercise
  - o EORTC QLQ-C30/BR23
  - o Godin Leisure-Time Exercise Questionnaire and
  - o Körperliche Aktivitäts-Skalen (KAS)
- Administration of Afinitor® and therapy sequences
  - o Duration of treatment with Afinitor® and exemestane in daily practice
  - o Routinely treatment of breast cancer (previous therapies, follow-up treatment, reason for discontinuation of previous treatment)
  - o Rate of dose changes, rate of dose interruptions, type of dose change, duration of dose interruption, reason for interruption
  - o Rate and reason for discontinuation
- Stomatitis management
  - o prophylaxis measures
  - o treatment of stomatitis

- duration and intensity of stomatitis

9.4.3 Safety variables

The safety analysis was performed with the full analysis set (FAS).

All safety variables were analyzed by descriptive statistical methods (frequency tables or sample statistics). For details, see section 9.9.2.3.

9.4.4 Other variables

- Demographic data
- Medical history
- Eastern Cooperative Oncology group (ECOG) performance state

9.4.5 Variables not analyzed

Date of informed consent was not analyzed. Year of birth was not analyzed, but only used to compute the age of the patient. Date of primary diagnosis, date of primary confirmation of metastasis or relapse were not analyzed, but used to calculate durations since the respective event. Date of most recent receptor status examination, proliferation marker (antigen Ki-67, nuclear protein) Ki-67-index assessment, date of antineoplastic surgeries, start- and end date of previous radiation therapy, start- and end date of prior antineoplastic medication was not analyzed. Start- and end date of prior antineoplastic medication was used to determine duration of prior treatment and to determine last medication. Free text on medication, AE, and cause of death was not analyzed, but coded values were used instead. Specifications of mouth rinses, measures for cooling and other measures used for stomatitis prophylaxis or treatment were only listed. Dates for single dosages of Afinitor® or exemestane were not analyzed, but used to calculate durations and mean dosage. Information on the manufacturer of exemestane was not analyzed.

9.4.6 Variable definitions

9.4.6.1 Age, durations, number of therapies, average dose

Age was calculated as year of baseline visit – year of birth.

Additionally, age was categorized: < 65 years; 65-74 years; ≥74 years.

Patients were classified according to their BMI into the following categories:

- underweight BMI < 18.5
- normal $18.5 \leq$ BMI < 25
- overweight $25 \leq$ BMI < 30
- obese $30 \leq$ BMI.

For Cox regression analysis, the BMI was categorized as follows: < 20; 20-25; 26-29 and ≥ 30.

Time since primary diagnosis in month was calculated as (date of baseline visit – date of diagnosis). In case, date of diagnosis was incomplete and missing, month was imputed as "6".

The average dose of Afinitor® was calculated as sum of (time periods times dose) divided by the total documentation period. Periods with interruption of Afinitor® were included with a dose of "0 mg".

The relative dose intensity for Afinitor® was calculated as sum of (time periods times dose) divided by (total documentation period * 10 mg) in percent.

The study duration per patient was calculated as (date of last visit – date of first visit + 1)/365.25.

9.4.6.2 EORTC QLQ-C30/BR23

The EORTC QLQ-C30 version 3.0 was used. The questionnaire resulted into the following scales "global health status/QoL" (based on questions 29 and 30), the functional scales "physical functioning" (based on questions 1-5), "role functioning" (based on questions 6 and 7), "emotional functioning" (based on questions 21-24), "cognitive functioning" (based on questions 20 and 25), "social functioning" (based on questions 26 and 27), and the symptom scales "fatigue" (based on questions 10, 12, 18), "nausea and vomiting" (based on questions 14 and 15), "pain" (based on questions 9 and 19), "dyspnoea" (question 8), "insomnia" (question 11), "appetite loss" (question 13), "constipation" (question 16), "diarrhoea" (question 17), "financial difficulties" (question 28).

The breast cancer module BR23 incorporated five multi-item scales to assess "systemic treatment side effects" (based on questions 1-4 and 6-8; symptom scale), "arm symptoms" (based on questions 17-19; symptom scale), "breast symptoms" (based on questions 20-23; symptom scale), "body image" (based on questions 9-12; functional scale) and "sexual functioning" (based on questions 14-15; functional scale). In addition, single items assessed "sexual enjoyment" (based on question 16, functional scale), "upset by hair loss" (based on question 5; symptom scale) and "future perspective" (based on question 13; functional scale). "Sexual enjoyment" had to be set to missing, if question 15 was answered "not at all". "Upset by hair loss" had to be set to missing, if question 4 was answered "not at all".

Based on the mentioned questions a raw score was calculated as mean of answered items divided by the number of answered items. Scales were then transformed to a range from 0 to 100 (100 representing high functioning and high quality of life, but also a high level of symptomatology) using the following two formulas:

Functional scales $S = (1 – (\text{raw score} – 1)/ \text{item range})*100$

Symptom scale/QoL $S = (\text{raw score} -1)/ \text{item range}*100$.

The item range is "6" for the "Global health status/QoL" scale and "3" of all other scales. In case more than half of the questions were not answered, the respective scale was set to "missing".

9.4.6.3 Godin Leisure-Time Exercise Questionnaire

The weekly leisure-time activity score (WLTAS) was calculated (Godin 2011) as

9*number of strenuous activities +

5*number of moderate activities +

3*number of mild activities.

Based on the Godin Leisure-Time exercise questionnaire the following three subgroups were developed:

active:	if 9*number of strenuous activities + 5*number of moderate activities ≥ 24
moderately active:	if 9*number of strenuous activities + 5*number of moderate activities was between [14 and 23]
insufficiently active:	if 9*number of strenuous activities + 5*number of moderate activities < 14.

9.4.6.4 Physical exercise scale (KAS)

Questions 1 and 2 of the physical exercise scales (KAS) were categorized in three equally sized parts: 0-33 = little, 34-66 = somewhat and 67-100 = very active.

9.4.6.5 Time to event

The following applied for the calculation of the times mentioned below: If the death of a patient was documented as an AE, the start of this event was used as date of death.

Progression-free survival (PFS) was defined as the time between

(Date of the first progression after baseline and date of the baseline visit + 1) in the event of progression or death. If the day or the month was missing in the date of progression, this was replaced by "1".

For final analysis, patients were followed up until progression or death. Patients were only censored due to lost-to-follow up or survival without progression or death until the official study end.

Time to first occurrence of stomatitis was defined as the time between

(Start date of the first AE with term "stomatitis" and date of the baseline visit + 1) in the event of occurrence of stomatitis. If the day or the month was missing in the start date of stomatitis, this was replaced by "1".

Patients without stomatitis during the documentation period were censored with the date of the premature discontinuation or the date of final documentation.

In case AEs were not coded at the time of interim analysis, date of visit was used as start date of stomatitis.

Duration of treatment was defined as the time between

(end of combination therapy with Afinitor® and exemestane - start date of combination therapy with Afinitor® and exemestane +1).

In case documentation ended without end of combination treatment, the date of last contact was used.

Time until first worsening of at least 5% in QLQ-C30 subscale "Global health status/QoL" was defined as the time between

(date of QLQ-C30 questionnaire with a deterioration of at least 5% percentage points compared to baseline – data of basel QLQ-C30 questionnaire +1).

9.4.6.6 Best overall response

Best overall response was defined as the best response reached for the patient until study end i.e. no confirmation of a given response was required. The variable was analyzed twice, once as documented in the eCRF (end-of-study) and once derived from data documented within each visit.

9.4.6.7 Safety related definitions

In case causality was missing for an AE, the causality was assessed as "related".

AEs were classified according to their duration (<1 week; 1-<2 weeks; 2-< 4 weeks; 4-<12 weeks; 12-<24 weeks; 24-<48 weeks; ≥48 weeks; duration unknown) and the analyses were repeated by those duration categories.

Duration was calculated as end date – start date + 1. In case start- or end date are incomplete, but the duration can be classified unambiguously to an interval (e.g. start date 28/12/13 and end date -/12/13 → <1 week; start date -/01/12 and end date -/02/13 → ≥48 weeks), this interval was used for analysis. Otherwise the event was analyzed as "unknown" (e.g. start date 21/12/13 and end date -/12/13 → unknown).

9.4.6.8 Charlson Comorbidity Index (CCI)

The presence of the following comorbidities were scored with

- a value of "1": infarction, heart failure, dementia, peripheral artery occlusive disease, chronic lung disease, connective tissue disease, ulcer disease, diabetes without target organ damage, TIA/ apoplexy without severe residuals, mild liver disease
- a value of "2": moderately severe or severe renal disease, diabetes with target organ damage, leukemia, lymphoma, hemiplegia
- a value of "3": moderately severe or severe liver disease
- a value of "6": acquired immune deficiency syndrome (AIDS).

Additionally to the continuous score, three categories were defined based on the CCI. "No comorbidity" was defined as a CCI = 0, "Moderate comorbidity" was defined as a CCI of 1 or 2 and "Severe comorbidity" was defined as a CCI of 3 or more.

9.4.6.9 Visceral metastases

A metastasis was summarized as "visceral" metastasis, if the location was documented as "lung", "liver" or "cns".

9.4.6.10 Stomatitis and pneumonitis

Stomatitis was selected from all AEs using the preferred term (PT) code "10042128".

Any AE with the PTs "mouth ulceration (10028034)", "tongue ulceration (10043991)", "aphthous stomatitis (10002958)", "stomatitis (10042128)", "mucosal ulceration (10028124)", "gingival swelling (10018291)", "gingival ulceration (10049398)", "gingival pain (10018286)", "glossitis (10018386)", "glossodynia (10018288)", "lip ulceration (10024572)" and "mucosal inflammation (10028116)" were defined as stomatitis related events.

Pneumonitis was selected from all AEs using the PT code "10035742".

For calculation of duration between occurrence of stomatitis and occurrence of pneumonitis the onset dates were used. In case a patient experienced more than one event of the same kind, the smallest duration was used for calculating tables.

9.4.6.11 Patient questionnaire on stomatitis prophylaxis

With amendment 3, an additional patient questionnaire on prophylaxis measures against stomatitis was implemented. For each measure frequencies were planned to be provided for the answer categories: "several times a day", "several times a week" and "several times a month".

In order to correlate stomatitis prophylaxis measures and later occurrence of stomatitis the following two categories were planned to be applied:

A stomatitis is directly following a prophylactic measure, if the stomatitis occurred between the visit the questionnaire was answered and the next visit.

A stomatitis is never following a prophylactic measure, if the stomatitis occurred at any time after the visit the questionnaire was completed.

9.5 Data sources and measurement

An overview on measurements during the course of the study is given in this section. Data were collected on the study-specific eCRF and on paper questionnaires (EORTC QLQ-C30/BR23, KAS, WLTAS). Details regarding the variables are provided in section 9.4.

9.5.1 Observed parameters at baseline visit

After written informed consent in study participation:

- Date start of observation/baseline visit
- Demographic data (incl. height and weight) and baseline characteristics, disease history (primary diagnosis, metastases, localization, prior therapies, concomitant therapies, tumor resection, tumor biology)
- ECOG performance state

- Current tumor anamnesis (TNM state, localization of metastases, last imaging)
- Reason for change of treatment to Afinitor®
- Comorbidity
- Antiresorptive treatment for prevention of complications in case of bone metastases
- Planned prophylactic measures regarding stomatitis
- QoL: patient questionnaires EORTC QLQ-C30/BR23
- Physical activity: questionnaires: "Godin Leisure-Time Exercise Questionnaire" and "Körperliche Aktivitäts-Skalen" (physical activity score, KAS)
- Compliance
- Prescription of Afinitor®
- Planned follow-up

9.5.2 Observed parameters 2 weeks after start of documentation (prospectively, since implementation of amendment 2 in eCRF)

If according to practice routine, a visit took place approximately 2 weeks after start of observation, the following parameters were documented:

- Date of follow-up
- Documentation of stomatitis treatment, as applicable
- Current tumor therapy with Afinitor®
- Documentation of AEs
- Planned follow-up

9.5.3 Observed parameters at follow-up visits

According to practice routine, the documentation of the following parameters was intended at regular visits (e.g. after 1 month, after 3 months and then at 3-monthly intervals):

- Date of follow-up
- ECOG performance state – if performed
- Weight
- Follow-up imaging (not at month 1)
- Assessment of treatment response (after imaging and/or clinical assessment of status according to practice routine)
- Current tumor treatment with Afinitor®
- Prophylactic measures regarding therapy management

- QoL: EORTC QLQ-C30/BR23 questionnaires
- Physical activity: questionnaires: "Godin Leisure-Time Exercise Questionnaire" and "Körperliche Aktivitäts-Skalen" (physical activity score, KAS)
- Compliance
- Documentation of stomatitis treatment, as applicable
- Patient questionnaire regarding stomatitis prophylaxis
- Current tumor treatment with Afinitor®
- Documentation of AEs
- Planned follow-up

9.5.4 Final visit at the end of observation

The documentation of the end of treatment with Afinitor® was not related to the intended observation interval, but should have been performed at the next possible time in accordance with practice routine. The following parameters were observed:

- Reason for discontinuation of documentation
- Afinitor® treatment
- Reason for end of treatment
- Assessment of treatment response (after imaging and/or clinical assessment of status according to practice routine)
- Planned follow-up treatment
- Documentation of AEs

9.6 Bias

This non-interventional, uncontrolled, open-label study collected data based on variables, which were assessed and documented in daily routine. No study-specific measures to assess and address potential sources of bias were performed. However, due to the large sample size and a high number of participating study centers, a selection bias should be sufficiently controlled. Some general inclusion criteria also contribute to a homogenous study population.

9.7 Study size

The sample size of about 3,000 is approximately 11% of the total population with this indication, based on the assumption that treatment with Afinitor® in combination with exemestane according to the system organ class (SOC) would be appropriate during patient inclusion (October 2012 to December 2014) for about 24,000 to 26,000 patients. The sample size of up to 3,000 allowed sufficiently large subgroups, to perform a comparative analysis between patients with higher and lower physical activity regarding effectiveness and QoL.

The representativeness of the participating approximately 400 study centers was ensured by the nationwide and nearly continuous regional distribution. The selection of a study center was only based on its involvement in the care of the evaluated patient collective and the interest of the center in the participation of a structured case documentation and evaluation. As no explicit exclusion criteria were defined (i.e. all patients, who fulfilled the documentation criteria, were allowed to be documented), the representativeness of the selection within the centers was ensured.

9.8 Data transformation

No transformations on data were performed. All scores were calculated according to the respective descriptions. Details on calculations are provided in section 8.4 and the SAP.

9.9 Statistical methods

9.9.1 Main summary measures

Categorical data were analyzed by presenting frequency tables (absolute and relative adjusted frequencies). For numerical data, the sample statistics mean, standard deviation, median, minimum, and maximum, the 5% and 95% percentiles and quartiles were calculated.

Data measured several times during the study were analyzed by visit presenting absolute and relative differences to baseline for numerical data and shift tables for categorical data.

Correlations between different continuous parameters were analyzed presenting Spearman's Rank Correlation Coefficient.

Time-to-event data were analyzed using Kaplan-Meier-estimators.

9.9.2 Main statistical methods

Main statistical methods are also described in the SAP in Appendix 5.

According to the methodological features of an observational NIS, all statistical analyses were considered purely descriptive.

The analysis was generated using the SAS-software, version 9.2. Further specification of the used soft- and hardware are listed in the document "System_specifications_140102.doc" which was regarded as part of this statistical analysis plan. Further documentation on validation can be provided upon request.

9.9.2.1 Statistical analysis of the primary parameter

The primary parameter was PFS under a combination therapy with Afinitor® and exemestane in relation to extent of physical exercise.

The relationship was analyzed presenting Kaplan-Meier estimates for PFS for the activity-based subgroups based on Godin Leisure-time activity questionnaire.

Multivariate analysis of PFS was done using a Cox-regression model including the following categorized parameters: start dose (5 vs. 10 mg); age and BMI categories, ECOG (0 vs. ≥ 1), therapy line (1st vs 2nd/3rd vs 4th and above) and presence of visceral metastases (yes vs no).

9.9.2.2 Methods used to examine subgroups and interactions

The following subgroup analyses were planned:

- First 500 patients (only for IA1 and IA2; was not planned to be part of final analysis and final clinical study report)
- Fist 1,000 patients (only for IA3, not planned to be part of final analysis and final clinical study report)
- Activity subgroups based on Godin Leisure-time activity questionnaire
- By therapy line
- By start dose

Single analyses (e.g. on progression-free survival) were repeated for the following subgroups:

- Prior treatment with exemestane yes/no
- Prior chemotherapy in advanced setting yes/no
- By type of metastases (only bone, only visceral, single visceral, multiple visceral)
- By therapy line
- If first line therapy, then further divided by time to recurrence/metastasis ≤12 months, ≤24 months, ≤60 months, >60 months after primary diagnosis
- By severity of stomatitis
- By KI-67 index
- By number of AEs
- By sensitivity to prior hormonal therapy

Analysis related to the topic "stomatitis" were repeated once based on "stomatitis" and once based on "stomatitis related events".

9.9.2.3 Safety analysis

The incidence of AEs was computed for all AEs, non-serious AEs (nsAEs), serious AEs (SAEs), non-serious not-related AEs (nsAEnr), non-serious drug-related adverse reactions (nsADR), serious not-related AEs (SAEnr) and serious drug-related adverse reactions (SADR). The incidence was defined as the number of patients with at least one AE of the respective type divided by the number of patients at risk. The patients at risk were all patients of the FAS.

AEs were analyzed by duration categories (see section 9.4.6.7 for definition) and intensity.

Additionally the frequency of AEs was analyzed by KAS categories (see section 9.4.6.4). The relationship of the activity / exercise at baseline on the occurrence of an AE was analyzed using a logistic regression.

All nsAEnr and nsADR were listed separately presenting the following information: patient–ID (center + patient no.), age, sex, study treatment (dose and duration), start date, duration, intensity, action taken, outcome, causality, event verbatim, PT, concomitant medication, prior and concomitant diseases.

All SAEnr and SADR (excluding deaths) were listed separately presenting the following information: patient–ID (center + patient no.), age, sex, study treatment (dose and duration), start date, duration, intensity, action taken, outcome, causality, event verbatim, preferred term, concomitant medication, prior and concomitant diseases.

All deaths (separated by SAEnr and SADR) were listed presenting the following information: patient–ID (center + patient no.), age, sex, study treatment (dose and duration), start date, duration, intensity, action taken, outcome, causality, event verbatim, preferred term, concomitant medication, prior and concomitant diseases, date of death, cause of death.

Pregnancies (if any) were listed presenting the following information: patient-ID (center + patient no.), age, outcome of pregnancy, AEs (if occurred).

Adverse events of special interest (AESI) were presented for this final analysis. The events were defined in the Novartis Product Guidance Document for Afinitor/Votubia (everolimus) that was valid at time of final analysis.

9.9.3 Missing values

Generally, missing values were not imputed. Handling of missing values for data from patient questionnaires and censoring of missing data for time-to-event data was also described in section 9.4.6.

Data being implausible after completion of the data management process were set to missing.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

No amendments were made to the plan of data analysis included in the study protocol. SAP version 2.0 (21 June 2014) included the addition of an analysis.

SAP version 3.0 (10 December 2014) integrated the changes of amendment 4 of the observation plan: addition of an analysis (stomatitis prophylaxis, incidence and therapy), the change in relevant study population for IA3 (PFS 18 months after inclusion of 500 patients), the analyses of the per protocol set and time to progression (TTP) were deleted.

An analysis of deaths during this NIS was performed post-hoc (October 2016) to cope with safety requirements.

SAP version 4.0 (09 March 2018) contained the adaptation to consider progression follow-up documentation after end of study treatment and the adaptation to the final analysis requirements.

9.9.6 Analysis sets

Analyses were based on subjects with a documented application of Afinitor® and at least one follow-up under treatment (including documentation of an AE) (FAS).

Subjects from FAS with an age below 18 years or with a diagnosis different to the one required were excluded from the per protocol set.

9.10 Quality control

Evaluation of data and queries

Documentation, except for the questionnaires used as paper version, was made by the treating physician only online using the eCRF. Data entry was followed by [redacted] according to agreements. Free text entries of new entered or actualized data were checked within the stipulated timelines by the data management regarding AEs. Data queries were planned to be performed online via eCRF module. In exceptional cases, queries could be sent as agreed upon by contract. A signed copy of these queries had to be kept at the study center.

The patient questionnaires had to be completed manually. During or at the end of the NIS in a center, the completed questionnaires had to be sent to [redacted] Physicians were obliged to screen the completed questionnaires for hidden/unreported (S)AEs prior to transfer to [redacted] Incoming questionnaires were checked for hidden/unreported AEs by [redacted] within the stipulated timelines. Follow-up procedures and guidelines regarding SAE and cumulative AE reporting were done according to respective standard operating procedures (SOPs) of Novartis Pharma GmbH.

Monitoring/source data verification

Monitoring and source data verification (SDV) procedures were planned in detail in the observation plan and the monitoring plan.

9.11 Protection of human subjects

Patient information and informed consent form

Each patient was informed before inclusion into the NIS about the goals, kind and extent of the documentation by the treating physician. As the medication was already approved, a special patient information exceeding the information provided in the package leaflet was not necessary.

A patient was not allowed to be included into the NIS without written consent to the documentation of her data during the NIS as well as the insight into her patient file for data verification. However, patients were also allowed to be included into the documentation if the treatment with Afinitor® and exemestane was already started at the latest 6 weeks before declaration of the informed consent in participation of the NIS and they were receiving Afinitor® and exemestane at that time point. The handling of the personal data during the

verification of the evaluated data with the data file (SDV) was subject of the EU-guidance 95/46/EC and the national regulations for data protection.

Ethics committee approval

An ethics committee approval was obtained from the Ethics Committee of the [redacted], responsible for the principal investigator of the NIS before study start and according to the recommendations by BfArM and PEI for planning, implementation and evaluation of observational studies and according to a recommendation of the VFA for improvement of quality and transparency of NISs.

Data protection

The protection of the patient's data was guaranteed. The patient data evaluated during the NIS were documented in a pseudonymized way in the eCRF i.e. only with a patient number and without mentioning name, initials, birth date, or address of a patient.

In case of a publication of the study results, it was only allowed to use the personal data in an anonymized way. Insight into the personal data was only allowed to authorized employees of the sponsor obliged to secrecy, to the responsible authorities, as far as necessary for the regular verification of the conduct of the NIS.

The medical staff responsible for the documentation of data from the patient file was informed about their responsibility regarding data protection law.

Law and regulatory principles, notification

This NIS was conducted according to the SOPs of Novartis Pharma GmbH based on the following recommendations and guidelines:

- § 4 section 23, subsection 3 (AMG)
- The BfArM, the "National Association of Statutory Health Insurance Physicians" (German "Kassenärztliche Bundesvereinigung"), and the National Association of Health Insurance Funds (German "Spitzenverband der Krankenkassen, gesetzliche wie private") were notified about the conduct of this NIS according to § 67, section 6 (AMG).
- § 63 b (AMG)
- Directive 2001/83/EC of the European Parliament and of the Council and changes with directive 2010/84/EC of the European Parliament and of the Council
- Pharmacovigilance Guidelines of Volume 9A of "The Rules Governing Medicinal Products in the EU"
- Guideline on good Pharmacovigilance practices (GVP), Module VI - Management and reporting of adverse reactions to medicinal products
- Common "recommendation(s) for planning, implementation and evaluation of observational studies with medicinal products" of BfArM and the PEI (07 July 2010)

- The study was also entered into the officially available register for NIS at the VFA before study start (http://www.vfa.de/de/forschung/nisdb/)
- Recommendations of VFA for improvement of quality and transparency of NIS from 31 January 2007 and 23 April 2007
- FSA codex for collaboration with experts – Federal Gazette (German "Bundesanzeiger, 07 May 2008").

10 Results

This report describes the results of the planned final analysis based on the data of all patients during the observation period from 30th August 2012 until 29th December 2017 (see PT-Table 14.1.1-3.1).

10.1 Participants

It was planned to analyze 3000 patients in 400 centers in Germany during this NIS. Two thousand and one-hundred (2100) patients (70.0% of the planned number) were included in 341 centers (post-text-Table [PT-Table] 14.1.1-1.2). Two thousand and seventy-four (2074) patients were included in the FAS. Twenty-six patients were not included in the FAS, on the one hand because no Afinitor® application had been documented and on the other hand because no follow-up was available under therapy (PT-Table 14.1.1-1.1).

One thousand nine hundred and eighty-seven (1987) patients (94.6%) discontinued the study prematurely (PT-Table 14.1.1-2.1.1). Reason for premature discontinuation of documentation was mainly therapy discontinued (1767 patients, 84.1%). Reasons for premature discontinuation of combination therapy were mainly progression of disease (1170 patients, 55.7%) and AEs (546 patients, 26.0%, see PT-Table 14.1.1-2.2.1). A summary of patients' disposition and reasons for premature discontinuation is provided in Table 10-1.

Table 10-1 Patient disposition and reasons for premature discontinuation

Patients	All patients N=2100 n (%)
Planned	3000
Entered study data base[a]	2100 (100.0)
Included in FAS	2074 (98.8)
Completed study	70 (3.3)
Discontinued prematurely	1987 (94.6)
Reason for premature discontinuation of documentation	
Therapy discontinued prematurely	1767 (84.1)
Death	145 (6.9)
Lost to follow-up	75 (3.6)
Formal study end reached	70 (3.3)
Consent withdrawn[a]	0 (0.0)
Missing	43 (2.0)
Reason for premature discontinuation of combination therapy	
Progression	1170 (55.7)
Adverse event	546 (26.0)
Patient's wish	199 (9.5)
Poor compliance	32 (1.5)
Missing	153 (7.3)

a Data from patients with missing informed consent or consent withdrawn were not included into the study database.

In total N = 212 patients were excluded either due to missing informed consent or consent withdrawn.

Source: PT-Tables 14.1.1-1.1, 14.1.1-2.1.1, and 14.1.1-2.2.1

Reasons for premature discontinuation of documentation of all patients by start dose are provided in PT-Tables 14.1.1-2.1.2 (5 mg start dose), and 14.1.1-2.1.3 (10 mg start dose).

Reasons for premature discontinuation of combination therapy for all patients who started with 5 mg or 10 mg Afinitor® are provided in PT-Tables 14.1.1-2.2.2 and 14.1.1-2.2.3.

Reasons for premature discontinuation of documentation by reason for premature discontinuation of therapy were also analyzed for all patients. Respective data are provided in PT-Tables 14.1.1-2.3.1, 14.1.1-2.3.2, and 14.1.1-2.3.3.

Table 10-2 summarizes the performed study visits and the time period between the respective visit and the baseline visit. PT-Table 14.1.1-5 lists the number of patients by study visit. Beyond the study visit at month 24 the number of patients decreased below 100. At the visit month 51 only six patients were documented.

Table 10-2 Study visits performed

FAS Period between study visit and baseline (days)	n	Mean ± SD	All patients N=2074 Median [Min, Max]
Month 1	1930	33.8 ± 14.6	30.0 [0.0, 399.0]
Month 3	1538	95.3 ± 23.8	92.0 [25.0, 462.0]
Month 6	989	187.2 ± 43.6	183.0 [27.0, 1164.0]
Month 9	659	277.0 ± 34.0	274.0 [161.0, 636.0]
Month 12	463	371.1 ± 41.9	365.0 [226.0, 931.0]
Month 15	319	463.2 ± 37.6	457.0 [253.0, 623.0]
Month 18	228	558.2 ± 45.2	553.0 [182.0, 690.0]
Month 21	164	649.2 ± 41.6	645.0 [483.0, 800.0]
Monat 24	124	746.7 ± 42.6	740.5 [634.0, 885.0]
Monat 27	87	841.9 ± 46.7	838.0 [718.0, 989.0]
Monat 30	67	940.7 ± 52.2	938.0 [797.0, 1085.0]
Monat 33	49	1036.9 ± 56.4	1030.0 [900.0, 1190.0]
Monat 36	36	1123.8 ± 63.3	1135.0 [944.0, 1275.0]
Monat 39	26	1218.8 ± 77.1	1218.5 [1071.0, 1369.0]
Monat 42	20	1309.7 ± 83.5	1308.0 [1168.0, 1452.0]
Monat 45	17	1404.8 ± 93.8	1414.0 [1259.0, 1570.0]
Monat 48	10	1495.3 ± 113.8	1489.0 [1343.0, 1696.0]
Monat 51	6	1534.8 ± 109.7	1527.5 [1427.0, 1661.0]

Source: PT-Table 14.1.1-3.2

Numbers of patients included by study month are provided in PT-Table 14.1.1-3.3.

PT-Table 14.1.1-4 shows the protocol deviations. One patient each did not have the diagnosis of breast cancer (advanced hormone-ER2/neu negative) or a pre-treatment with non-steroidal aromatase inhibitor.

10.2 Descriptive data

10.2.1 Demographic data

The median age of the patients was 66.0 years (P5%; P95%: 48.0; 81.0), the median weight was 70.0 kg (P5%; P95%: 51.7; 98.0), the median height 164.0 cm (P5%; P95%: 154.0; 175.0), and the median BMI 25.7 kg/m^2 (P5%; P95%: 19.7; 36.3). Most patients (1525, 91.2%) had a normal or restricted ECOG performance state of 0 (837, 50.1%) and 1 (688, 41.1%). An ECOG of 2 or higher was documented for 147 patients (8.8%) (PT-Table 14.1.2). Table 10-3 summarizes demographic data and ECOG performance state for the patients.

Table 10-3 Demographic data and ECOG performance state

		N=2074 n (%)
Continuous data		
Age (years)	n, Mean ± SD	2074, 65.3 ± 10.3
	Median (P5%; P95%)	66.0 (48.0; 81.0)
Weight (kg)	n, Mean ± SD	2019, 71.6 ± 14.5
	Median (P5%; P95%)	70.0 (51.7; 98.0)
Height (cm)	n, Mean ± SD	2044, 164.2 ± 6.5
	Median (P5%; P95%)	164.0 (154.0; 175.0)
BMI (kg/m^2)	n, Mean ± SD	2015, 26.6 ± 5.2
	Median (P5%; P95%)	25.7 (19.7; 36.3)
Categorical data [n (%)]		
ECOG		
0 – normal, unrestricted activity like prior to disease		837 (50.1)
1 – Restricted in physical effort, but able to walk		688 (41.1)
2 – Able to walk, self-sufficiency possible, but unfit for work		126 (7.5)
3 – Only limited self-sufficiency possible, >= 50% of waking hours confined to bed/chair		20 (1.2)
4 – Completely dependent on care, self-sufficiency not possible		1 (0.1)
Missing		402

BMI = body mass index, ECOG = Eastern Cooperative Oncology Group, SD = standard deviation, P = percentile
Source: PT-Table 14.1.2

10.2.2 Medical history

Tumor anamnesis

Tumor anamnesis of all patients at the time of primary diagnosis and the time of first recurrence or detection of metastases is provided in PT-Table 14.1.3-1.

The tumor was diagnosed in the median 7.1 years ago (P5%; P95%: 1.3; 22.5). The median time since first diagnosis of recurrence or occurrence of metastases was 2.1 years (P5%; P95%: 0.1; 11.1). Tumors were graded according to the TNM stadium. Most patients were classified into T stadium 2 or 1 (882, 42.8% and 580, 28.2%), N stadium 1 or 0 (742, 36.0% and 582, 28.2%), and M stadium 0 or 1 (1362, 66.3% and 523, 25.5%) (PT-Table 14.1.3-1).

Histological grading, measuring the differentiation of a tumor, revealed that most of the patients had G2 (moderately differentiated, 1312, 66.8%) or G3 (poorly differentiated, 547 patients, 27.8%) tumors. The histological subtype was mainly invasive ductal (1404, 70.2%), followed by invasive lobular (415, 20.8%) and "other subtype" (180, 9.0%). Metastases were specified for 2069 patients, mainly located in the bones (1391, 67.2%), lymph nodes (480, 23.2%), lung (460, 22.2%) or liver (426, 20.6%). "Only bone metastases", "bone and other metastases", and "only other metastases" were documented for about one third of patients, respectively. Visceral metastases [lung, liver, central nervous system (CNS)] were documented for 796 patients

(38.5%), visceral and bone metastases for 480 patients (23.2%), and visceral without bone metastases for 316 patients (15.3%). At the time of primary diagnosis, 421 patients (20.4%) had M1 metastases. For 416 patients (20.1%), time of primary diagnosis and first metastases was identical (PT-Table 14.1.3-1).

Current tumor status

At study entry, the current stadium of disease was assessed as "metastasized" for 2009 patients (97.6%). The median time since last radiological image prove was 0.8 months ago (P5%; P95%: 0.1; 5.8). Most patients were classified into T stadium X (tumor cannot be evaluated; 980, 49.3%) or 2 (size and extension of primary tumor; 447, 22.5%), N stadium X (lymph nodes cannot be evaluated; 882, 44.3%) or 1 (regional lymph node metastasis present; 442, 22.2%), and M stadium 1 [metastasis to distant organs (beyond regional lymph nodes); 1770, 88.4%]. Data are provided in PT-Table 14.1.3-2.

Localization of current metastases

Localization of metastases is provided in PT-Table 14.1.3-2. For 2066 patients, localization of metastases was specified. Most metastases were located in the bones (1538, 74.4%), liver (736, 35.6%), lung (576, 27.9%), lymph nodes (564, 27.3%), skin (113, 5.5%), CNS (43, 2.1%), and other localization (350, 16.9%). "Bone and other metastases" were documented for half of the patients (1012, 49.0%), "only bone metastases" for 526 patients (25.5%), and "only other metastases" for 507 patients (24.5%). More than half of the patients (1117, 54.1%) had visceral metastases, 768 patients (37.2%) had visceral and bone metastases.

Imaging of metastases is summarized in Table 10-4. Metastases in bones, liver, lung, lymph nodes, and "other metastases" were mainly localized by computed tomography (CT) scan, while CNS metastases were mainly localized by magnetic resonance imaging (MRI) and skin metastases by "other methods" not further specified.

Table 10-4 Imaging of metastases

Procedure of medical imaging by localization		N=2074 n (%)
Patients with bone metastases		1538 (100.0)
	CT scan	758 (50.2)
	Bone scan	495 (32.8)
	MRI	186 (12.3)
	PET/PET-CT	36 (2.4)
	Conventional X-ray	20 (1.3)
	Other	14 (0.9)
	Missing	29
Patients with liver metastases		736 (100.0)
	CT scan	517 (72.4)
	MRI	100 (14.0)
	PET/PET-CT	18 (2.5)
	Bone scan	3 (0.4)
	Conventional X-ray	3 (0.4)
	Other	73 (10.2)
	Missing	22

Table 10-4 Imaging of metastases

Procedure of medical imaging by localization		N=2074 n (%)
Patients with lung metastases		576 (100.0)
	CT scan	512 (89.5)
	PET/PET-CT	19 (3.3)
	Conventional X-ray	18 (3.1)
	MRI	10 (1.7)
	Bone scan	5 (0.9)
	Other	8 (1.4)
	Missing	4
Patients with lymph node metastases		564 (100.0)
	CT scan	401 (71.9)
	PET/PET-CT	27 (4.8)
	MRI	24 (4.3)
	Bone scan	8 (1.4)
	Conventional X-ray	5 (0.9)
	Other	93 (16.7)
	Missing	6
Patients with skin metastases		113 (100.0)
	CT scan	30 (27.8)
	PET/PET-CT	3 (2.8)
	MRI	1 (0.9)
	Conventional X-ray	1 (0.9)
	Bone scan	0 (0.0)
	Other	73 (67.6)
	Missing	5
Patients with CNS metastases		43 (100.0)
	MRI	28 (66.7)
	CT scan	10 (23.8)
	Bone scan	1 (2.4)
	PET/PET-CT	0 (0.0)
	Conventional X-ray	0 (0.0)
	Other	3 (7.1)
	Missing	1
Patients with other metastases		350 (100.0)
	CT scan	253 (72.7)
	MRI	23 (6.6)
	Conventional X-ray	12 (3.4)
	PET/PET-CT	11 (3.2)
	Bone scan	2 (0.6)
	Other	47 (13.5)
	Missing	2

CNS = central nervous system, CT = computed tomography, PET = positron emission tomography, MRI = magnetic resonance imaging,

Source: PT-Table 14.1.3-2

Current HER2/neu and hormone receptor status

The status of hormone receptors (estrogen receptor [ER], progesterone receptor [PgR]) and of HER2/neu receptor, and Ki-67 for the patients is provided in PT-Tables 14.1.3-3.1, 14.1.3-3.2, 14.1.3-4.

The most recent examination of hormone receptors was in the median 22.0 months ago (P5%; P95%: 0.0; 146.0). For the current receptor status examination, the primary tumor was used in more than half of the patients (1126, 55.1%), "other tumor" was used in 918 patients (44.9%). Hormone status for the ER and the PgR was positive in 2034 (98.3%) and 1562 (75.5%) patients. For 1527 patients (73.8%), a combination of ER/PgR was tested positive. HER2/neu receptor status documentation was missing in 4 patients, for the remaining 2070 patients, no HER2/neu was detected in any of the examined tumors.

The Ki-67 index was >20% in 428 patients (24.3%), 15-20% in 260 patients (14.7%), <10% in 177 patients (10.0%), and 10-14% in 153 patients (8.7%). In 42.3% (n=746) of the patients the index was unknown. Ki-67 antigen is a nuclear protein associated with cellular proliferation.

Prior antineoplastic therapy

A total of 1899 of the patients (91.6%) had at least one prior antineoplastic surgery. This was mainly a mastectomy (1070, 51.6%), followed by segment resection (880, 42.4%), lumpectomy (387, 18.7%), and resection of metastases (355, 17.1%). Other surgeries were performed in 19 patients (0.9%) (PT-Table 14.1.3-5.1.1).

PT-Table 14.1.3-5.1.2 shows the number of patients with at least one specification regarding residual disease, hormone receptor status, HER2/neu receptor status, and Ki67-index.

Data on prior antineoplastic therapy regarding tumor anamnesis and time since primary diagnosis are provided in PT-Table 14.1.3-5.1.3.

At least one prior antineoplastic radiation was performed in 1675 patients (80.8%), mainly at the following localizations in adjuvant (1227 patients, 73.3%), palliative (829 patients, 49.5%), or neoadjuvant (23 patients, 1.4%) setting (PT-Table 14.1.3-5.2):

- breast (972, 46.9%)
- bones (599, 28.9%)
- thorax (440, 21.2%)
- lymph nodes (276, 13.3%)
- other localization (127, 6.1%)
- pelvis/abdomen (25, 1.2%)
- head/neck (24, 1.2%)
- whole brain (24, 1.2%)
- brain, focused on tumor (13, 0.6%).

Prior antineoplastic therapy (medication) received by patients according to line of treatment is provided in PT-Table 14.1.3-5.3.1.1.1. All of the 2074 patients (100.0%) received letrozole/anastrozole, chemotherapy was given to 1068 patients (51.5%), tamoxifen was given to 879 patients (42.4%), fulvestrant was given to 635 patients (30.6%), exemestane was given to 370 patients (17.8%), GnRH analogue was given to 95 patients (4.6%), PI3K/Akt inhibitor was given in one patient (0.05%).

A total of 1006 patients (48.5%) had not received prior chemotherapies.

Prior antineoplastic therapy by type of metastases is provided in PT-Table 14.1.3-5.3.1.1.2.

Prior antineoplastic therapy received as last medication prior to start of treatment by line of treatment is provided in PT-Table 14.1.3-5.3.1.2.1. Last antineoplastic therapy prior to start of treatment by type of metastases is provided in PT-Table 14.1.3-5.3.1.2.2. PT-Figures 14.1.3-5.3.1 to 14.1.3-5.3.6 show prior antineoplastic medication in total and by line.

PT-Table 14.1.3-5.3.2.1 shows the reason for discontinuation of, the best response to, and the setting of the prior antineoplastic medication. In total data for 6506 patients were available. In more than 50% (3360 patients, 52.0%) the reason for discontinuation was “progression”. The most frequent best response with prior antineoplastic medication was “stable disease” in 1776 patients (27.3%), followed by “unknown” in 1454 patients (22.3%), and “progression” in 1183 patients (18.2%). In more than 55% (3695 patients, 56.8%) the setting for the prior antineoplastic medication was “palliative”.

The previous therapies in the advanced setting by oncologist vs. gynecologist and doctor´s office vs. clinic/medical center are shown in PT-Tables 14.1.3-5.3.3.1, 14.1.3-5.3.3.2, and 14.1.3-5.3.3.3.

Therapy line

A summary of therapy line and number of previous therapies of the patients is provided in Table 10-5 (PT-Table 14.1.3-5.4.1). Most patients included were second line (662, 31.9%), followed by first line patients (595, 28.7%), and third line patients (376, 18.1%). The patients had received a median of 1.0 previous therapies (P5%; P95%: 0.0; 5.0).

Table 10-5 Line of previous treatment

Line of treatment	N=2074 n (%)
First line	595 (28.7)
Second line	662 (31.9)
Third line	376 (18.1)
Fourth line	221 (10.7)
Fifth line (and later)	220 (10.6)
No. of previous therapies	
Mean ± SD	1.6 ± 1.7
Median (P5%; P95%)	1.0 (0.0; 5.0)

P = percentile, SD = standard deviation

Source: PT-Table 14.1.3-5.4.1

Data regarding treatment line by groups of 200 patients sorted by time, by oncologist vs. gynecologist and by 200 first and 200 most recent patients are provided in PT-Tables 14.1.3-5.4.2, 14.1.3-5.4.3, and 14.1.3-5.4.4. PT-Figures 14.1.3-5.4.1 to 14.1.3-5.4.3 show the proportion of treatment lines of all patients, for the first 200 and most recent 200 patients included.

Duration until relapse under the previous therapy

Two hundred and sixty-six of 405 first line patients (266, 65.7%) were "fast progressors" under the last adjuvant therapy, i.e. relapse occurred below or within 12 months after this therapy. In 78 patients (19.3%) relapse occurred between 24-60 months thereafter, for 31 patients (7.7%) relapse occurred >60 months after the last therapy, and for 30 patients (7.4%) relapse occurred 12-24 months (PT-Table 14.1.3-5.5).

Concomitant diseases – Charlson comorbidity index

The CCI predicts the ten-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned a score of 1, 2, 3, 4, 5 or 6, depending on the risk of dying associated with each one. Scores are summed to provide a total score to predict mortality. The higher the score, the higher the risk to die.

A total of 1141 of 2074 patients (55.0%) had at least one comorbidity. For 519 patients (25.0%), these comorbidities were taken into account for the CCI. The most common comorbidities were (PT-Table 14.1.3-6.1.1):

- Diabetes mellitus without end organ damage (259, 12.5%), with end organ damage (17, 0.8%)
- Chronic lung disease (111, 5.4%)
- Congestive heart failure (83, 4.0%)
- Cerebrovascular disease: TIA/apoplexy without serious residuals (38, 1.8%), hemiplegia (2, 0.1%)
- Liver disease: mild liver disease (30, 1.5%), moderate or severe liver disease (7, 0.3%)
- Moderate or severe kidney disease (27, 1.3%)
- Peripheral vascular disease (25, 1.2%)
- Connective tissue disease (17, 0.8%)
- Ulcer (17, 0.8%)
- Myocardial infarction (13, 0.6%)
- Lymphoma (9, 0.4%)
- Dementia (6, 0.3%)
- AIDS (5, 0.2%)
- Leukemia (3, 0.1%).

The patients in this study had a median CCI of 0.0 (P5%; P95%: 0.0; 2.0). Of the 2068 patients with specifications, 1549 (74.9%) had no comorbidity, 464 (22.4%) had a moderate

comorbidity, and 55 (2.7%) had a severe comorbidity. The CCI with categories is summarized in Table 10-6.

Table 10-6 Charlson comorbidity index (CCI)

	N=2074
CCI	**n (%)**
0	1549 (74.9)
1	366 (17.7)
2	98 (4.7)
3	31 (1.5)
4	15 (0.7)
5	3 (0.1)
6	6 (0.3)
Missing	6
CCI categories	
No comorbidity (CCI=0)	1549 (74.9)
Moderate comorbidity (CCI=1 or 2)	464 (22.4)
Severe comorbidity (CCI≥3)	55 (2.7)
Missing	6
n, Mean ± SD	2068, 0.4 ± 0.8
Median (P5%; P95%)	0.0 (0.0; 2.0)

CCI = Charlson comorbidity index, P = percentile, SD = standard deviation
Source: PT-Table 14.1.3-6.1.1

Hypertension (905 subjects, 43.7%), osteoporosis (149, 7.2%), depression requiring therapy (83, 4.0%), and prior muscular disease (20, 1.0%) were common comorbidities but are not part of the definition of CCI (PT-Table 14.1.3-6.4). CCI by hypertonia, osteoporosis, depression, and prior muscular disease are provided in PT-Tables 14.1.3-6.1.2, 14.1.3-6.1.3, 14.1.3-6.1.4, and 14.1.3-6.1.5.

The correlation of CCI and global health status based on QLQ-C30 was analyzed at baseline and the last post-baseline value, and is summarized in Table 10-7 (high values correspond to a high quality of life). The global health status and the change from baseline to a post-baseline value were comparable in patients without comorbidity and with moderate comorbidity of CCI 1 or 2. For patients with a CCI of ≥3, an interpretation is not meaningful, due to the very small number of patients (PT-Table 14.1.3-6.2).

Table 10-7 Correlation between CCI and global health status

	Global health status (QoL)		
	No comorbidity (CCI=0)	**Moderate comorbidity (CCI=1 or 2)**	**Severe comorbidity (CCI≥3)**
At baseline			
n	1127	316	37
Mean ± SD	53.6 ± 23.1	48.0 ± 23.0	50.7 ± 23.1
Median (P5%; P95%)	50.0 (16.7; 91.7)	50.0 (16.7; 83.3)	50.0 (8.3; 83.3)
Difference to baseline[a]			
n	960	255	32
Mean ± SD	-5.1 ± 25.7	-3.0 ± 25.5	-1.3 ± 33.8
Median (P5%; P95%)	0.0 (-50.0; 37.5)	0.0 (-50.0; 41.7)	-4.2 (-50.0; 75.0)

CCI = Charlson comorbidity index, P = percentile, SD = standard deviation

a difference to baseline = last post-baseline value – baseline value

Note: high values correspond with high quality of life, positive values describe an increase in quality of life

Source: PT-Table 14.1.3-6.2

The correlation between CCI, age and physical exercise was analyzed with Spearman's Rank correlation coefficients and is summarized together with the sample statistics in Table 10-8. Activity scores range between 0 for none and 100 for very much. The patients were analyzed with regard to their global health status according to the CCI. Overall, no remarkable correlations were observed between the CCI and exercises or activities at different extent. The results point to a weak correlation between increasing age and severity of comorbidity (0.198), exercise during last week and severity of comorbidity (-0.195), physical activity in everyday life during last week and severity of comorbidity (-0.154), and exercise during last ten years and severity of comorbidity (-0.177). Descriptively and with regard to physical exercise and activity at different extent, patients without comorbidity reported to be more active, than those with moderate or severe comorbidity. However, it has to be taken into account that the number of patients with severe comorbidity was very low compared to patients with no comorbidity (PT-Table 14.1.3-6.3.1.2).

Table 10-8 Correlation between CCI, age and physical exercise by comorbidity

	Global health status			
Baseline values	**No comorbidity (CCI=0)**	**Moderate comorbidity (CCI=1 or 2)**	**Severe comorbidity (CCI≥3)**	**Spearman correlation r (95% CI)**
Age (years)				
n	1549	464	55	2068
Mean ± SD	64.1 ± 10.2	68.6 ± 9.8	69.2 ± 11.0	0.198
Median (P5%; P95%)	65.0 (48.0; 80.0)	69.0 (51.0; 84.0)	72.0 (48.0; 86.0)	(0.157; 0.239)

Table 10-8 Correlation between CCI, age and physical exercise by comorbidity

	Global health status			
Baseline values	**No comorbidity (CCI=0)**	**Moderate comorbidity (CCI=1 or 2)**	**Severe comorbidity (CCI≥3)**	**Spearman correlation r (95% CI)**
Weekly leisure time activity score (WLTAS)[a]				
n	1162	330	42	1534
Mean ± SD	21.4 ± 20.8	19.0 ± 30.6	16.7 ± 21.6	-0.109
Median (P5%; P95%)	17.3 (0.0; 61.0)	13.8 (0.0; 59.0)	11.3 (0.0; 56.0)	(-0.158; -0.059)
Exercise during last week[a]				
n	1084	316	37	1437
Mean ± SD	16.1 ± 23.5	7.3 ± 16.9	7.5 ± 16.4	-0.195
Median (P5%; P95%)	3.0 (0.0; 69.0)	0.0 (0.0; 52.0)	1.0 (0.0; 58.0)	(-0.244; -0.144)
Physical activity in everyday life during last week[a]				
n	1111	317	39	1467
Mean ± SD	52.7 ± 30.5	41.3 ± 32.4	41.6 ± 33.0	-0.154
Median (P5%; P95%)	52.0 (0.0; 100.0)	38.0 (0.0; 100.0)	36.0 (0.0; 100.0)	(-0.204; --0.104)
Exercise during last 10 years[a]				
n	1096	312	38	1446
Mean ± SD	42.4 ± 31.8	30.4 ± 29.6	25.4 ± 30.6	-0.177
Median (P5%; P95%)	44.0 (0.0; 98.0)	26.0 (0.0; 86.0)	14.0 (0.0; 95.0)	(-0.226; -0.127)
Physical activity in everyday life during last 10 years[a]				
n	1125	316	39	1480
Mean ± SD	68.8 ± 26.2	63.2 ± 29.5	51.7 ± 34.7	-0.087
Median (P5%; P95%)	75.0 (17.0; 100.0)	65.5 (4.0; 100.0)	50.0 (0.0; 100.0)	(-0.138; -0.036)
Exercise during adolescence up to 20 years[a]				
n	1106	312	41	1459
Mean ± SD	49.8 ± 34.6	45.6 ± 35.6	35.5 ± 34.3	-0.062
Median (P5%; P95%)	50.0 (0.0; 100.0)	46.5 (0.0; 100.0)	24.0 (0.0; 100.0)	(-0.113; -0.010)
Physical activity in everyday life during adolescence up to 20 years[a]				
n	1119	319	40	1478
Mean ± SD	70.0 ± 27.7	68.6 ± 30.3	68.1 ± 33.1	0.007
Median (P5%; P95%)	77.0 (15.0; 100.0)	78.0 (8.0; 100.0)	76.0 (2.0; 100.0)	(-0.044; 0.058)
Exercise during whole life[a]				
n	1111	306	41	1458
Mean ± SD	48.0 ± 29.1	42.0 ± 30.1	31.0 ± 27.0	-0.111
Median (P5%; P95%)	50.0 (0.0; 98.0)	43.0 (0.0; 97.0)	32.0 (0.0; 84.0)	(-0.162; -0.060)
Physical activity in everyday life during whole life[a]				
n	1130	317	40	1487
Mean ± SD	72.9 ± 23.3	69.6 ± 27.7	63.4 ± 34.2	-0.030
Median (P5%; P95%)	78.0 (30.0; 100.0)	77.0 (17.0; 100.0)	76.5 (2.0; 100.0)	(-0.080; 0.021)

CCI = Charlson comorbidity index, P = percentile, SD = standard deviation

a activity scores: 0=none, 100=very much

Source: PT-Tables 14.1.3-6.3.1 and 14.1.3-6.3.2

10.3 Outcome data

10.3.1 Stomatitis prophylaxis and handling

For 1785 of 2065 patients (86.4%), at least one of the following prophylactic measures was performed: mild dental hygiene (1528, 74.0%), avoidance of hot, sour or salty food (1423, 68.9%), rinsing with tea (1280, 62.0%), cooling (e.g. sucking ice or frozen pineapple) (1158, 56.1%), avoidance of peroxide-/ alcohol-containing mouthwash solutions (984, 47.7%), rinsing with mouthwash solution (871, 42.2%), rinsing with NaCl (333, 16.1%), and "other" (172, 8.3%) (PT-Table 14.1.4-1).

For 921 of the 2074 patients (44.4%), data on at least one stomatitis event were available. Mainly stomatitis of grade 1 and 2 was documented (485, 23.4% and 335, 16.2%). The results are summarized in Table 10-9.

Table 10-9 Frequency and intensity of stomatitis

	No. of patients n (%)
Worst intensity of stomatitis	**N=2074**
No. of patients with at least 1 stomatitis event (any grade)	921 (44.4)
Grade 1	485 (23.4)
Grade 2	335 (16.2)
Grade 3	49 (2.4)
Grade 4	1 (<0.1)
Unknown	51 (2.5)

Grade 1: minimal symptoms, normal food intake possible
Grade 2: patient had symptoms/pain, but was able to eat adequately
Grade 3: no sufficient oral food and liquid intake possible
Grade 4: parenteral nutrition necessary, symptoms associated with life-threatening consequences
Source: PT-Table 14.1.4-2.1.1

The results regarding frequency and intensity of stomatitis by Godin-based subgroups are summarized in Table 10-10. These are based on the Godin Leisure-Time questionnaire regarding physical activity of patients (active, moderately active and insufficiently active). In the three subgroups of active, moderately active and insufficiently active patients, up to nearly 52% of patients suffered from stomatitis, mostly grade 1.

Table 10-10 Frequency and intensity of stomatitis by Godin-based subgroups

Worst intensity of stomatitis	No. of patients n (%)		
Godin-based subgroups	Active	Moderately active	Insufficiently active
All patients	N=332	N=212	N=897
Any grade	171 (51.5)	104 (49.1)	390 (43.5)
Grade 1	95 (28.6)	55 (25.9)	217 (24.2)
Grade 2	55 (16.6)	37 (17.5)	139 (15.5)
Grade 3	10 (3.0)	4 (1.9)	15 (1.7)
Grade 4	0 (0.0)	0 (0.0)	1 (0.1)
Unknown	11 (3.8)	8 (3.8)	18 (2.0)

Grade 1: minimal symptoms, normal food intake possible
Grade 2: patient had symptoms/pain, but was able to eat adequately
Grade 3: no sufficient oral food and liquid intake possible
Grade 4: parenteral nutrition necessary, symptoms associated with life-threatening consequences
Source: PT-Table 14.1.4-2.1.2

Frequency and intensity of stomatitis by 1st and 2nd line is summarized in Table 10-11. Overall, the number of stomatitis events by intensity was comparable between patients with 1st treatment and 2nd line and later (PT-Table 14.1.4-2.1.3).

Table 10-11 Frequency and intensity of stomatitis by 1st vs. 2nd line or later

	No. of patients n (%)	
Worst intensity of stomatitis	1st line	2nd line and later
All patients	N=595	N=1479
Any grade	262 (44.0)	659 (44.6)
Grade 1	148 (24.9)	337 (22.8)
Grade 2	82 (13.8)	253 (17.1)
Grade 3	12 (2.0)	37 (2.5)
Grade 4	0 (0.0)	1 (<0.1)
Unknown	20 (3.4)	31 (2.1)

Grade 1: minimal symptoms, normal food intake possible
Grade 2: patient had symptoms/pain, but was able to eat adequately
Grade 3: no sufficient oral food and liquid intake possible
Grade 4: parenteral nutrition necessary, symptoms associated with life-threatening consequences
Source: PT-Table 14.1.4-2.1.3

Frequency and intensity of stomatitis by recommended prophylactic treatment were also analyzed. Overall, the number of patients with stomatitis events was comparable between patients with or without prophylactic treatment. Descriptively, there was almost no difference between patients who had stomatitis of grade 2 and who prophylactically treated stomatitis by rinsing with tea, compared to patients who did not use this prophylaxis (yes: 16.0% vs. no:

16.6%). However, the proportion of patients with grade 1 events was higher when this prophylaxis was performed (yes: 24.5% vs. no: 21.7%).

The proportion of patients with stomatitis events was higher when using "rinsing with mouthwash solution" than the proportion of patients who did not use this prophylactic treatment (yes: 47.4% vs. no: 42.5%). The results based are summarized in Table 10-12 (PT-Table 14.1.4-2.1.4).

Table 10-12 Frequency and intensity of stomatitis by recommended prophylactic treatment

	No. of patients n (%)	
Prophylactic treatment **Worst intensity of stomatitis**	**No**	**Yes**
Rinsing with tea	N=785	N=1280
Any grade	336 (42.8)	584 (45.6)
Grade 1	170 (21.7)	314 (24.5)
Grade 2	130 (16.6)	205 (16.0)
Grade 3	21 (2.7)	28 (2.2)
Grade 4	1 (0.1)	0 (0.0)
Unknown	14 (1.8)	37 (2.9)
Rinsing with NaCl	N=1732	N=333
Any grade	764 (44.1)	156 (46.8)
Grade 1	409 (23.6)	75 (22.5)
Grade 2	277 (16.0)	58 (17.4)
Grade 3	36 (2.1)	13 (3.9)
Grade 4	1 (<0.1)	0 (0.0)
Unknown	41 (2.4)	10 (3.0)
Rinsing with mouthwash solution	N=1194	N=871
Any grade	507 (42.5)	413 (47.4)
Grade 1	271 (22.7)	213 (24.5)
Grade 2	188 (15.7)	147 (16.9)
Grade 3	21 (1.8)	28 (3.2)
Grade 4	1 (<0.1)	0 (0.0)
Unknown	26 (2.2)	25 (2.9)
Avoidance of hot, sour, salty food	N=642	N=1423
Any grade	280 (43.6)	640 (45.0)
Grade 1	155 (24.1)	329 (23.1)
Grade 2	89 (13.9)	246 (17.3)
Grade 3	20 (3.1)	29 (2.0)
Grade 4	1 (0.2)	0 (0.0)
Unknown	15 (2.3)	36 (2.5)

Table 10-12 Frequency and intensity of stomatitis by recommended prophylactic treatment

	No. of patients n (%)	
Prophylactic treatment Worst intensity of stomatitis	**No**	**Yes**
Avoidance of peroxide-containing mouthwash solution	N=1081	N=984
Any grade	484 (44.8)	436 (44.3)
Grade 1	265 (24.5)	219 (22.3)
Grade 2	167 (15.4)	168 (17.1)
Grade 3	22 (2.0)	27 (2.7)
Grade 4	1 (<0.1)	0 (0.0)
Unknown	29 (2.7)	22 (2.2)
Cooling	N=907	N=1158
Any grade	397 (43.8)	523 (45.2)
Grade 1	219 (24.1)	265 (22.9)
Grade 2	135 (14.9)	200 (17.3)
Grade 3	21 (2.3)	28 (2.4)
Grade 4	1 (0.1)	0 (0.0)
Unknown	21 (2.3)	30 (2.6)
Mild dental hygiene	N=537	N=1528
Any grade	231 (43.0)	689 (45.1)
Grade 1	132 (24.6)	352 (23.0)
Grade 2	74 (13.8)	261 (17.1)
Grade 3	14 (2.6)	35 (2.3)
Grade 4	1 (0.2)	0 (0.0)
Unknown	10 (1.9)	41 (2.7)
Other prophylactic measure	N=1893	N=172
Any grade	836 (44.2)	84 (48.8)
Grade 1	436 (23.0)	48 (27.9)
Grade 2	306 (16.2)	29 (16.9)
Grade 3	46 (2.4)	3 (1.7)
Grade 4	1 (<0.1)	0 (0.0)
Unknown	47 (2.5)	4 (2.3)

Grade 1: minimal symptoms, normal food intake possible

Grade 2: patient had symptoms/pain, but was able to eat adequately

Grade 3: no sufficient oral food and liquid intake possible

Grade 4: parenteral nutrition necessary, symptoms associated with life-threatening consequences

Source: PT-Table 14.1.4-2.1.4

Frequency and intensity analyzed by BMI categories, weight, and KAS question 1 and 2 are provided in PT-Tables 14.1.4-2.1.5, 14.1.4-2.1.6 and 14.1.4-2.1.7.

Altogether, there were 1207 stomatitis events of any grade documented, 675 events (55.9%) were of grade 1 (minimal symptoms, normal food intake possible), 391 events (32.4%) were of grade 2 (patient had symptoms/pain, but was able to eat adequately), 50 events (4.1%) were of grade 3 (no sufficient oral food and liquid intake possible), one event (0.1%) was of grade 4

(parenteral nutrition necessary, symptoms associated with life-threatening consequences) and 90 events (7.5%) were of "unknown" intensity (PT-Table 14.1.4-2.2).

At least one therapeutical measure was documented for 1047 (86.7%) of the 1207 stomatitis events (PT-Table 14.1.4-3.1.1):

- Non-drug mouthwash solution (729, 60.4%),
- Cooling (e.g. sucking ice or frozen pineapple; 371, 30.7%),
- Drug intervention (333, 27.6%):
  - Systemic (243, 20.1%) with antibiotics/antimycotics/antiviral drugs (57, 4.7%) or systemic analgetics (24, 2.0%), or other medication (177, 14.7%),
  - Topical (131, 10.9%) with topical analgesics/anesthetics (112, 9.3%) and topical corticosteroids (22, 1.8%),
- Temporary interruption of Afinitor® therapy (291, 24.1%), and
- Temporary Afinitor® dose adjustment (172, 14.3%).

Action taken by grade of stomatitis is shown in PT-Table 14.1.4-3.1.2. Drug intervention (mainly systemic) was more often used in patients with grade 2 and 3 stomatitis (165, 42.2% and 24, 48.0%) than in patients with grade 1 stomatitis (132, 19.6%).

Other medication given (Anatomical Therapeutic Chemical [ATC] class and PT] for the treatment of stomatitis documented as AE are provided in PT-Table 14.1.4-3.2.

The median duration of all stomatitis events among the patients was 29.0 days (P5%; P95%: 5.0; 176.0). The duration of stomatitis by action taken is summarized in Table 10-13 (PT-Table 14.1.4-4). Descriptively, the median duration of stomatitis events was shorter after treatment interruption of Afinitor® or exemestane. Therapeutic measures also seemed to shorten the median duration of stomatitis events.

Table 10-13 Duration of stomatitis by action taken

	Duration of stomatitis (days)	
Action taken	**Action No**	**Action taken Yes**
No therapeutic measures		
n	756	319
Mean ± SD (days)	50.5 ± 76.5	54.3 ± 72.7
Median (P5%; P95%)	29.0 (5.0; 175.0)	30.0 (4.0; 210.0)
Medical therapy of event		
n	548	527
Mean ± SD (days)	47.1 ± 66.3	56.4 ± 83.6
Median (P5%; P95%)	27.5 (4.0; 148.0)	30.0 (5.0; 185.0)
Dose adjustment Afinitor®		
n	878	197
Mean ± SD (days)	51.6 ± 73.8	51.9 ± 82.5
Median (P5%; P95%)	29.0 (4.0; 183.0)	31.0 (6.0; 128.0)

Table 10-13 Duration of stomatitis by action taken

Action taken	Duration of stomatitis (days)	
	Action No	Action taken Yes
Afinitor® treatment interrupted		
n	769	306
Mean ± SD (days)	54.4 ± 74.4	44.8 ± 77.4
Median (P5%; P95%)	30.0 (4.0; 189.0)	22.5 (5.0; 123.0)
Dose adjustment exemestane		
n	1075	0
Mean ± SD (days)	51.6 ± 75.4	--
Median (P5%; P95%)	29.0 (5.0; 176.0)	--
Exemestane treatment interrupted		
n	1046	29
Mean ± SD (days)	51.5 ± 72.2	54.6 ± 152.5
Median (P5%; P95%)	29.0 (5.0; 176.0)	25.0 (4.0; 112.0)
Therapy discontinued		
n	991	84
Mean ± SD (days)	52.6 ± 77.9	40.0 ± 31.9
Median (P5%; P95%)	29.0 (5.0; 184.0)	31.5 (7.0; 92.0)

P = percentile, SD = standard deviation

Note: stomatitis and stomatitis-related events were taken into account

Source: PT-Table 14.1.4-4

The relation between stomatitis and QoL based on the QLQ-C30 was analyzed by the global health status in relation to the most recent value prior to first stomatitis event. High values correspond with high quality of life (PT-Table 14.1.4-5). The median values were the same for patients with the different grades of stomatitis.

PT-Tables 14.1.4-6.1 and 14.1.4-6.2 show a listing of other prophylactic/therapeutic measures.

An analysis of time to first occurrence of stomatitis is provided in PT-Table 14.1.4-7. The 25th percentile time to first occurrence (months) of stomatitis was 0.7 months with a 95% CI of [0.7; 0.8]. Most events occurred during the first 2 months. Incidences were calculated by the Kaplan-Meier method and are provided in PT-Figure 14.1.4-7.

Incidence of patients with only stomatitis was 888 (42.8%), with only pneumonitis was 53 (2.6%), and with stomatitis and pneumonitis was 60 (2.9%). For the latter, the median time between start of stomatitis and pneumonitis was 72.0 days (P5%; P95%: 4.0; 344.0, [PT-Table 14.1.4-8]).

PT-Table section 14.1.4-9 shows the answers of the patients to the questionnaires on stomatitis prophylaxis, PT-Table 14.1.4-9.1 shows the incidence of single prophylaxis measures by visit. The most frequently mentioned prophylactic measures throughout the study were “mild dental hygiene”, “rinsing with mouthwash solution” and “avoidance of hot, sour or salty food”.

PT-Table 14.1.4-9.2.1 shows the incidence of stomatitis following directly after each single prophylaxis measure (stomatitis events from stomatitis follow-up).

PT-Table 14.1.4-9.2.2 shows the incidence of stomatitis following directly after each single prophylaxis measure (stomatitis and stomatitis-related events from adverse events). PT-Table

14.1.4-9.3.1 shows the incidence of single measures by previously experienced stomatitis (stomatitis event from stomatitis follow-up). PT-Table 14.1.4-9.3.2 shows the incidence of single measures by previously experienced stomatitis (stomatitis and stomatitis-related events from adverse events). The number of patients using prophylactic measure after a previously experienced stomatitis increased from month 3 on. PT-Table 14.1.4-9.4 shows the frequency of application of single prophylaxis measures by visit. Overall, 23.2% of the patients performed the prophylactic measure several times per day. PT-Table 14.1.4-9.5.1 shows the incidence of stomatitis following directly after each single prophylaxis measure by frequency of application (stomatitis event from stomatitis follow-up), PT-Table 14.1.4-9.5.2 shows the incidence of stomatitis following directly after each single prophylaxis measure by frequency of application (stomatitis and stomatitis-related events from adverse events), and PT-Table 14.1.4-9.6 shows the used combinations of prophylaxis measures.

10.3.2 Concomitant medication

Antiresorptive therapy is common in oncological practice in patients with breast cancer and bone metastases. One thousand five hundred forty-two of the 2061 patients (1542, 74.8%) received antiresorptive therapy, mainly bisphosphonates (950, 61.5%) and antibody therapy (e.g. denosumab; 582, 37.7%) (see PT-Table 14.1.5).

10.3.3 Information on exposure

Reason for change of a prior therapy to therapy with Afinitor® and exemestane was mainly "progression proven by imaging methods" (1268, 61.3%) and "clinically proven progression" (643, 31.1%). "Not progression-induced" or "patient's wish" were documented for 129 (6.2%) and 28 (1.4%) patients, respectively. For 6 patients, documentation was missing (PT-Table 14.1.6-1 and PT Figure 14.1.6-1).

Start and end doses of Afinitor® are summarized in Table 10-14. Most patients started treatment according to usual practice and received a daily dose of 10.0 mg Afinitor® (1306, 63.0%) and 25.0 mg exemestane (2056, 99.2%). The mostly preferred end doses of Afinitor® were 5.0 and 10.0 mg (670 subjects, 32.3% and 912, 44.0%, respectively), while 25 mg remained the preferred dose for exemestane in most subjects at the end of treatment (1952, 94.2%) (PT-Tables 14.1.6-2.1a and 14.1.6-2.9).

Table 10-14 Start and end doses of Afinitor®

	N=2074		
Start dose	**n (%)**	**End dose**	**n (%)**
0.0 mg	--	0.0 mg	386 (18.6)
1.0 mg	--	1.2 mg	1 (0.05)
1.2 mg	--	2.0 mg	1 (0.05)
2.5 mg	46 (2.2)	2.5 mg	53 (2.6)
5.0 mg	707 (34.1)	5.0 mg	670 (32.3)
7.5 mg	14 (0.7)	6.5 mg	1 (0.05)
10.0 mg	1306 (63.0)	7.5 mg	49 (2.4)
20.0 mg	1 (0.05)	10.0 mg	912 (44.0)
30.0 mg	--	20.0 mg	1 (0.05)

Source: PT-Table 14.1.6-2.1a

Regarding the comparison between the 1st and the most recently included 200 patients, there were differences regarding the starting dose. The number of patients starting with 5.0 mg Afinitor® was lower among the first 200 patients compared to the most recent 200 patients (21 of the first 200 patients [10.5%] and 101 of the most recent 200 patients [50.5%]), while the vast majority of the first 200 patients (179, 89.5%) started with 10.0 mg compared to 79 patients (39.5%) of the most recent 200 patients. These data are provided in PT-Table 14.1.6-2.1b. PT-Table 14.1.6-2.1c shows these data for Afinitor® start and end dose comparing the patients who were included up to vs. after 30th June 2013.

Exemestane as prior or last prior antineoplastic therapy was documented for 370 (17.8%) and 168 (8.1%) patients, respectively (PT-Table 14.1.6-2.2).

The average daily dose of Afinitor® was in the median 8.4 mg (P5%; P95%: 4.3; 10.0 [PT-Table 14.1.6-2.11]).

Dose changes of Afinitor® are summarized in Table 10-15. Overall, a "dose change" was reported for 1291 of the patients (62.2%). A total of 1138 patients (54.9%) was reported with dose reductions (including reduction to 0 mg), 471 patients (22.7%) with a dose increase, and 728 patients (35.1%) with a temporary treatment interruption. Dose changes were most frequently documented for patients with an "other" start dose (88.5%, n=54), followed by patients with a start dose of 5 mg (68.5%, n=484) and a start dose of 10 mg (57.7%, n=753). A dose increase was mainly reported for patients with an "other" start dose and 5 mg start dose (78.7% and 46.8%, respectively), while patients with 10 mg start dose had more treatment interruptions (38.7%) than patients with an "other" start dose or 5 mg start dose (34.4% and 28.4%, respectively), which is according to the recommendation in the SmPC (PT-Table 14.1.6-2.3).

Table 10-15 Changes in dose of Afinitor®

	Patients, n (%)			
	Start dose			
No. of patients with[a]	5 mg N=707	10 mg N=1306	Other N=61	Total N=2074
Dose change	484 (68.5)	753 (57.7)	54 (88.5)	1291 (62.2)
Dose reduction[b]	348 (49.2)	753 (57.7)	37 (60.7)	1138 (54.9)
Dose increase	331 (46.8)	92 (7.0)	48 (78.7)	471 (22.7)
Treatment temporarily interrupted[c]	201 (28.4)	506 (38.7)	21 (34.4)	728 (35.1)

a multiple answers were possible
b including reduction to 0 mg
c treatment temporarily interrupted = reduction to dose 0 mg with subsequent treatment continuation
Source: PT-Table 14.1.6-2.3

Of 707 patients (34.1%) among 2074 patients, starting with 5 mg Afinitor®, 233 (11.2%) had reported a dose increase to 10 mg. Dose changes at the individual visits are shown in PT-Table 14.1.6-2.5.

Reasons for Afinitor® either dose changes by weeks or months of treatment are provided in PT-Table 14.1.6-2.4. The occurrence of an AE was mainly documented as reason for treatment interruption or dose change at different times during the observation. "Change of laboratory data", "patient's wish", "intake omitted", "no medication available", and "treatment success"

were other reasons documented infrequently. The median duration of 1170 treatment interruptions among the patients was 12.0 days (P5%; P95%: 1.0; 52.0, [PT-Table 14.1.6-2.8]).

A sample statistic regarding age, CCI, other non-CCI comorbidities, and ECOG by start dose is provided in PT-Table 14.1.6-2.6. Frequency tables for therapy line and start doses are provided in PT-Table 14.1.6-2.7.

Information on exposure to exemestane is provided in PT-Tables 14.1.6-2.9 and 14.1.6-2.10.

PT-Table 14.1.6-2.12 provides the dose density (sum of received day doses) of all patients. Distribution of start doses in centers is provided in PT-Table 14.1.6-2.13.

Most patients (276, 13.3%) had a treatment duration of > 2 to ≤ 3 months, followed by > 3 to ≤ 4 months (244, 11.8%), and > 1 to ≤ 2 months (211, 10.2%, [PT-Table 14.1.6-3.1]).

The average treatment duration of all patients is summarized in Table 10-16. Descriptively, the median treatment duration was slightly longer for patients starting with 10 mg Afinitor® than for patients starting with 5 mg Afinitor®. The results are provided in PT-Table 14.1.6-3.1.

Table 10-16 Treatment duration (FAS)

	Start dose			
	5 mg N=707	**10 mg N=1306**	**Other N=61**	**Total N=2074**
Mean ± SD [days]	220.1 ± 222.6	251.4 ± 278.9	207.3 ± 185.9	239.4 ± 259.0
Median (P5%; P95%)	140.0 (20.0; 695.0)	149.5 (21.0; 842.0)	146.0 (30.0; 589.0)	145.0 (20.0; 785.0)

P = percentile, SD = standard deviation

Source: PT-Table 14.1.6-3.1

Current treatment duration for the FAS is also provided in PT-Figures 14.1.6-3.1.1 to 14.1.6-3.1.3.

The Kaplan-Meier estimates for the median duration of treatment are provided in PT-Tables 14.1.6-3.2.1, and 14.1.6-3.2.2. The Kaplan-Meier estimates for the median duration of treatment by start dose, exercise categories, activity categories, age categories, ECOG, line, prior chemotherapy, KI-67 status, presence of visceral metastases, BMI categories, and CCI categories are provided in PT-Tables 14.1.6-3.3 to 14.1.6.-3.12 and PT-Figure 14.1.6-3.2 to PT-Figure 14.1.6-3.4. PT-Table 14.1.6-3.13 shows the correlation between treatment duration and selected baseline parameters.

Compliance

Throughout the observation period, compliance for Afinitor® was more than 90% for all patients up to visit on month 45 (PT-Table 14.1.6-4.1). Compliance for exemestane was more or at least about 95% for all patients (PT-Tables 14.1.6-4.2).

Follow-up therapy

The analysis resulted in 1450 of 2074 patients (69.9%) who were planned to receive a follow-up treatment after end of study. For 67 patients (3.2%) this documentation was missing, also due to death or for other reasons. If follow-up was planned, most patients were supposed to

receive chemotherapy (837, 40.4%), followed by endocrine therapy (562, 27.1%). The analysis of only patients whose CRF page "end of therapy" was already completed was almost the same (PT-Tables 14.1.6-5.1.1, and 14.1.6-5.1.2).

The results based on the patients with a CRF "end of therapy" completed are summarized in Table 10-17. Data analyzed by visceral metastases are provided in PT-Tables 14.1.6-5.2.1, and 14.1.6-5.2.2.

Table 10-17 Follow-up treatment after end of study

	Pre-treatment					
Follow-up treatment	**1st line**	**2nd line**	**3rd line**	**4th line**	**5th line (and later)**	**Total**
Follow-up planned	N=582	N=652	N=372	N=220	N=218	N=2044
Yes	382 (65.6)	460 (70.6)	285 (76.6)	164 (74.5)	159 (72.9)	1450 (70.9)
No	183 (31.4)	181 (27.8)	82 (22.0)	54 (24.5)	57 (26.1)	557 (27.3)
Missing	17 (2.9)	11 (1.7)	5 (1.3)	2 (0.9)	2 (0.9)	37 (1.8)
Type of follow-up treatment						
Chemotherapy	188 (32.3)	248 (38.0)	185 (49.7)	111 (50.5)	105 (48.2)	837 (40.9)
Endocrine therapy	171 (29.4)	197 (30.2)	93 (25.0)	52 (23.6)	49 (22.5)	562 (27.5)
Experimental therapy	18 (3.1)	13 (2.0)	7 (1.9)	1 (0.5)	4 (1.8)	43 (2.1)

Source: PT-Table 14.1.6-5.1.2

10.4 Main results

10.4.1 Primary effectiveness parameter

Primary effectiveness parameter in this study was PFS (PT-Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, 14.2.1.4, 14.2.1.5, 14.2.1.6, 14.2.1.7, 14.2.1.8, 14.2.1.9, 14.2.1.10, 14.2.1.11, 14.2.1.12, 14.2.1.13, 14.2.1.14, 14.2.1.15 and PT-Figures 14.2.1.1, 14.2.1.2, 14.2.1.3, 14.2.1.4, 14.2.1.5a, 14.2.1.5b, 14.2.1.6, 14.2.1.7, 14.2.1.8, 14.2.1.9a, 14.2.1.9b, 14.2.1.9c, 14.2.1.10, 14.2.1.11, 14.2.1.12.1, 14.2.1.12.2, 14.2.1.12.3, 14.2.1.12.4, 14.2.1.12.5, 14.2.1.12.6, 14.2.1.13, 14.2.1.14, 14.2.1.15). The results are described and summarized in Table 10-18:

- The median time of PFS was 6.6 months with a 95% CI of [6.3; 7.0].
- Descriptively, active patients (according to Godin) had a longer median PFS than moderately active or insufficiently active patients (8.1 vs. 7.0 vs. 6.7 months), however, 95% CIs were overlapping.
- Descriptively, patients with prior exemestane therapy had a lower median PFS than patients without prior exemestane therapy (6.2 vs. 6.7 months), however, 95% CIs were overlapping.
- Descriptively, patients without prior chemotherapy had a longer median PFS than patients with prior chemotherapy (7.2 vs. 5.4 months).

- Descriptively, patients with only visceral metastases had a shorter median PFS than patients with only bone metastases (5.5 vs. 9.1 months), and
- Patients with multiple visceral metastases had a shorter median PFS than patients with single visceral metastases (4.6 vs. 5.8 months, however, 95% CIs showed minor overlap), for the latter comparison.
- Patients with fast progression had a shorter median PFS than patients with a longer recurrence-free interval (6.9 vs. 11.0 months), however, overlapping 95% CIs have to be considered.
- There was almost no difference in median PFS between patients with stomatitis (of any grade) and with stomatitis of at least grade 2 (8.0 and 7.9 months), while patients without stomatitis descriptively had a shorter median PFS (5.9 months), however, overlapping 95% CIs have to be considered.
- Descriptively, the median PFS was longer the less treatments a patient had received before this study, except for 1st line, 2nd line treatment (7.1 vs. 7.4), 3rd line, 4th line, 5th line and later: 6.1 vs. 6.2 vs. 5.3, however, overlapping 95% CIs have to be considered.
- Patients with KI-67>20% descriptively had a shorter median PFS than patients with KI-67 ≤20% (6.2 vs. 7.0). Confidence intervals showed only minor overlap.
- The median PFS was 6.0 months in the subgroups of patients starting with Afinitor® 5 mg vs. 6.9 months for patients starting with Afinitor® 10 mg, however, 95% CIs showed minor overlap.

Further analyses of PFS can be found in PT-Tables 14.2.1.7, 14.2.1.8, 14.2.1.11, 14.2.1.13, and 14.2.1.14.

Table 10-18 Progression-free survival

		N at risk (baseline)
Total		2070
Time to event[a] (months, with 95% CI)	Lower quartile	3.2 [3.1; 3.4]
	Median	6.6 [6.3; 7.0]
	Upper quartile	13.9 [12.7; 14.7]
Active patients (Godin)		332
Time to event[a] (months, with 95% CI)	Lower quartile	3.7 [3.1; 4.6]
	Median	8.1 [7.0; 9.3]
	Upper quartile	15.8 [13.1; 18.9]
Moderately active patients (Godin)		212
Time to event[a] (months, with 95% CI)	Lower quartile	3.3 [3.0; 3.9]
	Median	7.0 [5.7; 7.9]
	Upper quartile	15.2 [11.7; 19.5]
Insufficiently active patients (Godin)		896
Time to event[a] (months, with 95% CI)	Lower quartile	3.3 [3.0; 3.5]
	Median	6.7 [6.1; 7.6]
	Upper quartile	14.0 [12.8; 15.5]

Table 10-18 Progression-free survival

		N at risk (baseline)
Without prior exemestane		1700
Time to event[a] (months, with 95% CI)	Lower quartile	3.3 [3.1; 3.5]
	Median	6.7 [6.3; 7.3]
	Upper quartile	14.3 [13.0; 15.0]
With prior exemestane		370
Time to event[a] (months, with 95% CI)	Lower quartile	3.0 [2.7; 3.2]
	Median	6.2 [5.3; 7.0]
	Upper quartile	12.1 [11.3; 14.0]
Without prior chemotherapy		1489
Time to event[a] (months, with 95% CI)	Lower quartile	3.4 [3.2; 3.6]
	Median	7.2 [6.6; 8.0]
	Upper quartile	14.8 [13.9; 16.4]
With prior chemotherapy		581
Time to event[a] (months, with 95% CI)	Lower quartile	2.9 [2.8; 3.2]
	Median	5.4 [5.0; 6.2]
	Upper quartile	11.3 [10.0; 12.4]
Patients with only bone metastases		525
Time to event[a] (months, with 95% CI)	Lower quartile	4.1 [3.8; 4.6]
	Median	9.1 [8.1; 10.6]
	Upper quartile	18.8 [16.6; 21.8]
Patients with only visceral metastases		207
Time to event[a] (months, with 95% CI)	Lower quartile	2.9 [2.3; 3.1]
	Median	5.5 [4.4; 6.3]
	Upper quartile	12.1 [9.4; 15.0]
Patients with single visceral metastases		889
Time to event[a] (months, with 95% CI)	Lower quartile	3.0 [2.8; 3.1]
	Median	5.8 [5.3; 6.3]
	Upper quartile	12.0 [11.0; 12.8]
Patients with multiple visceral metastases		227
Time to event[a] (months, with 95% CI)	Lower quartile	2.9 [2.6; 3.1]
	Median	4.6 [3.9; 5.6]
	Upper quartile	8.3 [7.4; 10.0]
Patients with fast progression		265
Time to event[a] (months, with 95% CI)	Lower quartile	3.4 [3.0; 3.8]
	Median	6.9 [6.0; 8.3]
	Upper quartile	14.7 [12.4; 16.6]
Patients with longer recurrence-free interval		139
Time to event[a] (months, with 95% CI)	Lower quartile	3.8 [3.1; 5.1]
	Median	11.0 [7.0; 16.7]
	Upper quartile	24.8 [19.6; 29.0]

Table 10-18 Progression-free survival

		N at risk (baseline)
Patients with stomatitis		947
Time to event[a] (months, with 95% CI)	Lower quartile	3.7 [3.4; 4.2]
	Median	8.0 [7.3; 8.6]
	Upper quartile	15.5 [13.9; 17.5]
Patients with stomatitis of at least grade 2		384
Time to event[a] (months, with 95% CI)	Lower quartile	3.7 [3.3; 4.4]
	Median	7.9 [6.6; 8.9]
	Upper quartile	16.1 [13.3; 18.4]
Patients without stomatitis		1123
Time to event[a] (months, with 95% CI)	Lower quartile	3.0 [2.8; 3.1]
	Median	5.9 [5.4; 6.3]
	Upper quartile	12.4 [11.5; 13.8]
First line patients		594
Time to event[a] (months, with 95% CI)	Lower quartile	3.5 [3.2; 3.8]
	Median	7.1 [6.2; 8.3]
	Upper quartile	16.7 [14.7; 18.9]
Second line patients		661
Time to event[a] (months, with 95% CI)	Lower quartile	3.4 [3.1; 3.8]
	Median	7.4 [6.5; 8.3]
	Upper quartile	13.6 [12.2; 15.4]
Third line patients		374
Time to event[a] (months, with 95% CI)	Lower quartile	3.2 [2.9; 3.6]
	Median	6.1 [5.2; 7.3]
	Upper quartile	14.0 [11.5; 17.4]
Fourth line patients		221
Time to event[a] (months, with 95% CI)	Lower quartile	3.0 [2.8; 3.5]
	Median	6.2 [4.9; 7.4]
	Upper quartile	12.1 [10.7; 14.5]
Fifth + line patients		220
Time to event[a] (months, with 95% CI)	Lower quartile	2.7 [2.3; 3.2]
	Median	5.3 [4.3; 6.3]
	Upper quartile	10.4 [9.0; 12.2]
KI-67 ≤20% **patients**		587
Time to event[a] (months, with 95% CI)	Lower quartile	3.4 [3.0; 3.8]
	Median	7.0 [6.3; 8.0]
	Upper quartile	13.6 [12.3; 16.1]
KI-67 >20% **patients**		428
Time to event[a] (months, with 95% CI)	Lower quartile	3.2 [2.9; 3.5]
	Median	6.2 [5.8; 7.2]
	Upper quartile	12.6 [10.6; 14.3]

Table 10-18 Progression-free survival

		N at risk (baseline)
Patients with Afinitor® start dose 5 mg		705
Time to event[a] (months, with 95% CI)	Lower quartile	3.0 [2.8; 3.3]
	Median	6.0 [5.6; 6.7]
	Upper quartile	12.1 [11.5; 13.6]
Patients with Afinitor® start dose 10 mg		1305
Time to event[a] (months, with 95% CI)	Lower quartile	3.4 [3.2; 3.7]
	Median	6.9 [6.5; 7.4]
	Upper quartile	14.7 [13.5; 16.2]

CI = Confidence interval
a event was progression or death
Incidences were calculated by the Kaplan-Meier method
For final analysis, patients were followed up until progression or death. Patients were only censored due to lost-to-follow up or survival without progression or death until the official study end.
PFS: (Date of first progression after baseline/death and date of baseline visit +1) in the event of progression/death
Source: PT-Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, 14.2.1.4, 14.2.1.5, 14.2.1.6, 14.2.1.9, 14.2.1.10, 14.2.1.12., 14.2.1.15

PT-Tables 14.2.1.16.1 (step 1: testing of possible prognostic factors), 14.2.1.16.2 (step 2: repetition of step 1 for prognostic factors found to be relevant), 14.2.1.16.3 (step 3: amendment of relevant prognostic factors with start dose), and 14.2.1.16.4 (step 4: model with interactions of remaining parameters and start dose) show the Cox proportional hazard models for PFS. BMI, presence of visceral metastases, and start dose of Afinitor® correlated significantly with the PFS (see Table 10-19). Further inclusion of bivariate interactions between Afinitor® start dose and the other selected covariates did not show any significant influence of this interaction on PFS (age: P=0.4296, duration diagnosis to 1st metastases: P=0.2869, tumor grading: 0.9007, visceral metastases: 0.2349, BMI: P=0.9377).

Table 10-19 Cox proportional hazard model for PFS: Step III Amendment of relevant prognostic factors with Afinitor® start dose (5 mg vs. 10 mg)

Parameter	Hazard Ratio	95% CI	P-value
BMI			
< 20 vs. 20-25	1.530	1.080-2.165	
< 20 vs. 26-29	1.740	1.227-2.466	
< 20 vs. ≥ 30	2.118	1.486-3.018	< 0.0001
20-25 vs. 26-29	1.137	1.012-1.279	
20-25 vs. ≥ 30	1.385	1.215-1.579	
26-29 vs. ≥ 30	1.218	1.065-1.392	
Visceral metastases			
No vs. yes	0.704	0.636-0.779	< 0.0001
Start dose Afinitor®			
5 mg vs. 10 mg	1.247	1.121-1.387	< 0.0001

Table 10-19 Cox proportional hazard model for PFS: Step III Amendment of relevant prognostic factors with Afinitor® start dose (5 mg vs. 10 mg)

Parameter	Hazard Ratio	95% CI	P-value
Age			
< 65 years vs. 65-74 years	0.942	0.840-1.056	
< 65 years vs. ≥ 75 years	1.104	0.960-1.269	0.1045
65-74 years vs. ≥ 75 years	1.172	1.012-1.357	
Duration diagnosis to 1st metastases			
0-2 years vs. > 2-5 years	0.998	0.873-1.140	
0-2 years vs. > 5 years	1.159	1.031-1.304	0.0193
> 2-5 years vs. > 5 years	1.162	1.020-1.323	
Tumor grading			
G1 vs. G2	0.688	0.540-0.877	
G1 vs. G3/G4	0.732	0.568-0.942	0.0084
G2 vs. G3/G4	1.064	0.951-1.190	

Source: PT-Table 14.2.1.16.3

PT-Table 14.2.1.17.1 and PT-Figure 14.2.17.1 (KAS question 1) show PFS by exercise categories. PT-Table 14.2.1.17.2 and PT-Figure 14.2.1.17.2 (KAS question 2) show PFS by activity categories.

PT-Tables 14.2.7.18.1 (step 1: amendment of relevant prognostic factors with physical activity subgroups) and PT-Table 14.2.7.18.2 (step 2: model with interactions of remaining parameters and physical activity subgroups) show the Cox proportional hazard models for PFS.

10.4.2 Secondary effectiveness parameters

Best overall response (BOR) was defined as the best response reached for a patient until study end, i.e. no confirmation of a given response was required. The variable was analyzed twice, once as documented in the eCRF (end-of-study) and once derived from data documented within each visit.

10.4.2.1 Best overall response

The analysis of BOR from end of study showed complete remission (CR) in 17 patients (0.8%) and partial remission (PR) in 150 patients (7.4%). Stable disease (SD) was documented in 842 patients (41.3%) and progression (PD) in 632 patients (31.0%), however, for about one fifth of patients (396, 19.4%), the result was unknown.

The analysis of BOR as documented by visit showed better results with CR in 2.3% of the patients, SD in 59.4% of patients, PR in 17.6% and PD in only 15.7%. Unknown results were documented for only about 5%. BOR for all patients is summarized in Table 10-20.

Table 10-20 Best overall response

		All patients
Response	**Result**	**N=2044 n (%)**
Best overall response from end of study	Complete remission (CR)	17 (0.8)
	Partial remission (PR)	150 (7.4)
	Stable disease (SD)	842 (41.3)
	Progression (PD)	632 (31.0)
	Unknown	396 (19.4)
	Missing	7
		N=1488 n (%)
Best overall response as documented by visits	Complete remission (CR)	29 (2.3)
	Partial remission (PR)	221 (17.6)
	Stable disease (SD)	744 (59.4)
	Progression (PD)	197 (15.7)
	Unknown	62 (4.9)
	Missing	235

Source: PT-Tables 14.2.2-1.1, and 14.2.2-1.2

BOR was mainly based on CT scans (608, 49.1%), followed by clinical assessment according to common practice (434, 35.0%[PT-Table 14.2.2-1.3]).

Sample statistics of KAS (question 1 and 2) by BOR from end of study and BOR as documented by visits are provided in PT-Tables 14.2.2-1.4.1 and 14.2.2-1.4.2. Tables 14.2.2-1.5.1 and 14.2.2-1.5.2 show BOR from end of study/as documented by visits by KAS 2 based subgroups. PT-Table 14.2.2.-2.1 describes BOR by activity subgroup based on the Godin Leisure-Time Exercise Questionnaire. PT-Table 14.2.2.-2.2 shows the course of WLTAS (based on Godin Leisure-Time Exercise Questionnaire) by BOR.

10.4.2.2 EORTC QLQ-C30 and BR23 questionnaires

EORTC QLQ-C30

Changes in global health status, according to the EORTC QLQ-C30 questionnaire subscales were analyzed from baseline to all post-baseline visits. Table 10-21 summarized the results for the mean and median differences from baseline to the last post-baseline values. The values were ranging from 0 to 100 (100 representing high functioning and high quality of life, but also a high level of symptomatology). No large changes, but an overall deterioration was observed for the functioning subscales of this questionnaire. A slight median difference was seen regarding the subscales “physical functioning” and “fatigue” with median change from baseline to the last post-baseline value of -6.7 (P5%; P95%: -40.0; 26.7) and 11.1 (P5%; P95%: -33.3; 55.6).

Table 10-21 Changes in EORTC QLQ-C30 from baseline to last post-baseline value

	FAS		
Subscale	**Baseline N=1667**	**Last post-baseline value N=1588**	**Difference**
Physical functioning			
n, mean ± SD [median] (P5%; P95%)	1495, 67.1 ± 24.5 [73.3] (20.0; 100.0)	1525, 61.9 ± 25.0 [66.7] (20.0; 100.0)	1278, -6.6 ± 20.1 [-6.7] (-40.0; 26.7)
Role functioning			
n, mean ± SD [median] (P5%; P95%)	1487, 57.4 ± 32.9 [66.7] (0.0; 100.0)	1512, 50.1 ± 31.7 [50.0] (0.0; 100.0)	1262, -9.0 ± 31.7 [0.0] (-66.7; 33.3)
Emotional functioning			
n, mean ± SD [median] (P5%; P95%)	1491, 60.2 ± 27.1 [66.7] (8.3; 100.0)	1514, 59.0 ± 26.4 [58.3] (8.3; 100.0)	1265, -1.6 ± 25.5 [0.0] (-41.7; 41.7)
Cognitive functioning			
n, mean ± SD [median] (P5%; P95%)	1493, 80.9 ± 23.6 [83.3] (33.3; 100.0)	1514, 77.2 ± 24.8 [83.3] (33.3; 100.0)	1268, -4.4 ± 21.1 [0.0] (-33.3; 33.3)
Social functioning			
n, mean ± SD [median] (P5%; P95%)	1487, 66.5 ± 32.2 [66.7] (0.0; 100.0)	1511, 62.6 ± 32.2 [66.7] (0.0; 100.0)	1261, -4.9 ± 30.3 [0.0] (-66.7; 50.0)
Global health status/QoL			
n, mean ± SD [median] (P5%; P95%)	1484, 52.4 ± 23.2 [50.0] (16.7; 83.3)	1502, 49.0 ± 22.6 [50.0] (8.3; 83.3)	1250, -4.6 ± 25.9 [0.0] (-50.0; 41.7)
Fatigue			
n, mean ± SD [median] (P5%; P95%)	1499, 47.4 ± 28.2 [44.4] (0.0; 100.0)	1519, 53.9 ± 27.5 [55.6] (11.1; 100.0)	1278, 8.6 ± 26.4 [11.1] (-33.3; 55.6)
Nausea/Vomiting			
n, mean ± SD [median] (P5%; P95%)	1497, 9.5 ± 18.6 [0.0] (0.0; 50.0)	1524, 13.9 ± 21.6 [0.0] (0.0; 66.7)	1278, 4.9 ± 21.4 [0.0] (-16.7; 50.0)
Pain			
n, mean ± SD [median] (P5%; P95%)	1501, 39.4 ± 33.4 [33.3] (0.0; 100.0)	1523, 42.2 ± 32.0 [33.3] (0.0; 100.0)	1281, 3.8 ± 31.6 [0.0] (-50.0; 50.0)
Dyspnoea			
n, mean ± SD [median] (P5%; P95%)	1481, 34.0 ± 32.9 [33.3] (0.0; 100.0)	1510, 40.0 ± 33.9 [33.3] (0.0; 100.0)	1255, 8.4 ± 33.0 [0.0] (-33.3; 66.7)
Insomnia			
n, mean ± SD [median] (P5%; P95%)	1493, 41.9 ± 35.6 [33.3] (0.0; 100.0)	1508, 44.7 ± 34.5 [33.3] (0.0; 100.0)	1267, 4.4 ± 34.0 [0.0] (-66.7; 66.7)
Appetite loss			
n, mean ± SD [median] (P5%; P95%)	1490, 26.7 ± 33.5 [0.0] (0.0; 100.0)	1514, 39.8 ± 37.2 [33.3] (0.0; 100.0)	1262, 15.3 ± 38.3 [0.0] (-33.3; 100.0)
Constipation			
n, mean ± SD [median] (P5%; P95%)	1484, 15.2 ± 26.6 [0.0] (0.0; 66.7)	1505, 14.0 ± 26.3 [0.0] (0.0; 66.7)	1255, 0.1 ± 27.3 [0.0] (-33.3; 33.3)

Table 10-21 Changes in EORTC QLQ-C30 from baseline to last post-baseline value

	FAS		
Subscale	**Baseline N=1667**	**Last post-baseline value N=1588**	**Difference**
Diarrhoea			
n, mean ± SD [median] (P5%; P95%)	1485, 12.0 ± 23.6 [0.0] (0.0; 66.7)	1509, 18.6 ± 29.3 [0.0] (0.0; 100.0)	1258, 7.5 ± 30.5 [0.0] (-33.3; 66.7)
Financial problems			
n, mean ± SD [median] (P5%; P95%)	1473, 19.0 ± 30.8 [0.0] (0.0; 100.0)	1489, 19.7 ± 30.5 [0.0] (0.0; 100.0)	1234, 0.5 ± 25.8 [0.0] (-33.3; 33.3)

EORTC = European Organization for Research and Treatment of Cancer, P = percentile, QLQ = Quality of Life Questionnaire, QLQ-C30 = QLQ core questionnaire, SD = standard deviation

The values are ranging from 0 to 100 (100 representing high functioning and high quality of life, but also a high level of symptomatology).

Source: PT-Table 14.2.2-3.1.1

The course of EORTC QLQ-C30 for first line patients is provided in PT-Table 14.2.2-3.1.2, for patients with follow-up of ≥ 9 months and ≥ 12 months in PT-Tables 14.2.2-3.1.3 and 14.2.2-3.1.4.

The relation between global health status/QoL (QLQ-C30) and tolerability (serious and nsAEs, serious and nsADR), in relation to Afinitor® and exemestane was analyzed in PT-Tables 14.2.2-3.2. Overall, the median global health status at baseline was the same in patients with AEs (median 50.0; P5%; P95%: 16.7; 83.3) and patients without AEs (median 50.0; P5%; P95%: 8.3; 100.0). For patients without any AE the median global health status at the last post-baseline visit was 58.3; P5%; P95%: 25.0; 100.0). All other types of AEs and ADRs did not show a difference between the median global health status at baseline and the last post-baseline value.

EORTC QLQ-BR23

Changes in quality of life according to the EORTC QLQ-BR23 subscales were analyzed from baseline to all post-baseline visits. Table 10-22 summarizes the results regarding the differences from baseline to the last post-baseline values. A slight median change was observed for the subscale "systemic therapy side effects" with median difference of 4.8 (P5%; P95%: -19.0; 38.1).

Table 10-22 Changes in EORTC QLQ-BR23 from baseline to last post-baseline value

	FAS		
Subscale	**Baseline N=1667**	**Last post-baseline value N=1588**	**Difference**
Functioning: body image			
n, mean ± SD [median] (P5%; P95%)	1611, 75.3 ± 27.6 [83.3] (16.7; 100.0)	1520, 72.9 ± 28.8 [83.3] (9.7; 100.0)	1339, -2.7 ± 22.7 [0.0] (-41.7; 33.3)
Functioning: sexual functioning			
n, mean ± SD [median] (P5%; P95%)	1394, 15.3 ± 22.6 [0.0] (0.0; 66.7)	1226, 13.7 ± 21.6 [0.0] (0.0; 66.7)	1038, -2.4 ± 19.0 [0.0] (-33.3; 33.3)
Functioning: sexual enjoyment			
n, mean ± SD [median] (P5%; P95%)	276, 61.4 ± 26.4 [66.7] (33.3; 100.0)	230, 54.5 ± 26.9 [66.7] (0.0; 100.0)	134, -7.5 ± 24.4 [0.0] (-33.3; 33.3)
Functioning: future perspective			
n, mean ± SD [median] (P5%; P95%)	1613, 29.7 ± 31.8 [33.3] (0.0; 100.0)	1536, 35.7 ± 32.9 [33.3] (0.0; 100.0)	1354, 5.7 ± 31.8 [0.0] (-33.3; 66.7)
Symptoms: arm symptoms			
n, mean ± SD [median] (P5%; P95%)	1641, 26.1 ± 26.9 [22.2] (0.0; 77.8)	1563, 27.4 ± 27.8 [22.2] (0.0; 88.9)	1387, 1.7 ± 25.0 [0.0] (-33.3; 44.4)
Symptoms: breast symptoms			
n, mean ± SD [median] (P5%; P95%)	1629, 13.2 ± 18.6 [8.3] (0.0; 58.3)	1549, 13.6 ± 18.6 [8.3] (0.0; 50.0)	1368, 0.7 ± 16.4 [0.0] (-25.0; 25.0)
Symptoms: systemic therapy side effects			
n, mean ± SD [median] (P5%; P95%)	1651, 26.7 ± 18.1 [23.8] (0.0; 61.9)	1575, 32.7 ± 19.0 [28.6] (4.8; 66.7)	1408, 7.0 ± 17.8 [4.8] (-19.0; 38.1)
Symptoms: upset by hair loss			
n, mean ± SD [median] (P5%; P95%)	1514, 15.1 ± 30.1 [0.0] (0.0; 100.0)	1415, 13.5 ± 28.0 [0.0] (0.0; 100.0)	1179, -0.1 ± 30.7 [0.0] (-66.7; 66.7)

EORTC = European Organization for Research and Treatment of Cancer, SD = standard deviation, P = percentile, QLQ = Quality of Life Questionnaire, QLQ-BR23 = breast cancer specific QLQ

Source: PT-Table 14.2.2-3.3.1

The course of EORTC QLQ-BR23 for the first-line patients is provided in PT-Table 14.2.2-3.3.2.

Time to first decrease in QoL

Time to first decrease in QoL of at least 5% was analyzed as a secondary parameter. Results are summarized in Table 10-23. The median time to first decrease in QoL was 3.1 months. The results are also shown in PT-Figure 14.2.2.-3.4.

Table 10-23 Time to first decrease in QoL

		All patients n at risk (baseline)
Total		1624
Time to first decrease of at least 5% (months, with 95% CI)	**Lower quartile**	1.2 [1.1; 1.2]
	Median	3.1 [3.0; 3.4]
	Upper quartile	9.4 [8.5; 12.2]

Incidences were calculated by the Kaplan-Meier method
Source: PT-Table 14.2.2-3.4

10.4.2.3 WLTAS and KAS

WLTAS course

The course of WLTAS was analyzed for all patients based on the Godin leisure-time exercise questionnaire during the study. The Godin WLTAS is calculated by adding up the weighted weekly frequencies of strenuous, moderate and mild exercises, with weighting factors nine, five and three, respectively. Changes from baseline to different time points and the last post-baseline value in total and by line are analyzed in PT-Tables 14.2.2-4.1.1, 14.2.2-4.1.2, 14.2.2-4.1.3, 14.2.2-4.1.4, 14.2.2-4.1.5, and 14.2.2-4.1.6.

The mean WLTAS at baseline and last post-baseline value were 20.7 ± 23.3 (median: 15.0; P5% to P95%: 0.0 to 61.0) and 19.9 ± 24.6 (median: 15.0; P5% to P95%: 0.0 to 61.5), the mean difference between the last post-baseline visit and baseline was -1.2 ± 22.6 (median: 0.0; P5% to P95%: -37.0 to 33.0). This means that no remarkable changes were observed during the study.

WLTAS assessment

The activity assessment during the study based on the Godin leisure-time exercise questionnaire is provided for all patients in PT-Table 14.2.2-4.2.1. Table 10-24 summarizes the activity assessment during the observation period. Throughout the observation period, most patients were assessed to be “insufficiently active”. There were no notable changes during the observation period.

Table 10-24 Activity assessment by the Godin Leisure-time exercise questionnaire

	Activity assessment, n (%)			
Visit	Active	Moderately active	Insufficiently active	Missing
Baseline	332 (23.0)	212 (14.7)	897 (62.2)	112
Visit 2 (Month 1)	294 (23.9)	171 (13.9)	764 (62.2)	104
Visit 3 (Month 3)	239 (25.5)	149 (15.9)	550 (58.6)	79
Visit 4 (Month 6)	167 (27.7)	119 (19.7)	317 (52.6)	42
Visit 5 (Month 9)	115 (28.9)	71 (17.8)	212 (53.3)	28
Visit 6 (Month 12)	68 (23.1)	53 (18.0)	173 (58.8)	12
Visit 7 (Month 15)	32 (29.6)	18 (16.7)	58 (53.7)	3
Visit 8 (Month 18)	18 (21.2)	14 (16.5)	53 (62.4)	1
Visit 9 (Month 21)	12 (20.3)	11 (19.6)	36 (61.0)	2
Visit 10 (Month 24)	17 (35.4)	6 (12.5)	25 (52.1)	2
Visit 11 (Month 27)	5 (18.5)	6 (22.2)	16 (59.3)	-
Visit 12 (Month 30)	5 (22.7)	4 (18.2)	13 (59.1)	-
Visit 13 (Month 33)	4 (25.0)	1 (6.3)	11 (68.8)	-
Visit 14 (Month 36)	1 (8.3)	3 (25.0)	8 (66.7)	-
Visit 15 (Month 39)	1 (12.5)	-	7 (87.5)	-
Visit 16 (Month 42)	3 (37.5)	-	5 (62.5)	-
Visit 17 (Month 45)	-	2 (40.0)	3 (60.0)	-
Visit 18 (Month 48)	1 (50.0)	-	1 (50.0)	-
Visit 19 (Month 51)	-	-	1 (100.0)	-
Last post-baseline visit	297 (21.1)	222 (15.8)	889 (63.1)	109

WLTAS = Weekly leisure-time activity score

Weighted weekly frequency of strenuous and moderate exercises with weighting factors nine and five: >= 24 is “active”, 14 - 23 is “moderately active” and 0 - 13 is “insufficiently active”

Source: PT-Table 14.2.2-4.2.1

Regarding all patients, 51 (4.4%) and 93 (8.1%) patients changed from “active” to “moderately active” or “insufficiently active” from baseline to the last post-baseline value. Patients who were assessed as “moderately active” at baseline (179, 15.6%) were assessed to be “active” (45, 3.9%), “moderately active” (58, 5.1%), or “insufficiently active” (76, 6.6%) at the last post-baseline visit. Patients who were assessed as “insufficiently active” at baseline (684, 59.6%) were assessed to be “active” (68, 5.9%), “moderately active” (75, 6.5%), or “insufficiently active” (541, 47.2%) at the last post-baseline value (PT-Table 14.2.2-4.2.2.1). Furthermore PT-Table 14.2.2-4.2.2.2 shows the activity assessment by therapy line.

WLTAS and tolerability

A relation between WLTAS and tolerability was analyzed for patients with AEs and ADRs (serious and non-serious), and in relation to Afinitor® and exemestane in PT-Table 14.2.2-4.3. Overall, patients without any events had a higher mean WLTAS than patients with events. No remarkable differences between baseline and the last post-baseline visit were observed.

The relation between WLTAS and therapy line is provided in PT-Table 14.2.2-4.4.

Course of KAS

The course of KAS with 0 = no (exercise) and 100 = very much (exercise), during the observation period was analyzed in PT-Tables 14.2.2-5.1.1, 14.2.2-5.1.2, 14.2.2-5.1.3, 14.2.2-5.1.4, 14.2.2-5.1.5, 14.2.2-5.1.6, 14.2.2-5.1.7, and 14.2.2-5.1.8. Exercises were jogging, walking, swimming, soccer, tennis, etc., physical activities in everyday life were gardening, taking the stairs, taking a walk, etc. In general, exercise during the last week showed the lowest mean values, while the scores for physical activity in everyday life during the last week and for exercise and physical activity during the last 10 years, during adolescence, and during the whole life showed higher mean values. Table 10-25 summarizes the results for baseline, month 12 and month 24 (the patient numbers for the visits at month 27 up to month 51 were very low, thus an interpretation of these time points seems to be not meaningful).

Table 10-25 Course of KAS during the observation period

Subscale	Baseline N=2074	Month 12 N=2074	Month 24 N=2074
KAS1 - Exercise during last week			
n, mean ± SD [median] (P5%; P95%)	1442, 13.9 ± 22.3 [2.0] (0.0; 64.0)	287, 19.8 ± 24.0 [10.0] (0.0; 71.0)	48, 17.5 ± 21.4 [7.0] (0.0; 62.0)
KAS2 - Physical activity in everyday life during last week			
n, mean ± SD [median] (P5%; P95%)	1471, 49.9 ± 31.4 [50.0] (0.0; 100.0)	286, 47.1 ± 28.1 [49.0] (1.0; 95.0)	49, 49.8 ± 26.3 [56.0] (0.0; 90.0)
KAS3 - Exercise during last 10 years			
n, mean ± SD [median] (P5%; P95%)	1451, 39.3 ± 31.7 [38.0] (0.0; 96.0)	289, 40.0 ± 28.0 [40.0] (0.0; 89.0)	50, 40,8 ± 27,0 [46.5] (0.0; 81.0)
KAS4 - Physical activity in everyday life during last 10 years			
n, mean ± SD [median] (P5%; P95%)	1485, 67.1 ± 27.4 [73.0] (12.0; 100.0)	292, 60.9 ± 26.1 [60.0] (10.0; 100.0)	50, 59.2 ± 25.5 [58.0] (5.0; 99.0)
KAS5 - Exercise during adolescence (up to 20 years)			
n, mean ± SD [median] (P5%; P95%)	1462, 48.5 ± 34.9 [49.5] (0.0; 100.0)	290, 50.7 ± 31.7 [50.5] (0.0; 99.0)	51, 51.9 ± 33.3 [47.0] (0.0; 100.0)
KAS5 - Physical activity in everyday life during adolescence (up to 20 years)			
n, mean ± SD [median] (P5%; P95%)	1482, 69.6 ± 28.4 [77.5] (12.0; 100.0)	294, 66.7 ± 27.3 [71.0] (15.0; 100.0)	51, 72.3 ± 24.2 [78.0] (21.0; 100.0)
KAS6 - Exercise during whole life			
n, mean ± SD [median] (P5%; P95%)	1462, 46.2 ± 29.4 [48.0] (0.0; 98.0)	293, 48.2 ± 27.1 [49.0] (0.0; 92.00)	49, 55.3 ± 27.1 [55.0] (5.0; 99.0)
KAS6 - Physical activity in everyday life during whole life			
n, mean ± SD [median] (P5%; P95%)	1491, 71.9 ± 24.7 [78.0] (24.0; 100.0)	294, 66.3 ± 24.7 [70.0] (21.0; 100.0)	51, 72.4 ± 20.6 [73.0] 41.0; 100.0)

SD=standard deviation, P = percentile

0=none, 100=very much

Source: PT-Tables 14.2.2-5.1.1, 14.2.2-5.1.2, 14.2.2-5.1.3, 14.2.2-5.1.4, 14.2.2-5.1.5, 14.2.2-5.1.6, 14.2.2-5.1.7, 14.2.2-5.1.8

KAS and tolerability

The relation between KAS and tolerability was analyzed in PT-Table 14.2.2-5.2. Allover, no remarkable differences were observed for patients with and without any event. However, patients with SAEs and SADR reported less exercise and physical activity in everyday life during the last week, than patients without SAE or SADR. The same is true regarding SADR related to Afinitor® and exemestane.

The relation between KAS and therapy line is analyzed in PT-Table 14.2.2-5.3.

Correlation between WLTAS, KAS, QoL, and BMI

The Spearman correlations between WLTAS, KAS, QoL, and BMI assessed at baseline are analyzed in PT-Table 14.2.2-6.1. A summary is provided in Table 10-26. Some correlations could be observed between WLTAS and different scores of the KAS. The highest correlations were found between WLTAS and exercise (KAS1) and physical activity (KAS2) during the last week (0.421 and 0.422, respectively). At least a weak correlation was observed between WLTAS and exercise (KAS3) and physical activity (KAS4) during the last 10 years (0.292 and 0.198, respectively) and between WLTAS and exercise during the whole life (KAS7, 0.253). Between WLTAS and global health status/QoL a weak correlation of 0.240 could be found, between KAS1 and KAS2 and global health status/QoL weak correlations of 0.274 and 0.335, respectively were observed. A weak negative correlation could be observed between KAS3 (exercise during last 10 years) and KAS7 (exercise during whole life) and BMI (-0.190 and -0.154, respectively).

Table 10-26 Correlation between WLTAS, KAS, QoL, and BMI at baseline

Correlation between		n	Spearman correlation [95% CI]	
WLTAS	KAS1	1377	0.421	[0.377; 0.464]
	KAS2	1407	0.422	[0.377; 0.463]
	KAS3	1385	0.292	[0.243; 0.340]
	KAS4	1418	0.198	[0.147; 0.247]
	KAS5	1398	0.136	[0.084; 0.187]
	KAS6	1411	0.067	[0.015; 0.119]
	KAS7	1395	0.253	[0.204: 0.302]
	KAS8	1421	0.114	[0.062; 0.165]
	Global health status/QoL	1367	0.240	[0.189; 0.289]
	BMI	1504	-0.101	[-0.151; -0.051]
KAS1	Global health status/QoL	1281	0.274	[0.223; 0.324]
	BMI	1407	-0.089	[-0.140; -0.036]
KAS2	Global health status/QoL	1307	0.335	[0.286; 0.382]
	BMI	1438	-0.084	[-0.136; -0.033]
KAS3	Global health status/QoL	1289	0.078	[0.024; 0.132]
	BMI	1418	-0.190	[-0.240; -0.139]
KAS4	Global health status/QoL	1321	0.056	[0.002; 0.109]
	BMI	1453	-0.082	[-0.133; -0.031]
KAS5	Global health status/QoL	1303	-0.016	[-0.071; 0.038]

Table 10-26 Correlation between WLTAS, KAS, QoL, and BMI at baseline

Correlation between		n	Spearman correlation [95% CI]	
	BMI	1428	-0.065	[-0.116; -0.013]
KAS6	Global health status/QoL	1320	-0.045	[-0.099; 0.009]
	BMI	1450	0.051	[-0.001; 0.102]
KAS7	Global health status/QoL	1300	0.052	[-0.003; 0.106]
	BMI	1428	-0.154	[-0.205; -0.103]
KAS8	Global health status/QoL	1331	-0.001	[-0.054; 0.053]
	BMI	1458	-0.046	[-0.097; 0.005]
Global health status/QoL	BMI	1453	-0.027	[-0.078; 0.025]

BMI = body mass index, CI = confidence interval, KAS = "Körperliche Aktivitäts-Skalen" (physical activity score), QoL = quality of life, WLTAS = weekly leisure time activity score

KAS1: exercise during last week, KAS2: physical activity in everyday life during last week
KAS3: exercise during last 10 years, KAS4: physical activity in everyday life during last 10 years
KAS5: exercise during adolescence, KAS6: physical activity in everyday life during adolescence
KAS7: exercise during whole life, KAS8: physical activity in everyday life during whole life

Source: PT-Table 14.2.2-6.1

QoL by exercise and activity categories is shown in PT-Figures 14.2.2-6.1.1 and 14.2.2-6.1.2. Relation between last post-baseline QoL assessment and exercise/activity during last week prior to baseline (KAS) is shown in PT-Tables 14.2.2-6.2.1 and 14.2.2-6.2.2.

Correlation between KAS, WLTAS and fatigue

The Spearman correlations between KAS, WLTAS and fatigue assessed at baseline are analyzed in PT-Table 14.2.2-7. The highest correlations were found between KAS1 and WLTAS (0.421) and KAS2 and WLTAS (0.422). A summary is provided in Table 10-27.

Table 10-27 Correlation between KAS, WLTAS, and fatigue at baseline

Correlation between		n	Spearman correlation [95% CI]
KAS1	WLTAS	1377	0.421 [0.377; 0.464]
	Fatigue	1294	- 0.269 [-0.319; - 0.218]
KAS2	WLTAS	1407	0.422 [0.377; 0.463]
	Fatigue	1319	- 0.355 [-0.401; - 0.307]
KAS3	WLTAS	1385	0.292 [0.243; 0.340]
	Fatigue	1302	- 0.090 [-0.144; - 0.036]
KAS4	WLTAS	1418	0.198 [0.147; 0.247]
	Fatigue	1334	- 0.052 [-0.105; 0.002]
KAS5	WLTAS	1398	0.136 [0.084; 0.187]
	Fatigue	1316	0.018 [-0.037; 0.071]
KAS6	WLTAS	1411	0.067 [0.015; 0.119]
	Fatigue	1333	0.071 [0.017; 0.124]
KAS7	WLTAS	1395	0.253 [0.204; 0.302]
	Fatigue	1313	- 0.049 [-0.103; 0.005]
KAS8	WLTAS	1421	0.114 [0.062; 0.165]
	Fatigue	1344	0.029 [-0.025; 0.082]
WLTAS	Fatigue	1382	- 0.267 [-0.316; - 0.218]

CI = confidence interval, KAS = “Körperliche Aktivitäts-Skalen” (physical activity score), WLTAS = weekly leisure time activity score

KAS1: exercise during last week
KAS2: physical activity in everyday life during last week
KAS3: exercise during last 10 years
KAS4: physical activity in everyday life during last 10 years
KAS5: exercise during adolescence
KAS6: physical activity in everyday life during adolescence
KAS7: exercise during whole life
KAS8: physical activity in everyday life during whole life

Source: PT-Table 14.2.2-7

10.5 Other analyses

No other analyses were performed.

10.6 Adverse events/adverse reactions

10.6.1 Summary of adverse events

Out of 2074 patients, 1900 (91.6%) experienced any AE, 1789 patients (86.3%) experienced non-serious (ns)AEs, and 963 patients (46.4%) experienced non-serious AEs considered to be not related (nsAEnr) to Afinitor® or exemestane. A total of 1668 patients (80.4%) experienced any nsADR that was considered related to Afinitor® in 1655 patients (79.8%) and related to exemestane in 957 patients (46.1%).

A total of 914 patients (44.1%) experienced any SAE. In 660 patients (31.8%) SAEs were considered not related (SAEnr) to Afinitor® or exemestane. SADR were reported for 478 patients (23.0%), in 443 patients (21.4%) considered related to Afinitor® and in 246 patients (11.9%) considered related to exemestane. Four hundred and forty-six patients (21.5%) experienced an AE leading to death and 116 patients (5.6%) an ADR leading to death.

In addition, AESIs as defined in the Product Guidance Document for Afinitor/Votubia (everolimus) were analyzed. A total of 767 patients (37.0%) experienced AESIs.

The number of AEs which were assessed as non-serious by the investigator, but as serious by the patient-safety department of the sponsor (see PT-Table 14.3.1-1.3.5) was 665 (32.1%). An overview of all AEs and ADRs is given in Table 10-28.

Table 10-28 Overview of (S)AEsnr and (S)ADRs

AE type	Total n (%)
Patients at risk	2074 (100.0)
No. of patients with	
any AE	1900 (91.6)
any nsAE	1789 (86.3)
any nsAEnr	963 (46.4)
any nsADR	1668 (80.4)
any nsADR (Afinitor®)	1655 (79.8)
any nsADR (exemestane)	957 (46.1)
any SAE	914 (44.1)
any SAEnr	660 (31.8)
any AEnr leading to death	446 (21.5)
any SADR	478 (23.0)
any SADR (Afinitor®)	443 (21.4)
any SADR (exemestane)	246 (11.9)
any ADR leading to death	116 (5.6)
any AESI	767 (37.0)
any AE with differing seriousness assessment[a]	665 (32.1)

a Adverse event assessed as non-serious by investigator and as serious by patient-safety department

ADR = adverse drug reaction, AE = adverse event, AESI = adverse event of special interest, ns = non serious, nr = not related, SADR = serious ADR, SAE = serious AE

Source: PT-Table 14.3.1-1.1

Most of the 2074 patients experienced events of moderate (1407, 67.8%) or mild (1386, 66.8%) intensity, in 702 patients (33.8%) the intensity was severe. Three hundred and ninety-three patients (393, 18.9%) experienced 714 life-threatening AEs (345 patients with serious AEs, 47 patients with serious ADRs related to Afinitor®, 39 patients with serious ADRs related to exemestane, and 1 patient with nsAEnr, [PT-Tables 14.3.1-1.3.4.1, 14.3.1-1.3.4.2, 14.3.1-1.3.4.3 and 14.3.1-1.3.4.4]). The intensity of AEs by event is provided in PT-Tables 14.3.1-1.4.1, 14.3.1-1.4.2, 14.3.1-1.4.3, and 14.3.1-1.4.4.

10.6.1.1 Subgroup analyses of (S)AEsnr/(S)ADRs

Analyses of (S)AEs and (S)ADRs were also performed by treatment line, for patients with at least 3 months of follow-up, by Afinitor® starting dose (5 mg/10 mg), and by practice (oncologist or gynecologist) (PT-Table 14.3.1-1.1).

Number of patients with (S)AEsnr/(S)ADRs by treatment line and by follow-up

No remarkable differences in number of patients with (S)AEs and (S)ADRs were observed comparing data by treatment line or by patients with at least 3 months of follow-up (PT-Table 14.3.1-1.1).

Number of patients with (S)AEsnr/(S)ADRs by starting dose

Patients with a starting dose of 10 mg Afinitor® were somewhat more likely to experience AEs (1205 patients, 92.3%) than patients with a starting dose of 5 mg (641 patients, 90.7%). This could be observed for all types of AEs and ADRs as summarized in Table 10-29. The only exception were AEs where the seriousness assessment of the investigator differed from the assessment of the patient-safety department of the sponsor, here the percentage of patients with a starting dose of 5 mg and 10 mg were almost the same (32.7% vs. 31.8%).

Table 10-29 Summary of patients with (S)AEsnr and (S)ADRs by starting dose

AE type	Start dose 5 mg, n (%)	Start dose 10 mg, n (%)
Patients at risk	707 (100.0)	1306 (100.0)
No. of patients with		
any AE	641 (90.7)	1205 (92.3)
any nsAE	604 (85.4)	1133 (86.8)
any nsAEnr	322 (45.5)	618 (47.3)
any nsADR	558 (78.9)	1062 (81.3)
any nsADR (Afinitor®)	552 (78.1)	1055 (80.8)
any nsADR (exemestane)	301 (42.6)	631 (48.3)
any SAE	285 (40.3)	601 (46.0)
any SAEnr	209 (29.6)	435 (33.3)
any AE leading to death	143 (20.2)	294 (22.5)
any SADR	134 (19.0)	328 (25.1)
any SADR (Afinitor®)	124 (17.5)	303 (23.2)
any SADR (exemestane)	64 (9.1)	177 (13.6)
any ADR leading to death	31 (4.4)	83 (6.4)
any RMP event	231 (32.7)	513 (39.3)
any AE with differing seriousness assessment[a]	231 (32.7)	415 (31.8)

a Adverse event assessed as non-serious by investigator and as serious by patient-safety department

ADR = adverse drug reaction, AE = adverse event, ns = non serious, nr = not related, RMP = risk management plan, SADR = serious ADR, SAE = serious AE

Source: PT-Table 14.3.1-1.1

Analysis of patients with (S)AEsnr/(S)ADRs by practice

Eight hundred and twenty-nine (829) patients were treated in an oncology practice, 1200 patients in a gynecology practice. The rates of patients for whom any AEs were reported were similar for oncologists and gynecologists. Descriptively, a slightly higher rate of SAEs was reported at gynecologists. (PT-Table 14.3.1-1.1).

Analysis of patients with (S)AEsnr/(S)ADRs by intensity of comorbidities

An analysis of patients with (S)AEsnr/(S)ADRs by intensity of comorbidities based on all patients is provided in PT-Table 14.3.1-1.2. Table 10-30 summarizes the results. Descriptively, the subgroup with moderate comorbidities was more likely to experience SAEs (related and unrelated) and SADRs than the subgroup without/severe comorbidity. The subgroup with severe comorbidities was more likely to experience nsAEs (related and unrelated) and nsADRs than the subgroups without/moderate comorbidity. Overall, there was no clear trend regarding the incidence of AEs differentiated by the presence/severity of comorbidities. Comparison of the comorbidity subgroups was hampered by the different numbers of patients in the subgroups “no comorbidity” (N=1549), “moderate comorbidity” (N=464), and “severe comorbidity” (N=55).

Table 10-30 Summary of (S)AEsnr and (S)ADRs by intensity of comorbidities

	Comorbidity n (%)		
AE type	**No comorbidity (CCI = 0)**	**Moderate comorbidity (CCI = 1 or 2)**	**Severe comorbidity (CCI ≥ 3)**
Patients at risk	1549 (100.0)	464 (100.0)	55 (100.0)
No. of patients with			
any AE	1418 (91.5)	426 (91.8)	53 (96.4)
any nsAE	1350 (87.2)	388 (83.6)	50 (90.9)
any nsAEnr	740 (47.8)	198 (42.7)	24 (43.6)
any nsADR	1257 (81.1)	364 (78.4)	46 (83.6)
any nsADR (Afinitor®)	1248 (80.6)	361 (77.8)	45 (81.8)
any nsADR (exemestane)	709 (45.8)	217 (46.8)	31 (56.4)
any SAE	618 (39.9)	265 (57.1)	29 (52.7)
any SAEnr	444 (28.7)	192 (41.4)	22 (40.0)
any AEnr leading to death	291 (18.8)	140 (30.2)	14 (25.5)
any SADR	322 (20.8)	144 (31.0)	12 (21.8)
any SADR (Afinitor®)	298 (19.2)	134 (28.9)	11 (20.0)
any SADR (exemestane)	169 (10.9)	70 (15.1)	7 (12.7)
any ADR leading to death	73 (4.7)	40 (8.6)	3 (5.5)
any RMP event	575 (37.1)	169 (36.4)	22 (40.0)
any AE with differing seriousness assessment[a]	476 (30.7)	169 (36.4)	19 (34.5)

a Adverse event assessed as non-serious by investigator and as serious by patient-safety department

ADR = adverse drug reaction, AE = adverse event, CCI = Charlson comorbidity index, ns = non serious, nr = not related, RMP = risk management plan, SADR = serious ADR, SAE = serious AE

Source: PT-Table 14.3.1-1.2

Analysis of patients with AEs differentiated by extent of exercise during the last week prior to baseline

The rate of patients with AEs by exercise during the last week prior to baseline is provided in PT-Table 14.3.1-2.1.1. Table 10-31 summarizes the results. Descriptively, the number of patients with an AE was lower in patients who were "very active" (55 patients, 83.3%) during the last week prior to baseline compared to patients who had less exercise.

Table 10-31 Rate of patients with AE by exercise during last week prior to baseline

Number of patients	**Little (0-33)**	**Somewhat (34-66)**	**Very active (67-100)**	**Total**
- at risk	1198 (100.0%)	178 (100.0%)	66 (100.0%)	1442 (100.0%)
- with any AE	1122 (93.7%)	167 (93.8%)	55 (83.3%)	1344 (93.2%)

Source: PT-Table 14.3.1-2.1.1

PT-Table 14.3.1-2.2.1 provides a logistic regression analysis for occurrence of AEs by exercise during the last week prior to baseline.

Analysis of patients with AEs by activity during the last week prior to baseline

The rate of patients with AEs by activity during the last week prior to baseline is provided in PT-Table 14.3.1-2.1.2. Table 10-32 summarizes the results. Descriptively, the number of patients with an AE was somewhat lower in patients who were "very active" (445 patients, 91.2%) during the last week prior to baseline compared to patients who were less active.

Table 10-32 Rate of patients with AE by activity during last week prior to baseline

Number of patients	Little (0-33)	Somewhat (34-66)	Very active (67-100)	Total
- at risk	487 (100.0%)	496 (100.0%)	488 (100.0%)	1471 (100.0%)
- with any AE	462 (94.9%)	467 (94.2%)	445 (91.2%)	1374 (93.4%)

Source: PT-Table 14.3.1-2.1.2

PT-Table 14.3.1-2.2.2 provides a logistic regression analysis for occurrence of AEs by activity during the last week prior to baseline.

10.6.2 Analysis and description of non-serious adverse events and adverse drug reactions

The tabulation of patients with AEsnr and ADRs by Medical Dictionary for Regulatory Activities (MedDRA) primary System Organ class (PSOC) and preferred term (PT) is provided in PT-Tables 14.3.1-1.3.1, 14.3.1-1.3.2, 14.3.1-1.3.3 and 14.3.1-1.3.6.

10.6.2.1 Non-serious adverse events not related

Nine hundred sixty-three (963, 46.4%) of patients experienced at least one nsAEnr during the observation period. The highest incidence was seen in patients with nsAEsnr referring to the following MedDRA SOCs:

- "Infections and infestations" (271 patients, 13.1%), such as "nasopharyngitis" (89 patients, 4.3%), "urinary tract infection" (31 patients, 1.5%), and "bronchitis" (25 patients, 1.2%);
- "General disorders and administration site conditions" (265 patients, 12.8%), with "fatigue" (72 patients, 3.5%), "oedema peripheral" (65 patients, 3.1%), and "general physical health deterioration" (32 patients, 1.5%);
- "Musculoskeletal and connective tissue disorders" (242 patients, 11.7%), such as "pain in extremity" (49 patients, 2.4%), "arthralgia" (43 patients, 2.1%) and "back pain" (41 patients, 2.0%), being the most common AEs on PT level;
- "Gastrointestinal disorders" (230 patients, 11.1%), with "diarrhoea" (66 patients, 3.2%), "nausea" (34 patients, 1.6%) and "vomiting" (27 patients, 1.3%);

Table 10-33 lists the incidence rates of all nsAEsnr on PSOC level and the most common AEs (occurring in ≥ 10 subjects in total) on PT level during the study.

Table 10-33 Number of patients (%) with non-serious adverse events not related (occurring in ≥ 10 patients) by SOC and by most common PTs

Primary SOC PT (MedDRA)	**Total** **N = 2074** **n (%)**
Subjects with any non-serious adverse event not related	**963 (46.4)**
Infections and infestations	**271 (13.1)**
Nasopharyngitis	89 (4.3)
Urinary tract infection	31 (1.5)
Bronchitis	25 (1.2)
Pneumonia	12 (0.6)
Gastrointestinal infection	11 (0.5)
Upper respiratory tract infection	10 (0.5)
General disorders and administration site conditions	**265 (12.8)**
Fatigue	72 (3.5)
Oedema peripheral	65 (3.1)
General physical health deterioration	32 (1.5)
Pyrexia	28 (1.4)
Peripheral swelling	24 (1.2)
Pain	17 (0.8)
Asthenia	10 (0.5)
Chills	10 (0.5)
Musculoskeletal and connective tissue disorders	**242 (11.7)**
Pain in extremity	49 (2.4)
Arthralgia	43 (2.1)
Back pain	41 (2.0)
Bone pain	34 (1.6)
Musculoskeletal pain	19 (0.9)
Spinal pain	14 (0.7)
Muscle spasms	11 (0.5)
Musculoskeletal chest pain	10 (0.5)
Myalgia	10 (0.5)
Osteonecrosis of jaw	10 (0.5)
Gastrointestinal disorders	**230 (11.1)**
Diarrhoea	66 (3.2)
Nausea	34 (1.6)
Vomiting	27 (1.3)
Abdominal pain upper	19 (0.9)
Constipation	19 (0.9)
Stomatitis	18 (0.9)
Ascites	15 (0.7)
Toothache	10 (0.5)
Respiratory, thoracic and mediastinal disorders	**196 (9.5)**
Cough	60 (2.9)
Dyspnoea	50 (2.4)
Pleural effusion	39 (1.9)

Table 10-33 Number of patients (%) with non-serious adverse events not related (occurring in ≥ 10 patients) by SOC and by most common PTs

Primary SOC PT (MedDRA)	**Total** **N = 2074** **n (%)**
Epistaxis	25 (1.2)
Dyspnoea exertional	23 (1.1)
Oropharyngeal pain	11 (0.5)
Investigations	**125 (6.0)**
Weight decreased	35 (1.7)
Blood creatinine increased	16 (0.8)
Eastern Cooperative Oncology Group Performance Status worsened	15 (0.7)
Skin and subcutaneous tissue disorders	**119 (5.7)**
Rash	26 (1.3)
Pruritus	15 (0.7)
Erythema	11 (0.5)
Nervous system disorders	**109 (5.3)**
Headache	35 (1.7)
Dizziness	19 (0.9)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**103 (5.0)**
Malignant neoplasm progression	54 (2.6)
Metastases to bone	20 (1.0)
Metastases to liver	13 (0.6)
Vascular disorders	**83 (4.0)**
Lymphoedema	44 (2.1)
Hypertension	11 (0.5)
Metabolism and nutrition disorders	**78 (3.8)**
Decreased appetite	36 (1.7)
Psychiatric disorders	**61 (2.9)**
Sleep disorder	18 (0.9)
Depression	15 (0.7)
Insomnia	11 (0.5)
Blood and lymphatic system disorders	**55 (2.7)**
Anaemia	35 (1.7)
Injury, poisoning and procedural complications	**42 (2.0)**
Renal and urinary disorders	**27 (1.3)**
Eye disorders	**27 (1.3)**
Surgical and medical procedures	**23 (1.1)**
Cardiac disorders	**17 (0.8)**
Reproductive system and breast disorders	**17 (0.8)**
Hepatobiliary disorders	**11 (0.5)**

MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term; SOC = System organ class.

Patients with multiple occurrences of an AE are counted only once within the corresponding AE category and SOC, respectively.

Source: PT-Table 14.3.1-1.3.6

Intensity of non-serious AEs not related

The intensity of nsAEsnr for all patients is analyzed in PT-Tables 14.3.1-1.3.4.1 (mild events, by patient), 14.3.1-1.4.1 (mild events, by event), PT-Table 14.3.1-1.3.4.2 (moderate events, by patient), 14.3.1-1.4.2 (moderate events, by event), PT-Table 14.3.1-1.3.4.3 (severe events, by patient), and 14.3.1-1.4.3 (severe events, by event).

Six hundred and twenty-seven (627, 30.2%) of the patients experienced a total of 1382 nsAEsnr of mild intensity. Such AEs occurring in at least 10 patients on PT level were (PT-Table 14.3.1-1.3.4.1):

- 64 patients (3.1%): "nasopharyngitis"
- 43 patients (2.1%): "fatigue"
- 39 patients (1.9%): "diarrhoea"
- 38 patients (1.8%): "oedema peripheral"
- 36 patients (1.7%): "cough"
- 24 patients (1.2%): "back pain"
- 23 patients (1.1%): "nausea", "pain in extremity", "lymphoedema"
- 22 patients (1.1%): "arthralgia"
- 21 patients (1.0%): "headache", "dyspnoea", epistaxis"
- 20 patients (1.0%): "weight decreased"
- 19 patients (0.9%): "decreased appetite", "pyrexia", "dyspnoea exertional"
- 18 patients (0.9%): "peripheral swelling", "dizziness"
- 17 patients (0.8%): "vomiting", "rash"
- 15 patients (0.7): "abdominal pain upper"
- 13 patients (0.6%): "sleep disorder"
- 12 patients (0.6%): "blood creatinine increased", "bone pain", "bronchitis", "constipation", "stomatitis"
- 11 patients (0.5%): "Eastern Cooperative Oncology Group Performance Status worsened", "pruritus"
- 10 patients (0.5%): "muscle spasms", "musculoskeletal pain", "myalgia".

Five hundred fifty-one (551, 26.6%) of the patients experienced a total of 1079 nsAEsnr of moderate intensity. Such AEs occurring in at least 10 patients on PT level were (PT-Table 14.3.1-1.3.4.2):

- 30 patients (1.4%): "nasopharyngitis"
- 28 patients (1.4%): "fatigue"
- 27 patients (1.3%): "oedema peripheral"
- 25 patients (1.2%): "pain in extremity"
- 23 patients (1.1%): "diarrhoea", "urinary tract infection", "cough"

- 22 patients (1.1%): "general physical health deterioration", "arthralgia", "malignant neoplasm progression", "pleural effusion"
- 21 patients (1.0%): "anaemia", "dyspnoea"
- 18 patients (0.9%): "bone pain", "lymphoedema"
- 17 patients (0.8%): "back pain"
- 14 patients (0.7%): "bronchitis", "weight decreased", "decreased appetite"
- 13 patients (0.6%): "headache"
- 11 patients (0.5%): "nausea", "pneumonia"
- 10 patients (0.5%): "ascites", "vomiting", "osteonecrosis of jaw", "metastases to bone".

One hundred and fifteen (115, 5.5%) of the patients experienced a total of 181 nsAEsnr of severe intensity. Such AEs occurring in at least 3 patients on PT level were (PT-Table 14.3.1-1.4.3):

- 20 patients (1.0%): "malignant neoplasm progression"
- 6 patients (0.3%): "anaemia", "general physical health deterioration", "metastases to liver", "dyspnoea"
- 5 patients (0.2%): "pleural effusion"
- 4 patients (0.2%): "ascites", "pain", "C-reactive protein increased", "bone pain"
- 3 patients (0.1%): "diarrhoea", "metastases to lung".

10.6.2.2 Non-serious adverse drug reactions

10.6.2.2.1 Non-serious adverse drug reactions related to Afinitor®

A total of 1655 (79.8%) of the patients experienced at least one non-serious ADR related to Afinitor® during the observation period. The highest incidence was seen referring to the MedDRA SOCs:

- "Gastrointestinal disorders" (1199 patients, 57.8%), with "stomatitis" (859 patients, 41.4%), "nausea" (235 patients, 11.3%), and "diarrhoea" (219 patients, 10.6%) being the most common nsADRs on PT level;
- "Skin and subcutaneous tissue disorders" (597 patients, 28.8%), with "rash" (208 patients, 10.0%), "pruritus" (112 patients, 5.4%), and "dry skin" (63 patients, 3.0%);
- "General disorders and administration site conditions" (578 patients, 27.9%), such as "fatigue" (323 patients, 15.6%), "peripheral oedema" (110 patients, 5.3%), and "general physical health deterioration" (52 patients, 2.5%);
- "Respiratory, thoracic and mediastinal disorders" (463 patients, 22.3%), such as "cough" (156 patients, 7.5%), "dyspnoea" (141 patients, 6.8%) and "epistaxis" (100 patients, 4.8%).

The tabulation of all patients with nsADRs related to Afinitor® by primary MedDRA SOC and PT is provided in PT-Table 14.3.1-1.3.2. Table 10-34 summarizes the number of patients with nsADRs related to Afinitor® occurring in at least 20 patients.

Table 10-34 Number of patients (%) with non-serious ADRs related to Afinitor® by SOC and by most common PTs (occurring in ≥ 20 patients)

Primary SOC PT (MedDRA)	**Total** **N = 2074** **n (%)**
Subjects with any non-serious adverse drug reactions related to Afinitor®	**1655 (79.8)**
Gastrointestinal disorders	**1199 (57.8)**
Stomatitis	859 (41.4)
Nausea	235 (11.3)
Diarrhoea	219 (10.6)
Dry mouth	73 (3.5)
Vomiting	70 (3.4)
Aphthous ulcer	62 (3.1)
Upper abdominal pain	46 (2.2)
Constipation	30 (1.4)
Abdominal pain	22 (1.1)
Skin and subcutaneous tissue disorders	**597 (28.8)**
Rash	208 (10.0)
Pruritus	112 (5.4)
Dry skin	63 (3.0)
Erythema	49 (2.4)
Alopecia	44 (2.1)
Palmar-plantar erythrodysaesthesia syndrome	35 (1.7)
Acne	31 (1.5)
Nail disorder	27 (1.3)
Onychoclasis	25 (1.2)
Pruritic rash	25 (1.2)
Skin fissures	21 (1.0)
General disorders and administration site conditions	**578 (27.9)**
Fatigue	323 (15.6)
Peripheral oedema	110 (5.3)
General physical health deterioration	52 (2.5)
Asthenia	39 (1.9)
Pyrexia	34 (1.6)
Peripheral swelling	33 (1.6)
Oedema	21 (1.0)
Mucosal inflammation	20 (1.0)
Respiratory, thoracic and mediastinal disorders	**463 (22.3)**
Cough	156 (7.5)
Dyspnoea	141 (6.8)
Epistaxis	100 (4.8)

Table 10-34 Number of patients (%) with non-serious ADRs related to Afinitor® by SOC and by most common PTs (occurring in ≥ 20 patients)

Primary SOC PT (MedDRA)	**Total** **N = 2074** **n (%)**
Pneumonitis	72 (3.5)
Exertional dyspnoea	42 (2.0)
Pleural effusion	25 (1.2)
Investigations	**321 (15.5)**
Weight decreased	109 (5.3)
Blood creatinine increased	29 (1.4)
Blood glucose increased	27 (1.3)
C-reactive protein increased	26 (1.3)
Haemoglobin decreased	25 (1.2)
Gamma-glutamyltransferase increased	24 (1.2)
Alanine aminotransferase increased	22 (1.1)
Aspartate aminotransferase increased	22 (1.1)
Eastern Cooperative Oncology Group Performance Status worsened	20 (1.0)
Nervous system disorders	**302 (14.6)**
Dysgeusia	147 (7.1)
Headache	72 (3.5)
Dizziness	51 (2.5)
Metabolism and nutrition disorders	**287 (13.8)**
Decreased appetite	195 (9.4)
Diabetes mellitus	23 (1.1)
Hyperglycaemia	20 (1.0)
Infections and infestations	**257 (12.4)**
Nasopharyngitis	38 (1.8)
Pneumonia	27 (1.3)
Pustular rash	26 (1.3)
Bronchitis	20 (1.0)
Musculoskeletal and connective tissue disorders	**192 (9.3)**
Arthralgia	60 (2.9)
Pain in extremity	42 (2.0)
Bone pain	29 (1.4)
Back pain	26 (1.3)
Myalgia	20 (1.0)
Blood and lymphatic system disorders	**156 (7.5)**
Anaemia	89 (4.3)
Thrombocytopenia	41 (2.0)
Leukopenia	34 (1.6)
Psychiatric disorders	**98 (4.7)**
Sleep disorder	34 (1.6)
Depression	21 (1.0)
Insomnia	20 (1.0)

Table 10-34 Number of patients (%) with non-serious ADRs related to Afinitor® by SOC and by most common PTs (occurring in ≥ 20 patients)

Primary SOC PT (MedDRA)	Total N = 2074 n (%)
Vascular disorders	**95 (4.6)**
Hot flush	26 (1.3)
Lymphoedema	20 (1.0)
Eye disorders	**78 (3.8)**
Lacrimation increased	20 (1.0)
Renal and urinary disorders	**47 (2.3)**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**44 (2.1)**
Malignant neoplasm progression	31 (1.5)
Cardiac disorders	**41 (2.0)**
Injury, poisoning and procedural complication	**24 (1.2)**
Immune system disorders	**21 (1.0)**

ADR = adverse drug reaction; MedDRA = Medical dictionary for drug regulatory activities; nsADR = non-serious adverse drug reaction; PT = Preferred term; SOC = System organ class.

Patients with multiple occurrences of an AE are counted only once within the corresponding AE category and SOC, respectively.

Source: PT-Table 14.3.1-1.3.2

Intensity of non-serious ADRs related to Afinitor®

The intensity of nsADRs related to Afinitor® for all patients is analyzed PT-Table 14.3.1-1.3.4.1 (mild events, by patient), PT-Table 14.3.1-1.3.4.2 (moderate events, by patient), and PT-Table 14.3.1-1.3.4.3 (severe events, by patient).

Thousand two hundred thirty-three (1233, 59.5%) of the patients experienced a total of 3965 nsADRs related to Afinitor® of mild intensity. nsADRs related to Afinitor® occurring in at least 10 patients on PT level were (PT-Table 14.3.1-1.3.4.1):

- 509 patients (24.5%): "stomatitis"
- 193 patients (9.3%): "fatigue"
- 139 patients (6.7%): "diarrhoea"
- 134 patients (6.5%): "nausea"
- 126 patients (6.1%): "decreased appetite"
- 125 patients (6.0%): "rash"
- 98 patients (4.7%): "dysgeusia"
- 91 patients (4.4%): "cough"
- 85 patients (4.1%): "epistaxis"
- 79 patients (3.8%): "pruritus"
- 76 patients (3.7%): "dyspnoea"
- 66 patients (3.2%): "dry mouth", "oedema peripheral"

- 51 patients (2.5%): "headache"
- 50 patients (2.4%): "dry skin"
- 49 patients (2.4%): "weight decreased"
- 45 patients (2.2%): "vomiting"
- 37 patients (1.8%): "alopecia"
- 36 patients (1.7%): "dizziness"
- 35 patients (1.7%): "aphthous ulcer"
- 33 patients (1.6%): "arthralgia"
- 29 patients (1.4%): "anaemia", "dyspnoea exertional", "erythema"
- 27 patients (1.3%): "acne"
- 24 patients (1.2%): "sleep disorder"
- 23 patients (1.1%): "abdominal pain upper", "constipation", "nail disorder"
- 22 patients (1.1%): "nasopharyngitis", "pain in extremity"
- 21 patients (1.0%): "onychoclasis"
- 17 patients (0.8%): "asthenia", "pneumonitis", "skin toxicity"
- 16 patients (0.8%): "thrombocytopenia", "lacrimation increased", "bone pain", "myalgia"
- 15 patients (0.7%): "leukopenia", "abdominal pain", "rash pustular", "blood glucose increased", "insomnia"
- 14 patients (0.7%): "palmar-plantar erythrodysaesthesia", "rash pruritic", "skin fissures", "hot flush"
- 13 patients (0.6%): "peripheral swelling", "paraesthesia", "polyneuropathy"
- 12 patients (0.6%): "dyspepsia", "mucosal dryness", "aspartate aminotransferase increased", "blood lactate dehydrogenase increased", "back pain", "peripheral sensory neuropathy", "skin exfoliation"
- 11 patients (0.5%): "general physical health deterioration", "Eastern Cooperative Oncology Group Performance Status worsened", "hyperglycaemia", "depression"
- 10 patients (0.5%): "eyelid oedema", "conjunctivitis", "alanine aminotransferase increased", "muscle spasms", "nasal dryness".

Four-hundred-and-ninety-six (1095, 52.8%) of the patients experienced a total of 2566 nsADRs related to Afinitor® of moderate intensity. nsADRs related to Afinitor® occurring in at least 10 patients on PT level were (PT-Table 14.3.1-1.3.4.2):

- 384 patients (18.5%): "stomatitis"
- 113 patients (5.4%): "fatigue"
- 97 patients (4.7%): "nausea"
- 84 patients (4.1%): "diarrhoea"
- 82 patients (4.0%): "rash"

- 65 patients (3.1%): "decreased appetite"
- 52 patients (2.5%): "anaemia"
- 51 patients (2.5%): "weight decreased"
- 50 patients (2.4%): "cough", "dyspnoea"
- 46 patients (2.2%): "dysgeusia"
- 44 patients (2.1%): "pneumonitis"
- 36 patients (1.7%): "oedema peripheral"
- 31 patients (1.5%): "general physical health deterioration"
- 30 patients (1.4%): "pruritus"
- 25 patients (1.2%): "arthralgia"
- 24 patients (1.2%): "aphthous ulcer"
- 20 patients (1.0%): "thrombocytopenia", "abdominal pain upper", "vomiting", "erythema"
- 19 patients (0.9%): "pyrexia", "headache"
- 17 patients (0.8%): "palmar-plantar erythrodysaesthesia"
- 16 patients (0.8%): "leukopenia", "asthenia"
- 15 patients (0.7%): "pneumonia", "pain in extremity", "epistaxis"
- 14 patients (0.7%): "peripheral swelling", "blood creatinine increased", "dyspnoea exertional"
- 13 patients (0.6%): "nasopharyngitis", "urinary tract infection", "diabetes mellitus", "malignant neoplasm progression", "pleural effusion", "dry skin"
- 12 patients (0.6%): "bone pain", "hot flush"
- 11 patients (0.5%): "oedema", "herpes zoster", dizziness"
- 10 patients (0.5%): "mucosal inflammation", "bronchitis", "rash pustular", "haemoglobin decreased", "back pain", "lymphoedema".

Two hundred forty-seven (247, 11.9%) of the patients experienced a total of 348 nsADRs related to Afinitor® of severe intensity. nsADRs related to Afinitor® occurring in at least 10 patients on PT level were (PT-Table 14.3.1-1.3.4.3):

- 67 patients (3.2%): "stomatitis"
- 21 patients (1.0%): "fatigue"
- 10 patients (0.5%): "thrombocytopenia".

10.6.2.2.2 Non-serious adverse drug reactions related to exemestane

A total of 957 (46.1%) of the patients experienced at least one non-serious ADR related to exemestane during the observation period. The highest incidence was seen in patients with nsADRs related to exemestane referring to the MedDRA SOCs:

- "Gastrointestinal disorders" (394 patients, 19.0%), with "stomatitis" (139 patients, 6.7%), "nausea" (123 patients, 5.9%), and "diarrhoea" (101 patients, 4.9%) being the most common nsADRs related to exemestane on PT level;
- "General disorders and administration site conditions" (324 patients, 15.6%), such as "fatigue" (160 patients, 7.7%), "peripheral oedema" (79 patients, 3.8%), and "general physical health deterioration" (21 patients, 1.0%);
- "Skin and subcutaneous tissue disorders" (254 patients, 12.2%), with "rash" (79 patients, 3.8%), "pruritus" (52 patients, 2.5%), and "alopecia" (34 patients, 1.6%);
- "Investigations" (193 patients, 9.3%), such as "weight decreased" (40 patients, 1.9%), "haemoglobin decreased" (23 patients, 1.1%) and "C-reactive protein increased" (21 patients, 1.0%);
- "Musculoskeletal and connective tissue disorders" (193 patients, 9.3%), with "arthralgia" (66 patients, 3.2%), "pain in extremity" (40 patients, 1.9%), and "bone pain" (33 patients, 1.6%).

The tabulation of all patients with nsADRs related to exemestane by primary MedDRA SOC and PT is provided in PT-Table 14.3.1-1.3.3. Table 10-35 summarizes the number of patients with nsADRs related to exemestane occurring in at least 20 patients.

Table 10-35 Number of patients (%) with non-serious ADRs related to exemestane by SOC and by most common PTs (occurring in ≥ 20 patients)

Primary SOC PT (MedDRA)	**Total** **N = 2074** **n (%)**
Subjects with any non-serious adverse drug reactions related to exemestane	**957 (46.1)**
Gastrointestinal disorders	**394 (19.0)**
Stomatitis	139 (6.7)
Nausea	123 (5.9)
Diarrhoea	101 (4.9)
Vomiting	42 (2.0)
Upper abdominal pain	25 (1.2)
Dry mouth	22 (1.1)
Constipation	21 (1.0)
General disorders and administration site conditions	**324 (15.6)**
Fatigue	160 (7.7)
Peripheral oedema	79 (3.8)
General physical health deterioration	21 (1.0)
Pyrexia	20 (1.0)
Skin and subcutaneous tissue disorders	**254 (12.2)**
Rash	79 (3.8)
Pruritus	52 (2.5)
Alopecia	34 (1.6)
Erythema	25 (1.2)
Dry skin	22 (1.1)
Investigations	**193 (9.3)**
Weight decreased	40 (1.9)
Haemoglobin decreased	23 (1.1)
C-reactive protein increased	21 (1.0)
Gamma-glutamyltransferase increased	20 (1.0)
Musculoskeletal and connective tissue disorders	**193 (9.3)**
Arthralgia	66 (3.2)
Pain in extremity	40 (1.9)
Bone pain	33 (1.6)
Back pain	27 (1.3)
Myalgia	20 (1.0)
Respiratory, thoracic and mediastinal disorders	**178 (8.6)**
Cough	65 (3.1)
Dyspnoea	50 (2.4)
Epistaxis	27 (1.3)
Nervous system disorders	**178 (8.6)**
Dysgeusia	55 (2.7)
Headache	51 (2.5)
Dizziness	39 (1.9)

Table 10-35 Number of patients (%) with non-serious ADRs related to exemestane by SOC and by most common PTs (occurring in ≥ 20 patients)

Primary SOC PT (MedDRA)	Total N = 2074 n (%)
Infections and infestations	**123 (5.9)**
Nasopharyngitis	21 (1.0)
Metabolism and nutrition disorders	**118 (5.7)**
Decreased appetite	77 (3.7)
Vascular disorders	**92 (4.4)**
Hot flush	34 (1.6)
Psychiatric disorders	**67 (3.2)**
Sleep disorder	27 (1.3)
Neoplasms benign, malignant and unspecified	**50 (2.4)**
Malignant neoplasm progression	29 (1.4)
Blood and lymphatic system disorders	**49 (2.4)**
Anaemia	22 (1.1)
Eye disorders	**36 (1.7)**
Renal and urinary disorders	**33 (1.6)**
Cardiac disorders	**31 (1.5)**

ADR = adverse drug reaction; MedDRA = Medical dictionary for drug regulatory activities; nsADR = non-serious adverse drug reaction; PT = Preferred term; SOC = System organ class.

Patients with multiple occurrences of an AE are counted only once within the corresponding AE category and SOC, respectively.

Source: PT-Table 14.3.1-1.3.3

Intensity of non-serious ADRs related to exemestane

The intensity of nsADRs related to exemestane for all patients is analyzed in PT-Table 14.3.1-1.3.4.1 (mild events, by patient), PT-Table 14.3.1-1.3.4.2 (moderate events, by patient), and PT-Table 14.3.1-1.3.4.3 (severe events, by patient).

Six hundred and thirty-six (636, 30.7%) of the patients experienced a total of 1813 nsADRs related to exemestane of mild intensity. nsADRs related to exemestane occurring in at least 10 patients on PT level were (PT-Table 14.3.1-1.3.4.1):

- 100 patients (4.8%): “fatigue”
- 93 patients (4.5%): “stomatitis”
- 75 patients (3.6%): “nausea”
- 66 patients (3.2%): “diarrhoea”
- 55 patients (2.7%): “decreased appetite”
- 54 patients (2.6%) “rash”
- 48 patients (2.3%): “oedema peripheral”
- 41 patients (2.0%): “arthralgia”
- 39 patients (1.9%): “dysgeusia”, “headache”, “cough”
- 34 patients (1.6%): “pruritus”

- 30 patients (1.4%): "alopecia"
- 29 patients (1.4%): "vomiting", "dizziness"
- 23 patients (1.1%): "pain in extremity", "dyspnoea", epistaxis"
- 21 patients (1.0%): "weight decreased", "sleep disorder"
- 20 patients (1.0%): "bone pain"
- 18 patients (0.9%): "dry mouth", "hot flush"
- 15 patients (0.7%): "constipation", "back pain", "myalgia", "dry skin"
- 14 patients (0.7%): "nasopharyngitis"
- 13 patients (0.6%): "erythema"
- 12 patients (0.6%): "abdominal pain upper", "dyspnoea exertional", "acne"
- 11 patients (0.5%): "insomnia"
- 10 patients (0.5%): "lacrimation increased", "aphthous ulcer", "aspartate aminotransferase increased".

Four hundred and forty-six (446, 21.5%) of the patients experienced a total of 977 nsADRs related to exemestane of moderate intensity. nsADRs related to exemestane occurring in at least 10 patients on PT level were (PT-Table 14.3.1-1.3.4.2):

- 52 patients (2.5%): "fatigue"
- 45 patients (2.2%): "nausea", "stomatitis"
- 36 patients (1.7%): "diarrhoea"
- 25 patients (1.2%): "rash"
- 24 patients (1.2%): "oedema peripheral", "arthralgia"
- 19 patients (0.9%): "decreased appetite"
- 17 patients (0.8%): "hot flush"
- 16 patients (0.8%): "dysgeusia"
- 15 patients (0.7%): "pain in extremity", "cough"
- 14 patients (0.7%): "weight decreased"
- 12 patients (0.6%): "anaemia", "general physical health deterioration", "bone pain"
- 11 patients (0.5%): "erythema", "pruritus"
- 10 patients (0.5%): "vomiting", "asthenia", "pyrexia", "headache".

Seventy-five (75, 3.6%) of the patients experienced a total of 105 nsADRs related to exemestane of severe intensity. There were no nsADRs related to exemestane which occurred in at least 10 patients (PT-Table 14.3.1-1.3.4.3).

10.6.3 Analysis of serious adverse events not related and serious adverse drug reactions

10.6.3.1 Serious adverse events not related

A total of 660 (31.8%) of the patients experienced at least one SAEnr during the observation period. The highest incidence was seen in SAEsnr referring to the MedDRA SOCs:

- "Neoplasms benign, malignant and unspecified (incl. cysts and polyps)" (340 patients, 16.4%), with "malignant neoplasm progression[1]" (227 patients, 10.9%), "breast cancer metastatic" (76 patients, 3.7%), and "metastases to liver" (44 patients, 2.1%) being the most common SAEsnr on PT level;

- "General disorders and administration site conditions" (173 patients, 8.3%), such as "general physical health deterioration" (89 patients, 4.3%), "death" (31 patients, 1.5%), and "pyrexia" (16 patients, 0.8%);

- "Respiratory, thoracic and mediastinal disorders" (126 patients, 6.1%), such as "pleural effusion" (60 patients, 2.9%), "dyspnoea" (42 patients, 2.0%), and "pulmonary embolism" (15 patients, 0.7%);

- "Infections and infestations" (90 patients, 4.3%), such as "pneumonia" (23 patients, 1.1%);

- "Gastrointestinal disorders" (80 patients, 3.9%), such as "ascites" (27 patients, 1.3%).

Table 10-36 summarizes the number of patients with SAEsnr occurring in at least 10 patients.

[1] Please note that as per study protocol tumor progression was only required to be reported as adverse event in case it was serious and/or causally related to Afinitor®.

Table 10-36 Number of patients (%) with SAEsnr by SOC and by most common PTs (occurring in ≥ 10 patients)

Primary SOC PT (MedDRA)	**Total** **N = 2074** **n (%)**
Subjects with any SAEnr	**660 (31.8)**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**340 (16.4)**
Malignant neoplasm progression	227 (10.9)
Breast cancer metastatic	76 (3.7)
Metastases to liver	44 (2.1)
Metastases to bone	17 (0.8)
Metastases to central nervous system	17 (0.8)
Breast cancer	15 (0.7)
Metastases to pleura	13 (0.6)
Metastases to lung	11 (0.5)
General disorders and administration site conditions	**173 (8.3)**
General physical health deterioration	89 (4.3)
Death	31 (1.5)
Pyrexia	16 (0.8)
Multiple organ dysfunction syndrome	14 (0.7)
Pain	12 (0.6)
Respiratory, thoracic and mediastinal disorders	**126 (6.1%)**
Pleural effusion	60 (2.9)
Dyspnoea	42 (2.0)
Pulmonary embolism	15 (0.7)
Respiratory failure	12 (0.6)
Infections and infestations	**90 (4.3)**
Pneumonia	23 (1.1)
Gastrointestinal disorders	**80 (3.9)**
Ascites	27 (1.3)
Nausea	13 (0.6)
Vomiting	13 (0.6)
Musculoskeletal and connective tissue disorders	**57 (2.7)**
Osteonecrosis of jaw	13 (0.6)
Cardiac disorders	**49 (2.4)**
Cardiac failure	20 (1.0)
Nervous system disorders	**46 (2.2)**
Injury, poisoning and procedural complications	**42 (2.0)**
Fall	10 (0.5)
Renal and urinary disorders	**39 (1.9)**
Renal failure	16 (0.8)

Table 10-36 Number of patients (%) with SAEsnr by SOC and by most common PTs (occurring in ≥ 10 patients)

Primary SOC PT (MedDRA)	**Total** **N = 2074** **n (%)**
Hepatobiliary disorders	**32 (1.5)**
Hepatic failure	15 (0.7)
Vascular disorders	**32 (1.5)**
Investigations	**31 (1.5)**
Metabolism and nutrition disorders	**28 (1.4)**
Blood and lymphatic system disorders	**24 (1.2)**
Anaemia	15 (0.7)
Psychiatric disorders	**13 (0.6)**
Skin and subcutaneous tissue disorders	**11 (0.5)**

MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term; SOC = System organ class.

Patients with multiple occurrences of an AE are counted only once within the corresponding AE category and SOC, respectively.

Source: PT-Table 14.3.1-1.3.6

Intensity of SAEsnr

The intensity of SAEsnr for all patients is analyzed in PT-Tables 14.3.1-1.3.4.1 (mild events, by patient), PT-Table 14.3.1-1.3.4.2 (moderate events, by patient), and PT-Table 14.3.1-1.3.4.3 (severe events, by patient), PT-Table 14.3.1-1.3.4.4 (life-threatening events, by patient).

Thirty (30, 1.4%) of the patients experienced a total of 39 SAEsnr of mild intensity. None of the SAEsnr occurred in more than 2 patients (PT-Table 14.3.1-1.3.4.1).

One hundred and eighty-nine (189, 9.1%) of the patients experienced a total of 326 SAEsnr of moderate intensity. Moderate SAEsnr occurring in more than 1 patient on PT level were (PT-Table 14.3.1-3.2.2.2):

- 22 patients (1.1%): “pleural effusion”
- 11 patients (0.5%): “general physical health deterioration”
- 9 patients (0.4%): “malignant neoplasm progression”, “dyspnoea”
- 8 patients (0.4%): “pyrexia”, “osteonecrosis of jaw”
- 6 patients (0.3%): “anaemia”, “cardiac failure”, “pain”, “pneumonia”
- 5 patients (0.2%): “metastases to liver”, “dyspnoea exertional”
- 4 patients (0.2%): “ascites”
- 3 patients (0.1%): “diarrhoea”, “erysipelas”, “urinary tract infection”, “hyponatraemia”, “cough”

- 2 patients (<0.1%): "coronary artery disease", "left ventricular dysfunction", "pericardial effusion", "gastritis erosive", "nausea", "vomiting", "asthenia", "impaired healing", "cholecystitis", "cholelithiasis", "urosepsis", "fall", "hypokalaemia", "arthralgia", "flank pain", "musculoskeletal chest pain", "spinal pain", "metastases to meninges", "metastases to pleura", "metastases to spine", "dizziness", "syncope", "renal failure", "urinary retention", "respiratory distress", "hypertensive crisis", "thrombosis".

Two hundred and eighty-two (282, 13.6%) of the patients experienced a total of 620 SAEsnr of severe intensity. Severe SAEsnr occurring in more than 1 patient on PT level were (PT-Table 14.3.1-1.3.4.3):

- 51 patients (2.5%): "malignant neoplasm progression"
- 32 patients (1.5%): "general physical health deterioration"
- 28 patients (1.4%): "pleural effusion"
- 25 patients (1.2%): "dyspnoea"
- 14 patients (0.7%): "metastases to liver"
- 13 patients (0.6%): "ascites"
- 9 patients (0.4%): "nausea", "vomiting", "pneumonia", "breast cancer metastatic", "metastases to central nervous system"
- 8 patients (0.4%): "anaemia"
- 6 patients (0.3%): "cardiac failure", "osteonecrosis of jaw", "pain in extremity", malignant pleural effusion", "metastases to bone", "metastases to pleura"
- 5 patients (0.2%): "device related infection", "fall", "femur fracture", "dehydration"
- 4 patients (0.2%): "abdominal pain", "pyrexia", "erysipelas", "back pain", "acute kidney injury", "renal failure", "dyspnoea exertional", "pulmonary embolism"
- 3 patients (0.1%): "abdominal pain upper", "concomitant disease aggravated", "oedema peripheral", "pain", "bile duct stenosis", "jaundice", "urinary tract infection", "femoral neck fracture", "decreased appetite", "bone pain", "pathological fracture", "metastases to meninges", "metastases to peritoneum", "metastases to stomach", "hydronephrosis", "respiratory failure"
- 2 patients (<0.1%): "pancytopenia", "atrial fibrillation", "diplobia", "constipation", "duodenitis", "gastric haemorrhage", "gastrointestinal haemorrhage", "gastrooesophageal reflux

disease", "ileus", "subileus", "upper gastrointestinal haemorrhage", "varices oesophageal", "asthenia", "concomitant disease progression", "fatigue", "multiple organ dysfunction syndrome", "hepatic failure", "diverticulitis", "Escherichia urinary tract infection", "infection", "pyelonephritis", "upper respiratory tract infection", "lumbar vertebral fracture", "toxicity to various agents", "C-reactive protein increased", "gamma-glutamyltransferase increased", "haemoglobin decreased", "cachexia", "arthralgia", "intervertebral disc protrusion", "muscular weakness", "musculoskeletal chest pain", "osteitis", "lymphangiosis carcinomatosa", "malignant neoplasm of pleura", "metastases to lung", "metastases to lymph nodes", "dizziness", "epilepsy", "headache", "partial seizures", "somnolence", "transient ischaemic attack", "urinary tract obstruction", "pneumothorax", "respiratory distress", "hypertensive crisis".

Three hundred and forty-five (345, 16.6%) of the patients experienced a total of 620 life-threatening SAEsnr. Such events occurring in more than 1 patient on PT level were (PT-Table 14.3.1-1.3.4.4):

- 158 patients (7.6%): "malignant neoplasm progression"
- 65 patients (3.1%): "breast cancer metastatic"
- 41 patients (2.0%): "general physical health deterioration"
- 29 patients (1.4%): "death"
- 24 patients (1.2%): "metastases to liver"
- 13 patients (0.6%): "hepatic failure"
- 12 patients (0.6%): "breast cancer"
- 10 patients (0.5%): "multiple organ dysfunction syndrome", "renal failure", "dyspnoea"
- 9 patients (0.4%): "ascites"
- 8 patients (0.4%): "cardiac failure", "pulmonary embolism", "respiratory failure"
- 7 patients (0.3%): "metastases to bone", "metastases to central nervous system", "metastases to lung", "pleural effusion"
- 6 patients (0.3%): "pneumonia"
- 4 patients (0.2%): "myocardial infarction", "pain", "sepsis", "Eastern Cooperative Oncology Group Performance Status worsened", metastases to lymph nodes", "metastases to pleura", "acute kidney injury"

- 3 patients (0.1%): "cardiac arrest", "lymphangiosis carcinomatosa", "seizure", "circulatory collapse"
- 2 patients (<0.1%): "pancytopenia", "cardiopulmonary failure", "nausea", "vomiting", "asthenia", "concomitant disease progression", "disease progression", "inflammation", "pyrexia", "acute hepatic failure", "hepatorenal syndrome", "blood creatinine increased", "cachexia", "hypercalcaemia", "metastases to adrenals, "metastases to bone marrow", "metastases to meninges", "metastases to peritoneum", "second primary malignancy", "syncope", "completed suicide", "suicide attempt", "cough".

A detailed listing of all patients with unrelated AEs is provided in PT-Table 14.3.1-1.3.6.

10.6.3.2 Serious adverse drug reactions

10.6.3.2.1 Serious adverse drug reactions related to Afinitor®

A total of 443 patients (21.4%) of the patients experienced at least one SADR related to Afinitor® during the observation period. The highest incidence was seen in ADRs related to Afinitor® referring to the MedDRA SOCs:

- "Respiratory, thoracic and mediastinal disorders" (132 patients, 6.4%), with "dyspnoea" (52 patients, 2.5%). "pneumonitis" (38 patients, 1.8%), and "pleural effusion" (29 patients, 1.4%) being the most common AEs on PT level;

- "General disorders and administration site conditions" (114 patients, 5.5%), such as "general physical health deterioration" (48 patients, 2.3%), "pyrexia" (27 patients, 1.3%) and "fatigue" (13 patients, 0.6%);

- "Infections and infestations" (106 patients, 5.1%), with "pneumonia" (48 patients, 2.3%), "atypical pneumonia" (6 patients, 0.3%), and "urinary tract infection" (5 patients, 0.2%);

- "Gastrointestinal disorders" (93 patients, 4:5%), such as "nausea" (25 patients, 1.2%), "diarrhoea" (24 patients, 1.2%), and "vomiting" (23 patients, 1.1%).

The tabulation of the patients with all SADRs related to Afinitor® by MedDRA primary PSOC and PT is provided in PT-Table 14.3.1-1.3.2. Table 10-37 summarizes the number of patients with SADRs related to Afinitor® occurring in at least 10 patients.

In 11 patients the term "death" was reported as adverse event, although "death" should rather be reported as outcome of an event or result of disease progression. In all of the reported cases the cause of death was unknown to the reporter; in 10 cases the causal relationship to Afinitor® was reported as not assessable and in 1 case it was not reported (data on file). For the evaluation, all cases were conservatively considered as SADR.

Table 10-37 Number of patients (%) with SADRs related to Afinitor® (occurring in ≥ 10 patients) by SOC and by most common PTs

Primary SOC PT (MedDRA)	**Total N =2074 n (%)**
Subjects with any SADR related to Afinitor®	**443 (21.4)**
Respiratory, thoracic and mediastinal disorders	**132 (6.4)**
Dyspnoea	52 (2.5)
Pneumonitis	38 (1.8)
Pleural effusion	29 (1.4)
Cough	14 (0.7)
Exertional dyspnoea	11 (0.5)
General disorders and administration site conditions	**114 (5.5)**
General physical health deterioration	48 (2.3)
Pyrexia	27 (1.3)
Fatigue	13 (0.6)
Death	11 (0.5)
Infections and infestations	**106 (5.1)**
Pneumonia	48 (2.3)
Gastrointestinal disorders	**93 (4.5)**
Nausea	25 (1.2)
Diarrhoea	24 (1.2)
Vomiting	23 (1.1)
Stomatitis	15 (0.7)
Investigations	**51 (2.5)**
Weight decreased	11 (0.5)
Blood and lymphatic system disorders	**45 (2.2)**
Anaemia	26 (1.3)
Thrombocytopenia	15 (0.7)
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)	**38 (1.8)**
Malignant neoplasm progression	23 (1.1)
Renal and urinary disorders	**28 (1.4)**
Acute kidney injury	13 (0.6)
Metabolism and nutrition disorders	**26 (1.3)**
Vascular disorders	**19 (0.9)**
Skin and subcutaneous tissue disorders	**18 (0.9)**
Cardiac disorders	**18 (0.9)**
Nervous system disorders	**15 (0.7)**
Musculoskeletal and connective tissue disorders	**14 (0.7)**
Hepatobiliary disorders	**14 (0.7)**

MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term; SOC = System organ class.

Patients with multiple occurrences of an AE are counted only once within the corresponding AE category and SOC, respectively.

Source: PT-Table 14.3.1-1.3.2

Intensity of SADRs related to Afinitor®

The intensity of SADRs related to Afinitor® for all patients is analyzed in PT-Tables 14.3.1-1.3.4.1 (mild events, by patient), PT-Table 14.3.1-1.3.4.2 (moderate events, by patient), PT-Table 14.3.1-1.3.4.3 (severe events, by patient), and PT-Table 14.3.1-1.3.4.4 (life-threatening events, by patient).

Twenty-one (21, 1.0%) of the patients experienced a total of 34 SADRs related to Afinitor® of mild intensity. Mild SADRs related to Afinitor® occurring in more than 1 patient on PT level were (PT-Table 14.3.1-1.3.4.1):

- 3 patients (0.1%): "general physical health deterioration"
- 2 patients (<0.1%): "stomatitis", "pyrexia", "dyspnoea", "dyspnoea exertional"

One hundred and eighty-five (185, 8.9%) of the patients experienced a total of 319 SADRs related to Afinitor® of moderate intensity. Moderate SADRs related to Afinitor® occurring in more than 1 patient on PT level were (PT-Table 14.3.1-1.3.4.2):

- 16 patients (0.8%): "general physical health deterioration", "dyspnoea"
- 15 patients (0.7%): "anaemia"
- 14 patients (0.7%): "pneumonitis"
- 12 patients (0.6%): "diarrhoea", "vomiting"
- 11 patients (0.5%): "pyrexia", "pneumonia", "pleural effusion"
- 10 patients (0.5%): "nausea"
- 5 patients (0.2%): "atypical pneumonia", "weight decreased", "cough", "dyspnoea exertional"
- 4 patients (0.2%): "renal failure"
- 3 patients (0.1%): "ascites", "oedema peripheral", "peripheral swelling", "metastases to liver", "acute kidney injury", "interstitial lung disease"
- 2 patients (<0.1%): "thrombocytopenia", "cardiac failure", "ileus", "fatigue", cholestasis", "abscess", "bronchitis", "pneumonia Klebsiella", "toxicity to various agents", "blood creatinine increased", "transaminases increased", "dehydration", "hyperglycaemia", "arthralgia", "malignant neoplasm progression", "malignant pleural effusion", "alveolitis", "epistaxis", "pulmonary embolism", "rash pruritic", "skin ulcer".

Two hundred and fifty (250, 12.1%) of the patients experienced a total of 471 SADRs related to Afinitor® of severe intensity. Severe SADRs related to Afinitor® occurring in more than 1 patient on PT level were (PT-Table 14.3.1-1.3.4.3):

- 31 patients (1.5%): "pneumonia"
- 27 patients (1.3%): "general physical health deterioration"

- 24 patients (1.2%): "dyspnoea"
- 17 patients (0.8%): "nausea", "pneumonitis"
- 14 patients (0.7%): "pleural effusion"
- 12 patients (0.6%): "vomiting", "pyrexia"
- 11 patients (0.5%): "diarrhoea", "stomatitis"
- 10 patients (0.5%): "anaemia", "malignant neoplasm progression"
- 8 patients (0.4%): "asthenia", "fatigue", "acute kidney injury"
- 7 patients (0.3%): "chest pain"
- 6 patients (0.3%): "cough"
- 4 patients (0.2%): "cardiac failure", "blood creatinine increased", "weight decreased", "metastases to liver", "angioedema"
- 3 patients (0.1%): "swollen tongue", "mucosal inflammation", "urinary tract infection", "blood glucose increased", "haemoglobin decreased", "dehydration", "hyperglycaemia", "cerebrovascular accident", "renal failure", interstitial lung disease"
- 2 patients (<0.1%): "leukopenia", "pancytopenia", "vertigo", "abdominal pain", "aphthous ulcer", "ascites", "subileus", "oedema peripheral", "hepatotoxicity", "bronchitis", "infection", "oral candidiasis", "pneumocystis Jirovecii pneumonia", "sepsis", "liver function test abnormal", "decreased appetite", "diabetes mellitus", "type 2 diabetes mellitus", "bone pain", "pulmonary embolism", "pulmonary oedema", "respiratory distress", "pruritus", rash pruritic", "deep vein thrombosis", "hypertensive crisis", "thrombosis".

Forty-seven (47, 2.3%) of the patients experienced a total of 82 life-threatening SADRs related to Afinitor®. Those SADRs related to Afinitor® occurring in more than 1 patient on PT level were (PT-Table 14.3.1-1.3.4.4):

- 10 patients (0.5%): "death"
- 7 patients (0.3%): "malignant neoplasm progression"
- 5 patients (0.2%): "pneumonitis"
- 4 patients (0.2%): "pneumonia", "dyspnoea"
- 3 patients (0.1%): "hepatic failure"
- 2 patients (<0.1%): "general physical health deterioration", multiple organ dysfunction syndrome", "acute kidney injury", "renal failure", "respiratory failure".

10.6.3.2.2 Serious adverse drug reactions related to exemestane

A total of 246 patients (11.9%) of the patients experienced at least one SADR related to exemestane during the observation period. The highest incidence was seen in SADRs related to exemestane referring to the MedDRA SOCs (PT-Table 14.3.1-1.3.3):

- "General disorders and administration site conditions" (65 patients, 3.1%), such as "general physical health deterioration" (20 patients, 1.0%), "death" (17 patients, 0.8%) and "pyrexia" (7 patients, 0.3%);
- "Respiratory, thoracic and mediastinal disorders" (56 patients, 2.7%), with "dyspnoea" (26 patients, 1.3%). "pleural effusion" (13 patients, 0.6%), and "pneumonitis" (6 patients, 0.3%) being the most common AEs on PT level;
- "Neoplasms benign, malignant and unspecified" (52 patients, 2.5%), such as "malignant neoplasm progression (29 patients, 1.4%), "metastases to liver" (6 patients, 0.3%), "breast cancer metastatic" (5 patients, 0.2%), and "metastases to bone" (5 patients, 0.2%);
- "Infections and infestations" (36 patients, 1.7%), with "pneumonia" (18 patients, 0.9%);
- "Gastrointestinal disorders" (34 patients, 1.6%), such as "vomiting" (12 patients, 0.6%) and "nausea" (10 patients 0.5%);
- "Investigations" (31 patients, 1.5%), such as "weight decreased" (7 patients, 0.3%) and "C-reactive protein increased" (5 patients, 0.2%);
- "Blood and lymphatic system disorder" (22 patients, 1.1%), with "anaemia" (13 patients, 0.6%) and "thrombocytopenia" (8 patients, 0.4%).

The tabulation of the patients with all SADRs related to exemestane by MedDRA primary PSOC and PT is provided in PT-Table 14.3.1-1.3.3. Table 10-38 summarizes the number of patients with SADRs related to exemestane occurring in at least 10 patients.

In 17 patients death was reported as SADR related to exemestane, although "death" itself is not defined as AE or ADR, but should be reported as outcome of an event or result of disease progression.

Table 10-38 Number of patients (%) with SADRs related to exemestane (occurring in ≥ 10 patients) by SOC and by most common PTs

Primary SOC PT (MedDRA)	Total N = 2074 n (%)
Subjects with any SADR related to exemestane	**246 (11.9)**
General disorders and administration site conditions	**65 (3.1)**
General physical health deterioration	20 (1.0)
Death	17 (0.8)
Respiratory, thoracic and mediastinal disorders	**56 (2.7)**
Dyspnoea	26 (1.3)
Pleural effusion	13 (0.6)
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)	**52 (2.5)**
Malignant neoplasm progression	29 (1.4)
Infections and infestations	**36 (1.7)**
Pneumonia	18 (0.9)
Gastrointestinal disorders	**34 (1.6)**
Vomiting	12 (0.6)
Nausea	10 (0.5)
Investigations	**31 (1.5)**
Blood and lymphatic system disorders	**22 (1.1)**
Anaemia	13 (0.6)
Vascular disorders	**16 (0.8)**
Metabolism and nutrition disorders	**14 (0.7)**
Renal and urinary disorders	**14 (0.7)**
Hepatobiliary disorders	**14 (0.7)**
Cardiac disorders	**12 (0.6)**

MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term; SOC = System organ class.
Patients with multiple occurrences of an AE are counted only once within the corresponding AE category and SOC, respectively.
Source: PT-Table 14.3.1-1.3.3

Intensity of SADRs related to exemestane

The intensity of SADRs related to exemestane for all patients is analyzed in PT-Tables 14.3.1-1.3.4.1 (mild events, by patient), PT-Table 14.3.1-1.3.4.2 (moderate events, by patient), and PT-Table 14.3.1-1.3.4.3 (severe events, by patient), PT-Table 14.3.1-1.3.4.3 (life-threatening events, by patient).

Eleven (11, 0.5%) of the patients experienced a total of 15 SADRs related to exemestane of mild intensity. The only mild SADRs related to exemestane occurring in more than 1 patient on PT level was “stomatitis” in 2 patients (<0.1%) (PT-Table 14.3.1-1.3.4.1).

Seventy-nine (79, 3.8%) of the patients experienced a total of 142 SADRs related to exemestane of moderate intensity. Moderate SADRs related to exemestane occurring in more than 1 patient on PT level were (PT-Table 14.3.1-1.3.4.2):

- 8 patients (0.4%): "anaemia"
- 7 patients (0.3%): "general physical health deterioration", "dyspnoea"
- 6 patients (0.3%); "vomiting", "pleural effusion"
- 5 patients (0.2%): "nausea"
- 4 patients (0.2%): "pneumonia"
- 3 patients (0.1%): "ascites", "pyrexia", weight decreased"
- 2 patients (<0.1%): "thrombocytopenia", "ileus", "oedema peripheral", "metastases to liver", "cough", "dyspnoea exertional", "pneumonitis".

Ninety-eight (98, 4.7%) of the patients experienced a total of 184 SADRs related to exemestane of severe intensity. Severe SADRs related to exemestane occurring in more than 1 patient on PT level were (PT-Table 14.3.1-1.3.4.3):

- 12 patients (0.6%): "general physical health deterioration"
- 10 patients (0.5%): "dyspnoea"
- 9 patients (0.4%): "malignant neoplasm progression"
- 7 patients (0.3%): "pneumonia"
- 5 patients (0.2%): "nausea", "vomiting", "asthenia", "fatigue"
- 4 patients (0.2%): "pleural effusion"
- 3 patients (0.1%): "thrombocytopenia", "chest pain", "pyrexia", "metastases to liver"
- 2 patients (<0.1%): "anaemia", "cardiac failure", "vertigo", "subileus", "liver function test abnormal", "weight decreased", "dehydration", "cerebrovascular accident", "acute kidney injury", "pneumonitis", "pulmonary embolism", "angioedema", "hypertensive crisis".

Thirty-nine (39, 1.9%) of the patients experienced a total of 60 life-threatening SADRs related to exemestane. Such event occurring in more than 1 patient on PT level were (PT-Table 14.3.1-1.3.4.4):

- 13 patients (0.6%): "death"
- 10 patients (0.5%): "malignant neoplasm progression"
- 4 patients (0.2%): "pneumonia"
- 3 patients (0.1%): "hepatic failure", "acute kidney injury"
- 2 patients (<0.1%): "cardiac failure", "multiple organ dysfunction syndrome", "breast cancer", "breast cancer metastatic", "pneumonitis".

10.6.4 Analysis of adverse events of special interest

During the observation period, 767 of the patients (37.0%) experienced a total of 1235 AESIs indicative of risks described in the Afinitor® Risk Management Plan. AESIs based on all patients are provided in PT-Table 14.3.1-1.7.1 by risk class, PT and by patient, and in PT-Table 14.3.1-1.7.2 by event. Furthermore PT-Table 14.3.1-1.7.1 shows the number of AESIs related to Afinitor®.

AESIs for the following risks were observed (by patient, the three most frequent PTs):

- "Hypersensitivity reactions/anaphylactic reactions" (468 patients, 22.6% of patients)[2], "rash" (235 patients, 11.3%), "pruritus" (129 patients, 6.2%), and "erythema" (63 patients, 3.0%);
- "Congestive heart failure" (221 patients, 10.7%)[3] with "oedema peripheral" (186 patients, 9.0%), "cardiac failure" (35 patients, 1.7%), and "pulmonary oedema" (8 patients, 0.4%);
- "Non-infectious pneumonitis" (147 patients, 7.1%) with "pneumonitis" (113 patients, 5.4%), "lung infiltration" (13 patients, 0.6%), and "alveolitis" (12 patients, 0.6%);
- "Increased creatinine/renal failure/proteinuria and patients with renal impairment" (102 patients, 4.9%) with "blood creatinine increased" (56 patients, 2.7%), "renal failure" (34 patients, 1.6%), and "glomerular filtration rate decreased" (9 patients, 0.4%);
- "Severe infections" (5 patients, 0.2%), with "pneumocystis Jirovecii pneumonia" (3 patients, 0.1%), "infection reactivation" (1 patient, <0.1%), and "herpes simplex" (1 patient, <0.1%).

A summary of AESIs occurring in at least 10 patients in total in the patients is provided in Table 10-39.

[2] Please note that this analysis was based on the frequency of patients with events that were defined as indicative for possible hypersensitivity reactions/anaphylactic reactions including events such as stomatitis, rash and pruritus; the analysis did not take into account whether a hypersensitivity reaction/anaphylactic reaction was confirmed.

[3] Please note that this analysis included patients with events that were defined as indicative for possible congestive heart failure such as oedema or peripheral oedema; the analysis did not take into account whether in these cases the presence of congestive heart failure was confirmed.

Table 10-39 Number of patients (%) with AESIs by risk class and by most common PTs (occurring in ≥ 10 patients in total)

Risk class PT (MedDRA)	Total N = 2074 n (%)		
	Non-serious	**Serious**	**Any**
Subjects with any RMP event	**678 (32.7)**	**163 (7.9)**	**767 (37.0)**
Number of events	**1026 (100.0)**	**209 (100.0)**	**1235 (100.0)**
Hypersensitivity/anaphylactic reactions	**451 (21.7)**	**26 (1.3)**	**468 (22.6)**
Rash	233 (11.2)	3 (0.1)	235 (11.3)
Pruritus	126 (6.1)	4 (0.7)	129 (6.2)
Erythema	60 (2.9)	3 (0.1)	63 (3.0)
Swelling face	17 (0.8)	1 (<0.1)	18 (0.9)
Eyelid oedema	15 (0.7)	-	15 (0.7)
Eye swelling	10 (0.5)	-	10 (0.5)
Congestive heart failure	**188 (9.1)**	**49 (2.4)**	**221 (10.7)**
Oedema peripheral	176 (8.5)	12 (0.6)	186 (9.0)
Cardiac failure	5 (0.2)	31 (1.5)	35 (1.7)
Non infectious pneumonitis	**97 (4.7)**	**54 (2.6)**	**147 (7.1)**
Pneumonitis	75 (3.6)	39 (1.9)	113 (5.4)
Lung infiltration	10 (0.5)	3 (0.1)	13 (0.6)
Alveolitis	10 (0.5)	3 (0.1)	12 (0.6)
Interstitial lung disease	5 (0.2)	7 (0.3)	12 (0.6)
Increased creatinine/renal failure/proteinuria and patients with renal impairment	**67 (3.2)**	**46 (2.2)**	**102 (4.9)**
Blood creatinine increased	47 (2.3)	11 (0.5)	56 (2.7)
Renal failure	8 (0.4)	26 (1.3)	34 (1.6)

MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term

Patients with multiple occurrences of an AE are counted only once within the corresponding AE category and risk class, respectively.

Source: PT-Tables 14.3.1-1.7.1 and 14.3.1-1.7.2

10.6.5 Adverse events leading to discontinuation

A total of 797 patients experienced at least one AE during the observation period leading to discontinuation of the study drug (PT-Table 14.3.1-1.8.1). Of these 797 patients, the highest incidence was seen in AEs referring to the MedDRA SOCs:

- "Neoplasms benign, malignant and unspecified (incl. cysts and polyps)" (215 patients, 27.0%), with mainly "malignant neoplasm progression" (147 patients, 18.4%) on PT level;

- "Gastrointestinal disorders" (210 patients, 26.3%), with "stomatitis" (90 patients, 11.3%). "nausea" (45 patients, 5.6%), "vomiting" (22 patients, 2.8%), and "diarrhoea" (21, 2.6%) being the most common AEs on PT level;

- "General disorders and administration site conditions" (176 patients, 22.1%), such as "general physical health deterioration" (70, 8.8%), "fatigue" (39, 4.9%) and "asthenia" (16 patients, 2.0%);

- "Respiratory, thoracic and mediastinal disorders" (172, 21.6%), with "dyspnoea" (54, 6.8%), "pneumonitis" (47, 5.9%), "pleural effusion" (38, 4.8%), and "cough" (26, 3.3%) on PT level.

A summary of AEs leading to discontinuation occurring in at least 10 patients on PT level is provided in Table 10-40.

Table 10-40 Number of patients (%) with AEs leading to discontinuation by SOC and by most common PTs (occurring in ≥ 10 patients)

Primary SOC PT (MedDRA)	**Total** **N = 2074** **n (%)**
Subjects with any AE leading to discontinuation	**797 (100.0)**
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)	**215 (27.0)**
Malignant neoplasm progression	147 (18.4)
Metastases to liver	32 (4.0)
Breast cancer metastatic	25 (3.1)
Metastases to lung	16 (2.0)
Metastases to bone	14 (1.8)
Metastases to central nervous system	10 (1.3)
Gastrointestinal disorders	**210 (26.3)**
Stomatitis	90 (11.3)
Nausea	45 (5.6)
Vomiting	22 (2.8)
Diarrhoea	21 (2.6)
Ascites	16 (2.0)
General disorders and administration site conditions	**176 (22.1)**
General physical health deterioration	70 (8.8)
Fatigue	39 (4.9)
Asthenia	16 (2.0)
Pyrexia	14 (1.8)
Disease progression	10 (1.3)
Oedema peripheral	10 (1.3)
Respiratory, thoracic and mediastinal disorders	**172 (21.6)**
Dyspnoea	54 (6.8)
Pneumonitis	47 (5.9)
Pleural effusion	38 (4.8)
Cough	26 (3.3)
Respiratory failure	10 (1.3)
Infections and infestations	**79 (9.9)**
Pneumonia	29 (3.6)

Table 10-40 Number of patients (%) with AEs leading to discontinuation by SOC and by most common PTs (occurring in ≥ 10 patients)

Primary SOC PT (MedDRA)	Total N = 2074 n (%)
Investigations	**73 (9.2)**
Weight decreased	15 (1.9)
Blood creatinine increased	11 (1.4)
Skin and subcutaneous tissue disorders	**65 (8.2)**
Rash	24 (3.0)
Nervous system disorders	**47 (5.9)**
Metabolism and nutrition disorders	**41 (5.1)**
Decreased appetite	20 (2.5)
Musculoskeletal and connective tissue disorders	**41 (5.1)**
Renal and urinary disorders	**29 (3.6)**
Acute kidney injury	12 (1.5)
Renal failure	12 (1.5)
Cardiac disorders	**27 (3.4)**
Cardiac failure	12 (1.5)
Hepatobiliary disorders	**23 (2.9)**
Hepatic failure	10 (1.3)
Blood and lymphatic system disorders	**21 (2.6)**
Anaemia	11 (1.4)
Vascular disorders	**17 (2.1)**
Injury, poisoning and procedural complications	**13 (1.6)**
Psychiatric disorders	**11 (1.4)**

AE = adverse event; MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term; SOC = System organ class.
Patients with multiple occurrences of an AE are counted only once within the corresponding AE category and SOC, respectively.
Source: PT-Table 14.3.1-1.8.1

The median time to discontinuation was 3.0 months with a 95% CI of [2.8; 3.4] when it was due to AEs (PT-Table14.3.1-1.8.2.1). When discontinuation was due to disease progression, the median time to discontinuation was 5.9 months with a 95% CI of [5.4; 6.5] (PT-Table 14.3.1-1.8.2.2). A summary is provided in Table 10-41.

Table 10-41 Time to discontinuation due to AEs/disease progression

		Time to discontinuation due to	
Variable		**AEs N=795 n (%)**	**PD N=1165 n (%)**
Number of events		795 (99.7)	1160 (99.6)
Patients censored		2 (0.3)	5 (0.4)
Patients with event (Kaplan-Meier estimates, %) at	Month 1	16.2	2.0
	Month 2	31.7	8.3
	Month 3	49.4	20.0
	Month 6	73.2	50.7
	Month 9	82.4	65.7
	Month 12	90.2	76.7
	Month 18	95.0	88.9
	Month 21	96.2	92.4
	Month 24	97.1	95.0
	Month 27	97.5	96.5
	Month 30	97.9	97.7
	Month 33	98.5	98.8
	Month 36	98.9	99.1
Time to event (months, with 95% CI)	1st quartile	1.6 [1.3; 1.8]	3.3 [3.1; 3.4]
	Median	3.0 [2.8; 3.4]	5.9 [5.4; 6.5]
	3rd quartile	6.6 [5.7; 7.4]	11.5 [10.8; 12.3]

Source: PT-Tables 14.3.1-1.8.2.1 and 14.3.1-1.8.2.2

10.6.6 Adverse events leading to death

AEsnr leading to death

A total of 446 (21.5%) of the patients experienced AEsnr leading to death. Table 10-42 summarizes these AEsnr by primary SOC and PT (PT-Table 14.3.1-1.9.1).

Table 10-42 Number of patients (%) with AEsnr leading to death by SOC and by most common PTs (occurring in ≥ 10 patients)

Primary SOC PT (MedDRA)	**Total** **N = 2074** **n (%)**
Subjects with any AEnr leading to death	**446 (21.5)**
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)	**305 (14.7)**
Malignant neoplasm progression	214 (10.3)
Breast cancer metastatic	78 (3.8)
Metastases to liver	33 (1.6)
Breast cancer	17 (0.8)
Metastases to central nervous system	14 (0.7)
Metastases to lung	13 (0.6)
Metastases to bone	11 (0.5)
General disorders and administration site conditions	**144 (6.9)**
General physical health deterioration	63 (3.0)
Death	49 (2.4)
Multiple organ dysfunction syndrome	22 (1.1)
Respiratory, thoracic and mediastinal disorders	**59 (2.8)**
Dyspnoea	22 (1.1)
Respiratory failure	14 (0.7)
Pleural effusion	13 (0.6)
Pulmonary embolism	11 (0.5)
Gastrointestinal disorders	**36 (1.7)**
Ascites	13 (0.6)
Hepatobiliary disorders	**35 (1.7)**
Hepatic failure	23 (1.1)
Cardiac disorders	**29 (1.4)**
Cardiac failure	10 (0.5)
Investigations	**29 (1.4)**
Infections and infestations	**23 (1.1)**
Pneumonia	12 (0.6)
Renal and urinary disorders	**23 (1.1)**
Renal failure	12 (0.6)
Nervous system disorders	**17 (0.8)**
Vascular disorders	**12 (0.6)**

AE = adverse event; MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term; SOC = System organ class.

Patients with multiple occurrences of an AE are counted only once within the corresponding AE category and SOC, respectively.

Source: PT-Table 14.3.1-1.9.1

ADRs leading to death

A total of 72 (3.5%) of the patients experienced ADRs related to Afinitor® leading to death. Table 10-43 summarizes these ADRs by primary SOC and PT (PT-Table 14.3.1-1.9.1).

Table 10-43 Number of patients (%) with ADRs related to Afinitor® leading to death by SOC and by most common PTs (occurring in ≥ 10 patients)

Primary SOC PT (MedDRA)	**Total** **N = 2074** **n (%)**
Subjects with any ADR related to Afinitor® leading to death	**72 (3.5)**
General disorders and administration site conditions	**31 (1.5)**
Death	11 (0.5)
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)	**20 (1.0)**
Malignant neoplasm progression	12 (0.6)
Respiratory, thoracic and mediastinal disorders	**13 (0.6)**
Gastrointestinal disorders	**10 (0.5)**
Infections and infestations	**10 (0.5)**

ADR = adverse drug reaction; MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term; SOC = System organ class.
Patients with multiple occurrences of an ADR are counted only once within the corresponding ADR category and SOC, respectively.
Source: PT-Table 14.3.1-1.9.1

11 Discussion

11.1 Key results

This prospective, open-label, non-interventional, observational study was performed to gain insights from daily practice on the impact of physical exercise on effectiveness and quality of life, on prophylaxis and handling of stomatitis, and on therapy sequence, regarding treatment of patients with progressive or metastatic HR+ breast cancer with Afinitor® and exemestane. The observation period corresponded to the duration of therapy with Afinitor® combined with exemestane; if therapy with Afinitor® was discontinued prior to disease progression, observation was continued until progressive diseases or death. This final study report describes the results based on the data of all patients during the observation period from 30th August 2012 until 29th December 2017.

Two thousand and seventy-four patients (2074) were included in the FAS by 341 study centers. The median age of the patients was 66.0 years (P5%; P95%: 48.0; 81.0) and mostly normal to restricted ECOG performance state.

Premature discontinuation of therapy was mainly due to disease progression (1170 patients, 55.7%) or AEs (546 patients, 26.0%).

Tumor anamnesis revealed that the majority of the patients had G2/G3 tumors (1859, 94.6), mainly invasive ductal (70.2%), or invasive lobular (20.8%). At study entry the current tumor status was "metastasized" for the majority of patients (97.6%). After a median time of 0.8 (P5%; P95%: 0.1; 5.8) months after the last radiological prove, the localization of metastases – mainly performed by CT scan – was bones (67.2%), lymph nodes (23.2%), lung (22.2%), or liver (20.6%). As required by the observational plan, the majority of patients (98.3% and 75.5%) were ER+ or PgR+ positive. No HER2/neu receptor-positive patients were documented.

Most of the patients (91.6%) had received at least 1 prior antineoplastic therapy, mainly mastectomy (51.6%) and segment resection (42.4%). Radiation therapy (80.8% of the patients) was mainly performed in the breast (46.9%), bones (28.9%), and the thorax (21.2%). All patients included had received letrozole/anastrozole as prior medication and about half of the patients had a prior chemotherapy. Most patients were second (31.9%) or first (28.7%) line treatment with a median of 1.0 prior therapies.

The patients in this NIS had a median CCI of 0.0 (P5%; P95%: 0.0; 2.0), 74.9% were reported without comorbidity, and 22.4% with moderate comorbidity. Concomitant diseases with regard to CCI were mainly diabetes mellitus (12.5%), chronic lung disease (5.4%), and congestive heart failure (4.0%). Regarding the correlation between CCI and global health status, no notable differences between patients without and with moderate comorbidity were observed. Spearman rank analysis of CCI, age and physical exercise revealed no remarkable correlations; descriptively, patients without comorbidity reported to be more active than patients reported with moderate or severe comorbidities.

Stomatitis management was evaluated as secondary objective. Stomatitis prophylaxis was performed for 86.4% of the patients, mainly in form of mild dental hygiene, avoidance of hot, sour, or salty food, rinsing with tea, cooling, avoidance of peroxide- or alcohol-containing mouthwash solutions, and rinsing with mouthwash solution or NaCl.

Mainly grade 1 and 2 stomatitis was reported. Descriptively, active patients had more stomatitis events of any grade than moderate or insufficiently active patients (51.5% vs. 49.1% vs. 43.5%, respectively). Active patients had a higher proportion of grade 1 stomatitis events compared to moderately and insufficiently active patients (28.6% vs. 25.9% vs. 24.2%, respectively). Grade 2 events occurred in a comparable proportion of patients in active, moderately active and insufficiently active patients (16.6%, 17.5% and 15.5%, respectively). In the majority (86.7%), stomatitis was treated with non-drug mouthwash solution (60.4%), by cooling (30.7%), or drug intervention (27.6%). The median duration of all stomatitis events was 29.0 days (P5%; P95%: 5.0; 176.0).

The duration of therapy with Afinitor® and exemestane in daily practice was also analyzed. Most patients were treated according to usual practice and they received daily doses of 10.0 mg Afinitor® and 25.0 mg exemestane. Dose changes were mainly reductions (54.9%) and temporary interruptions (35.1%), mostly due to AEs. The median treatment duration was 145.0 days (P5%; P95%: 20.0; 785.0) In 70.9% of the patients, who completed "end of therapy", mainly chemotherapy (40.9%) was planned as follow-up therapy.

Primary effectiveness parameter in this study was PFS. The median time of PFS was 6.6 months with a 95% CI of [6.3; 7.0]. Descriptively, active patients (according to Godin) had a longer median PFS than moderately active or insufficiently active patients (8.1 vs. 7.0 vs. 6.7 months), and median PFS was longer the less treatments a patient had received before this study except for 1st line and 2nd line treatment (7.1 vs. 7.4; 3rd line, 4th line, 5th line and later: 6.1 vs. 6.2 vs. 5.3). The median PFS was longer for patients who had a start dose of 10 mg Afinitor® compared to a start dose of 5 mg (6.9 vs. 6.0 months). However overlapping 95% CIs have to be considered. Cox proportional hazard model for PFS showed a significant correlation with BMI, presence of visceral metastases and start dose of Afinitor®.

BOR as secondary effectiveness parameter was mainly based on CT scans and clinical assessment according to common practice. BOR, as documented by visit was SD or PR in most of the patients (59.4% and 17.6%). Results from end of study were less positive with only 41.3% and 7.4% of patients with SD and PR.

Analysis of QoL (EORTC QLQ-C30 and BR23) and physical exercises (WLTAS and KAS) were secondary endpoints in this NIS and were analyzed for all patients. QoL analyzed by the C30 questionnaire showed no large changes but an overall deterioration during the observation period for functioning subscales. QoL according to the BR23 subscales showed a slight median improvement for "systemic side effects". The median time to first decrease in QoL of at least 5% was 3.1 months. Regarding WLTAS no remarkable changes were observed during the study, most patients were assessed to be "insufficiently active". Regarding KAS "exercise during the last week" showed the lowest mean values. The assessment of the Spearman correlations between WLTAS, KAS, QoL, and BMI showed an at least weak correlation between WLTAS and exercise, as well as physical activity during the last week.

Safety was analyzed by frequency and intensity of AEsnr and ADRs by patients and by events.

Of the 2074 patients, 1900 (91.6%) experienced any AE, 1789 patients (86.3%) experienced nsAEs, and 963 patients (46.4%) experienced nsAEs considered to be unrelated to Afinitor® or exemestane. A total of 1668 patients (80.4%) experienced any nsADR that was considered

related to Afinitor® in 1655 patients (79.8%) and related to exemestane in 957 patients (46.1%). AEsnr leading to death were observed in 446 patients (21.5%), ADRs leading to death were observed in 116 patients (5.6%).

A total of 914 of the patients (44.1%) experienced SAEs, considered not related to Afinitor® or exemestane in 660 patients (31.8%). SADR were reported for 478 patients (23.0%), in 443 patients (21.4%) considered related to Afinitor® and in 246 patients (11.9%) considered related to exemestane. In addition, AESIs were analyzed for all patients. A total of 1235 AESIs were reported for 767 of the patients (37.0%), mainly rash, (11.3%) peripheral edema (9.0%), and pruritus (6.2%).

A total of 963 of the patients (46.4%) experienced at least one nsAEnr during the observation period, mainly referring to the MedDRA SOCs "infections and infestations" (13.1%), such as "nasopharyngitis" (4.3%), "urinary tract infection" (1.5%), and "bronchitis" (1.2%); "general disorders and administration site conditions" (12.8%), with "fatigue" (3.5%), "oedema peripheral" (3.1%), and "general physical health deterioration" (1.5%); and "musculoskeletal and connective tissue disorders" (11.7%), such as "pain in extremity" (2.4%), "arthralgia" (2.1%) and "back pain" (2.0%) being the most common AEs on PT level. The intensity of nsAEsnr was in most of the patients mild (30.2%) and moderate (26.6%).

A total of 1655 of the patients (79.8%) experienced at least one nsADR related to Afinitor® during the observation period, mainly referring to the MedDRA SOCs "gastrointestinal disorders" (57.8%), with "stomatitis" (41.4%), "nausea" (11.3%), and "diarrhoea" (10.6%); "skin and subcutaneous tissue disorders" (28.8%), with "rash" (10.0%), "pruritus" (5.4%), and "dry skin" (3.0%); "general disorders and administration site conditions" (27.9%), such as "fatigue" (15.6%), "peripheral oedema" (5.3%), and "general physical health deterioration" (2.5%) being the most common nsADRs related to Afinitor® on PT level. The intensity of nsADR was in most of the patients mild (59.5%) and moderate (52.8%).

A total of 957 of the patients (46.1%) experienced at least one nsADR related to exemestane during the observation period, mainly referring to the MedDRA SOCs "gastrointestinal disorders" (19.0%), with "stomatitis" (6.7%), "nausea" (5.9%), and "diarrhoea" (4.9%); "general disorders and administration site conditions" (15.6%), such as "fatigue" (7.7%), "peripheral oedema" (3.8%), and "general physical health deterioration" (1.0%); and "skin and subcutaneous tissue disorders" (12.2%), with "rash" (3.8%), "pruritus" (2.5%), and "alopecia" (1.6%) being the most common nsADRs related to exemestane on PT level. The intensity of nsADR was in most of the patients mild (30.7%) and moderate (21.5%).

A total of 660 of the patients (31.8%) experienced at least one SAEnr. The highest incidence was seen in SAEsnr referring to the MedDRA SOCs "neoplasms benign, malignant and unspecified [incl. cysts and polyps" (16.4%)], with "malignant neoplasm progression" (10.9%), "breast cancer metastatic" (3.7%), and "metastases to liver" (2.1%); "general disorders and administration site conditions" (8.3%), such as "general physical health deterioration" (4.3%), "death" (1.5%), and "pyrexia" (0.8%); and "respiratory, thoracic and mediastinal disorders" (6.1%), such as "pleural effusion" (2.9%), "dyspnoea" (2.0%), and "pulmonary embolism" (0.7%) being the most common SAEsnr on PT level. About 10% of the patients experienced SAEsnr of mild and moderate intensity, while 13.6% and 16.6% experienced severe and life-threatening SAEsnr.

A total of 443 of the patients (21.4%) experienced at least one SADR related to Afinitor®. The highest incidence was seen in SADRs referring to the MedDRA SOCs "respiratory, thoracic and mediastinal disorders" (6.4%), with "dyspnoea" (2.5%). "pneumonitis" (1.8%), and "pleural effusion" (1.4%); "general disorders and administration site conditions" (5.5%), such as "general physical health deterioration" (2.3%), "pyrexia" (1.3%) and "fatigue" (0.6%); and "infections and infestations" (5.1%), with "pneumonia" (2.3%), "atypical pneumonia" (0.3%), and "urinary tract infection" (0.2%) being the most common AEs on PT level. About 10% of the patients experienced SADRs of mild and moderate intensity, while 12.1% and 2.3% experienced severe and life-threatening SADRs.

A total of 246 of the patients (11.9%) experienced at least one SADR related to exemestane. The highest incidence was seen in SADRs referring to the MedDRA SOCs "general disorders and administration site conditions" (3.1%), such as "general physical health deterioration" (1.0%), "death" (0.8%) and "pyrexia" (0.3%); "respiratory, thoracic and mediastinal disorders" (2.7%), with "dyspnoea" (1.3%). "pleural effusion" (0.6%), and "pneumonitis" (0.3%); and "neoplasms benign, malignant and unspecified" (2.5%), such as "malignant neoplasm progression (1.4%), "metastases to liver" (0.3%), "breast cancer metastatic" (0.2%), and "metastases to bone" (5 patients, 0.2%) being the most common AEs on PT level. About 4% of the patients experienced SADRs of mild, moderate and severe intensity, while 1.9% experienced life-threatening SADRs.

A total of 767 of the patients (37.0%) experienced at least one AESI as defined in the Product Guidance Document for Afinitor/Votubia (everolimus) that was valid at time of final analysis. The highest incidence was seen in events referring to the MedDRA SOCs "hypersensitivity reactions/anaphylactic reactions" (22.6%) with "rash" (11.3%), "pruritus" (6.2%), and "erythema" (3.0%); "congestive heart failure" (10.7%) with "oedema peripheral" (9.0%), "cardiac failure" (1.7%), and "pulmonary oedema" (0.4%); and "non-infectious pneumonitis" (7.1%) with "pneumonitis" (5.4%), "lung infiltration" (0.6%), and "alveolitis" (0.6%) being the most common AEs on PT level.

A total of 446 of the patients (21.5%) experienced AEsnr leading to death. The highest incidence was observed regarding the MedDRA SOCs "neoplasms, benign, malignant and unspecified (incl. cysts and polyps)" (14.7%), "general disorders and administration site conditions" (6.9%) and "respiratory, thoracic and mediastinal disorders" (2.8%). ADRs related to Afinitor® leading to death were observed in 72 of the patients (3.5%). The highest incidence was observed regarding "general disorders and administration site conditions" (1.5%), "neoplasms, benign, malignant and unspecified [incl. cysts and polyps" (1.0%)] and "respiratory, thoracic and medistinal disorders" (0.6%).

A total of 797 of the patients experienced at least one AE leading to discontinuation. Main reasons were "malignant neoplasm progression" (18.4%), "stomatitis" (11.3%) and "general physical health deterioration" (8.8%). The median time to discontinuation was 3.0 months with a 95% CI of [2.8; 3.4] due to AEs and 5.9 months with a 95% CI of [5.4; 6.5] due to disease progression.

11.2 Limitations

Inherent limitations of non-interventional, observational studies in general are the risk of selection/ascertainment bias and the lack of a parallel control group, which complicate the interpretation of the causality between treatment and outcomes.

Furthermore, as with any "as observed" analysis, there is a potential risk of bias due to missing outcome data; the risk increases with increasing number of missing outcome data.

11.3 Interpretation

This prospective, open-label, non-interventional, observational study was performed at oncology and gynecology centers throughout Germany to evaluate insights from daily practice on impact of physical exercise on effectiveness and quality of life, prophylaxis and handling of stomatitis, and therapy sequence in patients with HR+ breast cancer treated with Afinitor® and exemestane.

The study population consisted of women with HR+ progressive or metastatic breast cancer as required by the observational plan. The majority of patients were treated with the recommended daily doses 10 mg Afinitor® and 25 mg exemestane. Dose changes, mainly reductions or temporary interruptions were documented for more than half of the patients. The occurrence of an AE was reported as main reason.

An insight into therapy sequence could be gained by this study. All patients had received a NSAI therapy with letrozole/anastrozole in a palliative or adjuvant setting prior to the treatment with Afinitor® in combination with exemestane. A follow-up treatment was planned for 70% of the patients. For patients who already had a completed “end of therapy” CRF page, mainly chemotherapy was planned as follow-up treatment.

The primary efficacy parameter, PFS, resulted in a median of 6.6 months with a 95% CI of [6.3; 7.0] which is in accordance with observations from earlier clinical studies that resulted in a median PFS of 7.8 months.

Data on handling and prophylaxis of stomatitis and impact of physical exercises could be evaluated.

At study entry, the current stadium of disease was assessed as “metastatic” for 97.6% of the patients. The treatment of metastatic breast cancer is palliative and therefore concentrates on reduction of tumor size. Therefore, decrease of disease progression and the reduction of complications associated with this disease are main objectives of treatment.

Stomatitis is one of the most common ADR known for Afinitor®. Consequently, the majority of patients received a stomatitis prophylaxis consisting of hygienic measures, avoidance of certain food or solutions, and rinsing with different fluids. About 40% of the patients were affected mainly by grade 1 and 2 stomatitis events. No clear conclusions can be drawn from the results regarding occurrence of stomatitis and activity of patients according to Godin Leisure-Time questionnaire. Analysis of intensity of stomatitis and prior chemotherapy or by line of treatment showed no differences in patients with and without prior treatment or with 1st or 2nd line treatment. Stomatitis was handled according to the recommendations in the SmPC of Afinitor®, namely by use of mouthwash solution, cooling, drug intervention, and by temporary

Afinitor® interruption or dose adjustment. The global health status of the patients did not seem to depend on the grade of stomatitis.

The analyses of the QLQ C-30 and BR23 of all patients revealed no large or remarkable changes during the observation period. Overall, slight deteriorations could be observed in functioning subscales. A slight median difference was found regarding an increase in fatigue as well as systemic therapy side effects (BR23). However, this might be expected, as all these symptoms are known ADR under the treatment with Afinitor® and exemestane and are listed in the current SmPCs for both medications. Overall, it has to be considered, that a kind of positive selection might be given, as no follow-up results were available for patients who dropped-out due to AEs or progression on one hand. On the other hand, patients for whom answers during the observation were available, might have provided a better estimation of their QoL.

Safety

The incidence and pattern of (serious) AEsnr and (serious) ADRs could be expected regarding the observed patient population and the underlying disease.

The present NIS data were also collected in order to gain results in patients with metastases in late chemotherapy lines or with previous medication not investigated in the approval study (BOLERO-2).

11.4 Generalizability

The generalizability of the results is limited, as this is a non-interventional analysis in a one-arm cohort, in which patients were treated according to physicians´ clinical assessments. However, results are reasonable and comparable with earlier findings. Therefore, the study gains insight into daily life with regard to therapy sequence, stomatitis prophylaxis, QoL of the patients, physical activity and also safety.

12 Other information

No other information is included.

13 Conclusion

Insights into therapy sequence were gained. All patients had received a NSAI therapy with letrozole/anastrozole prior to the study treatment. More than half of the patients were first or second line. Chemotherapy as follow-up treatment was planned also for more than half of the patients.

Stomatitis prophylaxis was performed for 86.4% of the patients, mainly in form of dental hygiene, avoidance of hot, sour, or salty food, rinsing with tea, cooling, avoidance of peroxide- or alcohol-containing mouthwash solutions, rinsing with mouthwash solution or NaCl. Reported stomatitis events were mainly of grade 1 and 2 with a median duration of 4 weeks.

The treatment with Afinitor® and exemestane observed was mainly according to the expected routine practice and according to the current SmPC. Dose changes were mainly reductions and temporary interruptions, mostly due to AEs.

Evaluation of the primary effectiveness parameter – PFS – descriptively showed a longer median PFS for active patients compared to moderately active patients. A lower number of previous treatments and an Afinitor® start dose of 10 mg seemed to correlate with a longer PFS.

The analysis of QoL showed no large changes during the observation period, but an overall deterioration.

The incidence and pattern of (serious) AEsnr and (serious) ADRs could be expected regarding the observed patient population and the underlying disease.

14 References

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Appendices

Annex 1 – List of stand-alone documents

Beobachtungsplan, Version 1.6, dated 10 November 2015

Statistical Analysis Plan, Version 4.0, dated 18 May 2018

Annex 2 – Additional information

List of investigators who agreed to be mentioned within the final study report.

Brawo final analysis, Post-Text Tables