Horizon Scanning in Oncology

Everolimus (Afinitor® or Votubia®) in combination with exemestane in postmenopausal women with oestrogen receptor positive, HER2-negative locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology Nr. 32
ISSN online 2076-5940

Horizon Scanning in Oncology

Everolimus (Afinitor® or Votubia®) in combination with exemestane in postmenopausal women with oestrogen receptor positive, HER2-negative locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole

Vienna, August 2012

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft in collaboration with EBM Review Center, Medical University of Graz (EBMRC; Austria)

Author(s):	Dr. med. Klaus Jeitler (EBMRC) Mag. Thomas Semlitsch (EBMRC)
Internal review:	Dr. med. Anna Nachtnebel, MSc (LBI-HTA)
External review:	Prof. Dr. med. Gunter von Minckwitz German Breast Group Forschungs GmbH Martin Behaim Strasse 12; 63263 Neu-Isenburg Germany

DISCLAIMER

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

CONTACT INFORMATION

Publisher:
Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at "http://eprints.hta.lbg.ac.at":

DSD: Horizon Scanning in Oncology Nr. 32
ISSN online 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

1 Drug description

Generic/Brand name/ATC code:

Everolimus /Afinitor® or Votubia®/ L01XE10 or L04AA18

Developer/Company:

Novartis AG

Description:

everolimus inhibits mTOR, a central regulator of tumour cell division

Everolimus, is an orally active immunosuppressant analogue of sirolimus, a macrolide antibiotic produced by Streptomyces hygroscopicus [1]. It inhibits mTOR (mammalian target of rapamycin), a serine-threonine kinase acting as a signal transducing protein, which is a central regulator of tumour cell division and blood vessel growth in cancer cells and signals information via the regulation of multiple downstream pathways [2]. The inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in-vitro and/or in-vivo. In addition, everolimus inhibits the expression of hypoxia-inducible factor (e.g., HIF-l) and reduces the expression of vascular endothelial growth factor (VEGF) [3].

exemestane: third generation aromatase inhibitor

Exemestane is a third generation aromatase inhibitor (AI) for the hormonal treatment of oestrogen–receptor (ER)-dependent tumours. It irreversibly suppresses oestrogen production by inhibiting steroidal aromatase [1].

tablets for oral administration

Afinitor® is available as 5 mg or 10 mg tablets, Votubia® as 2.5 mg, 5 mg and 10 mg tablets. Everolimus (Afinitor®/Votubia®) is administered orally with a recommended dosage of 10 mg once per day [2, 4, 5].

The most common adverse events (AEs) associated with everolimus include stomatitis, infections, rash, fatigue, diarrhoea, oedema, abdominal pain, nausea, fever, asthenia, cough, headache and decreased appetite [2, 4, 5].

2 Indication

combination with exemestane for postmenopausal women with ER-positive, HER2-negative BC

Everolimus (Afinitor® or Votubia®) in combination with exemestane is indicated for the treatment of postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer (BC) who are refractory to letrozole or anastrozole.

3 Current regulatory status

EMA: treatment of postmenopausal women with advanced HR-positive BC approved as new indication

Following the positive opinion adopted by the Committee for Medicinal Products for Human Use in June 2012 [6], the European Medicines Agency (EMA) granted market authorization of Afinitor®

- for the treatment of hormone receptor (HR)-positive, HER2-negative advanced BC, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor [2].

Beside this indication everolimus (Afinitor®/Votubia®) is also approved for the use in the European Union for the treatment of

for neuroendocrine tumours of pancreatic origin, renal cell carcinoma and subependymal giant cell astrocytoma

- patients with neuroendocrine tumours of pancreatic origin (unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease) [2].
- patients with renal cell carcinoma (advanced renal cell carcinoma, with progression on or after treatment with VEGF-targeted therapy) [2].
- patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex who require therapeutic intervention but are not amenable to surgery [5].

FDA: treatment of postmenopausal women with advanced HR-positive BC approved as new indication

In July 2012, the U.S. Food and Drug Administration (FDA) approved everolimus (Afinitor®) based on the results of a randomized, double-blind, multicenter trial:

- for the treatment of postmenopausal women with advanced HR-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole [7].

for advanced pancreas carcinoma, advanced renal carcinoma and subependymal giant cell astrocytoma

In the U.S. market Afinitor® is furthermore licensed for the treatment of [4]:

- advanced neuroendocrine tumours of pancreatic origin.
- advanced renal cell carcinoma.
- renal angiomyolipoma with tuberous sclerosis complex.
- subependymal giant cell astrocytoma.

4 Burden of disease

BC is most common type of cancer in women

Within the last 20 years, about 4,000 to 5,000 women were newly diagnosed with BC in Austria each year [8]. The mortality rate for BC was 1,500 in 2009 [9]. Thus, with a percentage of 28.5%, BC is the most common type of cancer in females [10]. In the US, the median age at diagnosis of BC was 61 years from 2005-2009 [11]. In Austria the majority of malignant neoplasms of the breast were diagnosed in women aged 55 to 74 years in 2007-2009 [8]. The age standardized (per 100,000 population, defined by WHO 2001) incidence rate for BC in women increased from 66.4 in 1992 to a maximum of

77.8 in 2001 and dropped again to 69.4 in Austria in 2009. In the same period, the age standardized death rate continuously declined from 24.7 (1992) to 17.3 (2009) [8].

risk factors

Several well-established factors have been associated with an increased risk of BC, including age, positive family history, nulliparity, early menarche, a personal history of BC and genetic factors [12].

TNM staging classification

The American Joint Committee on Cancer has designated a staging by Tumour Node Metastasis (TNM) classification to define BC. The TNM provides a strategy for grouping patients with respect to prognosis. Besides the staging of the primary tumour, the extent to which regional lymph nodes are involved and the absence or presence of distant metastases are taken into account, leading to four main stage groupings (stage T1 to T4) where locally advanced BC is coded as stage III and metastatic BC as stage IV [13, 14]. In 2007/2009, 23.9% of female patients in Austria with initially diagnosed BC had regional disease (spread to regional lymph nodes) and 5.2% had disseminated disease [15]. In the US, the 2002-2008 overall 5-year relative survival rate was 83.9% for regional BC and 23.8% for metastatic BC [11]. According to Statistik Austria the 5-year relative survival for regional or metastatic BC is 60% and 10%, respectively [16]. The median overall survival (OS) for women with metastatic BC approaches two years, with a range from a few months to many years [17], while the median survival for women with stage III disease is less than five years [18]. The above-mentioned survival data refer to locally advanced or metastatic BC irrespective of receptor status with a probably better prognosis associated with HR-positive, HER2-negative state.

in Austria 23.9% of women have regional disease and 5.2% have disseminated disease at diagnoses

60-70% of all invasive BC are HR-positive

Approximately 60% to 70% of all invasive BC are HR-positive at the time of diagnosis [19], resulting in about 2,400 – 3,500 women being diagnosed with HR-positive BC in Austria each year. Of these, about 90% are believed to be HER2-negative [1].

prognostic factors for advanced BC

Advanced BC comprises metastatic BC (stage IV) and locally advanced BC (stage III) [20]. Prognostic factors for advanced disease include the length of the relapse-free interval after the initial treatment, the number of metastases, locations involved (worse prognosis with hepatic, lymphangitic pulmonary metastases, carcinomatous meningitis) and biological markers (e.g., good prognosis is associated with HR-positive state). Additionally, weight loss, poor performance status and age less than 35 years in woman with early stage BC determine an unfavourable prognosis [17]. Biological markers for prognosis as well as for therapeutic decisions include oestrogen receptor, progesterone receptor and HER2-status [21].

5 Current treatment

choice of therapy based on prognostic and predictive factors

The choice of therapy for BC is based on a number of prognostic and predictive factors like tumour histology, characteristics of the primary tumour, axillary node status, HR- and HER2-status, presence of detectable metastatic disease, comorbid conditions, age, and menopausal status [22].

multimodality therapy: treatment of local disease and treatment of systemic disease

Advanced HR-positive, HER2-negative BC is best treated with a multimodality therapy including the treatment of the local disease with surgery, radiation therapy, or both, and the treatment of systemic disease with endocrine therapy, cytotoxic chemotherapy, biologic therapy or combinations of these. Neoadjuvant systemic therapy, in particular neoadjuvant chemotherapy, has become the standard approach for patients with locally advanced, inoperable BC [23]. When making treatment choices there is a trade-off between quality-of-life (QoL), the risks of toxicity and the likelihood of benefit in terms of improving symptoms or survival [24].

metastatic BC: palliative intent

For metastatic BC the therapy is mainly palliative in intent and the treatment should be tailored individually. Ultimately, the choice of therapy should be based on patient preferences. Clinical advice will take into account the presence or absence of comorbidities, prior treatment and treatment effectiveness, performance status, the site and extent of disease, the presence or absence of symptoms, and the rate at which the disease appears to progress [24].

Treatment options for locally advanced and metastatic BC are:

endocrine therapy

appropriate for ~ 70% of patients

tamoxifen

for postmenopausal women: aromatase inhibitors

- endocrine therapy

  Hormonal therapies are widely used in the management of advanced BC and are appropriate for approximately 70% of patients [24]. The first-line endocrine treatment for premenopausal women with HR-positive advanced BC is tamoxifen, while AIs (e.g. anastrozole, letrozole) are contraindicated. AIs, rather than tamoxifen, are suggested as first-line endocrine treatment for postmenopausal women with HR-positive advanced BC [25]. Although HR-positive tumours are most likely to respond to endocrine therapy, it is known that not all patients who have HR expressing tumours respond to endocrine manipulation (i.e. de novo resistance) and a substantial number of patients who do respond will develop disease progression or recurrence while on therapy (i.e. acquired resistance) [26]. On disease progression, other classes of AIs (e.g. exemestane) and the ER antagonists (e.g. fulvestrant, tamoxifen) are used as second-line treatment options. Some studies suggest a relative resistance of HER2-overexpressing tumours to endocrine therapy, which may be higher for ligand binding agents like tamoxifen and lower for ligand-depleting agents like AIs [27]. But as study results are conflicting, according to recommendations of an expert panel convened by the American Society of Clinical Oncology (ASCO) HER2 expression should not be used to make decisions regarding hormone therapy in either the adjuvant or metastatic disease setting [28].

- chemotherapy

  Chemotherapy is used for the treatment of both HR-positive and HR-negative patients with advanced BC [24]. Patients whose tumours have progressed on hormone therapy or patients with visceral metastases are also candidates for chemotherapy [29]. A number of different chemotherapy drugs, or classes of drug, are used, including taxanes, capecitabine, vinorelbine, alkylating agents, platinum-based drugs and anthracyclines [24]. Whether single-agent chemotherapy or combination chemotherapy is preferable for first-line treatment is unclear [29].

chemotherapy

taxanes

capecitabine

vinorelbine

gemcitabine

- local-regional treatment

  For patients with operable locally advanced BC the options for local-regional treatment of the primary tumour include breast-conserving surgery plus radiation therapy, mastectomy plus reconstruction, and mastectomy alone. Surgical staging of the axilla should also be performed. Radiation therapy is regularly employed after breast-conservation surgery. Adjuvant radiation therapy can be indicated for postmastectomy patients. The main goal of adjuvant radiation therapy is to eradicate residual disease thus reducing local recurrence [30].

  For patients with metastatic BC surgery may be indicated for selected groups. Examples include patients who need mastectomies for fungating (marked by ulcerations and necrosis)/painful breast lesions, parenchymal brain or vertebral metastases with spinal cord compression or isolated lung metastases [29]. In patients with metastatic BC radiation therapy has a major role in the palliation of localized symptomatic metastases. Indications include painful bone metastases, unresectable central nervous system metastases, bronchial obstruction, and fungating/painful breast or chest wall lesions. Radiation therapy is also used after surgery for decompression of intracranial or spinal cord metastases and following fixation of pathologic fractures [29]. For patients with bone metastases the use of bisphosphonates should also be considered to reduce skeletal morbidity [29].

local-regional treatment

surgery

radiation therapy

6 Evidence

A systematic literature search for primary literature in medical databases (Medline/Pubmed, Embase, Cochrane Central Register of Controlled Trials) was conducted on 3rd August 2012 and yielded 130 records after removal of duplicates. Of those, 7 records reporting on one phase III trial were included [31-37]. In addition a hand search was performed which included reference lists of topic related reviews (retrieved from the Cochrane databases and CRD) and the websites of the EMA and the FDA. This search resulted in 3 further publications belonging to the already identified RCT [38-40]. On request the manufacturer sent 5 additional conference posters relevant to the topic [41-45]. In summary 15 publications (2 full text publications, 1 letter and 12 conference abstracts) reporting on one relevant phase III trial (BOLERO-2) were identified [31-45].

one phase III trial

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title: Everolimus in Combination With Exemestane in the Treatment of Postmenopausal Women With Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer Who Are Refractory to Letrozole or Anastrozole [32, 33, 35-42]		
Study identifier	ClinicalTrial.gov: NCT00863655 EudraCT: 2008-008698-69 CRAD001Y2301	
Design	Randomised (2:1 ratio), two-arm double-blind, multi-centre (189), international (24 countries) study; N=724 allocation randomly to 2 treatment groups (485 everolimus-exemestane group, 239 placebo-exemestane group); stratification (presence of visceral metastasis and previous sensitivity to endocrine therapy), ECOG performance status (0 - 2) and number of prior chemotherapy regimens for advanced disease (0 or 1); ITT analysis	
	Duration	Enrolment: June 2009 to January 2011 Ongoing (Expected completion date: June 2014) Interim analysis (preplanned according to the protocol): 11 February 2011 at 359 documented PFS events Median follow-up: 7.5 months Median duration of exposure in everolimus-exemestane group: EVE 14.6 weeks, EXE 17.4 weeks Median duration of exposure in placebo-exemestane group: Placebo 12.0 weeks, EXE 12.0 weeks Updated analysis 1: 8 July 2011 at 457 documented PFS events Median follow-up: 12.5 months Updated analysis 2: 15 December 2011 at 510 documented PFS events Median follow-up: 18 months
Hypothesis	Superiority of progression-free survival (PFS)	
Funding	Novartis Pharmaceuticals	
Treatment groups	Intervention	Everolimus (EVE) + exemestane (EXE) EVE (10mg/day orally) and EXE (25mg/day orally). In case of adverse events two reductions in EVE dose (5mg/day, 5mg every other day) were allowed. Treatment was continued until disease progression, development of unacceptable toxicity or withdrawal of consent.
	Control	Placebo + exemestane (EXE) Placebo (2 times a day orally) and EXE (25mg/day orally). Maintenance of treatment and allowed reductions in placebo dose like in the intervention group.

Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Defined as time from the date of randomization to the date of the first documented progression or death due to any cause. PFS as assessed by the local investigators on the basis of radiographic studies (every 6 weeks) was the primary outcome. Patients without an event were treated as censored at the time of the last tumour assessment. In addition for a secondary supportive efficacy analyses a central assessment by an independent radiology committee was done. For patients with measurable disease at baseline objective response and disease progression were determined using the Response Evaluation Criteria in Solid Tumors (RECIST version 2). In patients with bone only lesions (lytic or mixed) at baseline disease progression was determined in case of a new lytic lesion in bone, an unequivocal progression of an existing bone lesion, or a new lesion outside of bone. Patients who discontinued study treatment (except for progression) were required to follow the same schedule of assessments.
	Overall survival (key secondary endpoint)	OS	Defined as the time from date of randomization to date of death due to any cause. In case of unknown survival status OS data were censored at the date of last contact.
	Overall response rate (secondary endpoint)	ORR	Defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR).
	Clinical benefit rate (secondary endpoint)	CBR	Defined as the proportion of patients with either a best overall response of CR, PR or SD lasting for 24 weeks or longer.
	Deterioration of ECOG performance status (secondary endpoint)	TTD-ECOG-PS	Time to definitive deterioration of ECOG performance status (0 fully active, pre-disease performance without restriction; 1 restricted in physically activity but able to work (light or sedentary nature); 2 all self-care but unable to work; 3 only limited self-care; 4 completely disabled; 5 dead).
	Quality of Life (secondary endpoint)	TTD-QoL	Time to definitive deterioration, defined as a 5% decrease in the global health status (GHS) score relative to baseline, with no subsequent increase above this threshold. For this evaluation the European Organization for Research and Treatment of Cancer quality of life core questionnaire (QLQ-C30) and the breast cancer module (QLQ-BR23) were used, with the subscale GHS as the predefined primary QoL variable of interest.

Results and analysis		
Analysis description	Primary efficacy analysis: PFS based on radiologic studies assessed by local investigators for the everolimus-exemestane group compared with the placebo-exemestane group. A log-rank test and a two-look Lan–DeMets group sequential design with an O'Brien–Fleming-type boundary at a one-sided cumulative 2.5% level of significance were used to detect a hazard ratio of 0.74 with 90% power. For the final analysis 528 PFS events (i.e. either progressed or died due to any cause) were required, which based on further assumptions resulted in 705 patients to be randomized. The interim analysis was prespecified after the observation of 359 PFS events. All randomly assigned patients were included in the efficacy (ITT) analysis.	
Analysis population	Inclusion	Postmenopausal women; ER-positive, HER2–negative advanced breast cancer; refractory to the NSAIs letrozole or anastrozole (defined as either recurrence during adjuvant treatment / within 12 months after its completion or as progression during the most recent systemic therapy for advanced disease / within 1 month after its completion); at least one measurable lesion or lytic/mixed bone lesions
	Exclusion	ECOG performance status of 3 or greater; more than one prior chemotherapy regimen for advanced disease; prior hormonal therapy with exemestane; prior mTOR inhibitor therapy; history of brain metastases
	Characteristics	724 women with ER-positive, HER2-negative advanced BC (72% progesterone-receptor-positive) *Control (n=239) vs. Intervention(n=485):* Median age (years [range]): 61 [28-90] vs. 62 [34-93] Ethnicity White/Asian/Black (%): 78/19/1 vs. 74/20/3 ECOG performance status 0/1/2 (%): 59/35/3 vs. 60/36/2 Disease-free interval: median (months [range]): 57 [5-316] vs. 58 [1-340] <12 mo/12-24 mo/>24 mo (%): 4/6/54 vs. 2/5/56 Measurable disease (%): 68 vs. 70 Visceral disease (%): 56 vs. 56 Metastases (%): lung/liver/bone: 33/30/77 vs. 29/33/76 ≥ 3 metastatic sites : 37 vs. 36 Previous endocrine therapy: any antiestrogen (%): 59 vs. 57 letrozole or anastrozole (%): 100 vs. 100 Previous sensitivity to endocrine therapy (%): 84 vs. 84 Prior chemotherapy (%) (neo-)adjuvant only/for metastatic disease: 40/26 vs. 44/26

Results (preplanned interim analysis 7.5 mo f/up [35, 36])	*Treatment group*	*Control (Placebo + EXE)*	*Intervention (EVE + EXE)*
	Number of subjects	239	485
	PFS, locA (months) median 95%CI	[157 events] 2.8 2.8-4.1	[202 events] 6.9 6.4-8.1
	PFS, centA (months) median 95%CI	[104 events] 4.1 2.8-5.8	[114 events] 10.6 9.5-not reached
	ORR, locA (%) 95% CI CR/PR/SD/PD/U	0.4 0.0-2.3 0.0/0.4/58.6/31.4/9.6	9.5 7.0-12.4 0.4/9.1/70.1/9.9/10.5
	ORR, centA (%) 95% CI CR/PR/SD/PD/U	0.4 0.0-2.3 0.0/0.4/64.4/21.8/13.4	7.0 4.9-9.7 0.0/7.0/74.6/5.6/12.8
	OS (months)	NR	NR
	Deaths	31 (13.0%)	52 (10.7%)
	TTD-ECOG-PS	NR	NR
	TTD-QoL	NR	NR
Effect estimate per comparison (interim analysis 7.5 mo f/up [35, 36])	*Comparison groups*		*Intervention vs Control*
	PFS, locA	HR	0.43
		95% CI	0.35-0.54
		P value	<0.001
	PFS, centA	HR	0.36
		95% CI	0.27-0.47
		P value	<0.001
	ORR, locA	Point estimate	NR
		Variability	NR
		P value	<0.001
	ORR, centA	Point estimate	NR
		Variability	NR
		P value	<0.001
	OS	Point estimate	NR
		Variability	NR
		P value	NR
	Deaths	Point estimate	NR
		Variability	NR
		P value	NR
	TTD-ECOG-PS	P value	ns
	TTD-QoL	P value	ns

Results (updated analysis 12.5 mo f/up [37, 38])	Treatment group	*Control (Placebo + EXE)*	*Intervention (EVE + EXE)*
	Number of subjects	239	485
	PFS, locA (months) median	3.2	7.4
	PFS, centA (months) median	4.1	11.0
	ORR, locA (%)	1.3	12.0
	CBR (%)	25.5	50.5
	OS (months)	NR	NR
	Deaths	54 (22.6%)	84 (17.3%)
	TTD-QoL (months)	NR	NR
Effect estimate per comparison (updated analysis 12.5 mo f/up [37, 38])	*Comparison groups*		*Intervention vs Control*
	PFS, locA	HR	0.44
		95% CI	0.36-0.53
		P value	<0.001
	PFS, centA	HR	0.36
		95% CI	0.28-0.45
		P value	<0.001
	ORR, locA	P value	<0.0001
	CBR	P value	<0.0001
	OS	P value	NR
	Deaths	P value	NR
	TTD-QoL	P value	ns
Results (updated analysis 18 mo f/up [2, 41, 42])	Treatment group	*Control (Placebo + EXE)*	*Intervention (EVE + EXE)*
	Number of subjects	239	485
	PFS, locA (months) median 95%CI	3.2 2.8-4.1	7.8 6.9-8.5
	PFS, centA (months) median 95%CI	4.1 2.9-5.6	11.0 9.7-15.0
	ORR, locA (%) 95%CI	1.7 0.5-4.2	12.6 9.8-15.9
	CBR (%) 95%CI	26.4 20.9-32.4	51.3 46.8-55.9
	OS (months)	NR	NR
	Deaths	77 (32.2%)	123 (25.4%)
	TTD-QoL (months) median 95%CI	5.8 4.2-7.2	8.3 7.0-9.7

Effect estimate per comparison (updated analysis 18 mo f/up [2, 41, 42])	*Comparison groups*		*Intervention vs Control*
	PFS, locA	HR	0.45
		95% CI	0.38-0.54
		P value	<0.0001
	PFS, centA	HR	0.38
		95% CI	0.31-0.48
		P value	<0.0001
	ORR, locA	P value	<0.0001
	CBR	P value	<0.0001
	OS	HR	0.77
		95% CI	0.57-1.04
		P value	ns
	Deaths	P value	NR
	TTD-QoL	HR	0.74
		95%CI	0.58 - 0.95
		P value	sig

BC … Breast cancer; CI … Confidence interval; CBR … Clinical benefit rate; centA … central assessment; CR … complete response; ECOG … Eastern Cooperative Oncology Group; ER … Estrogen-receptor; EVE … Everolimus; EXE … Exemestane; f/up … follow-up; GHS … Global health status; HER2 … Human epidermal growth factor receptor 2; HR … hazard ratio; ITT … Intent-to-treat; locA … local assessment; mTOR … mammalian target of rapamycin; mo … months; NR … Not reported; ns … not significant; NSAI … non steroidal aromatase inhibitor; ORR … Overall response rate; OS … Overall survival; PFS … Progression-free survival; PD … progressive disease; PR … partial response; QoL … Quality of Life; RECIST … Response Evaluation Criteria in Solid Tumors; SD … stable disease; sig … significant; TTD ECOG-PS … Time to definitive deterioration in ECOG performance status; TTD-QoL … Time to definitive deterioration in Quality of Life; U … unknown

Table 2: Most frequent adverse events (interim analysis at 7.5 months follow-up) [35, 36]

Grade (according to NCI CTCAE version 3.0)	Outcome	Control (Placebo + EXE) (N = 238)	Intervention (EVE + EXE) (N = 482)
SAE	All	12%	23%
	attributed to study treatment	1%	11%
Grade 3 (only AEs≥1% in one arm)	Stomatitis	1%	8%
	Anaemia	<1%	5%
	Dyspnoea	1%	4%
	Hyperglycaemia	<1%	4%
	Fatigue	1%	3%
	Aspartate aminotransferase level increased	1%	3%
	Pneumonitis	0%	3%
	Alanine aminotransferase level increased	2%	3%
	Diarrhoea	1%	2%
	Thrombocytopenia	0%	2%
	Asthenia	0%	2%
	Rash	0%	1%
	Decreased appetite	0%	1%
	Cough	0%	1%
	Decreased weight	0%	1%
	Arthralgia	0%	1%
	Peripheral oedema	<1%	1%
	Nausea	1%	<1%
	Back pain	1%	0%
Grade 4 (only AEs≥1% in one arm)	Anaemia	<1%	1%
	Thrombocytopenia	<1%	1%
Deaths attributed to SAEs	All (n)	1	7
	sepsis (n)	0	2
	pneumonia (n)	1	1
	tumour haemorrhage (n)	0	1
	cerebrovascular incident (n)	0	1
	renal failure (n)	0	1
	suicide (n)	0	1

AE … Adverse event; CTCAE … Common Terminology Criteria for Adverse Events; EVE … Everolimus; EXE … Exemestane; NCI … National Cancer Institute; Common Toxicity Criteria; SAE … Serious adverse event

study population and inclusion criteria

treatment group: everolimus + exemestane

control group: placebo + exemestane

In this international double-blind multi-centre trial [31-45], 724 postmenopausal women with ER-positive and HER2-negative advanced BC refractory to previous nonsteroidal aromatase inhibitors (letrozole or anastrozole) received exemestane either in combination with everolimus or with placebo. To be included, patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and not more than one prior chemotherapy for advanced disease. 485 women were randomly assigned to the intervention group treated orally with 10 mg everolimus (an mTOR inhibitor) plus 25 mg exemestane (an oral steroidal aromatase inhibitor) per day, and 239 women were allocated to the control arm receiving 10 mg matching placebo instead of everolimus. At baseline the randomized groups were similar in terms of patient characteristics, tumour status and prior therapies.

significantly longer PFS

For the primary endpoint, the preplanned interim analysis conducted after 359 documented PFS events showed a significantly longer PFS in the intervention group as determined by the local investigators (everolimus-exemestane group 6.9 months vs. placebo-exemestane group 2.8 months; HR 0.43 (95% CI 0.35-0.54; $p<0.001$)). The supportive efficacy analysis based on a central assessment by an independent radiology committee produced a similar group difference in PFS (HR 0.36 (95% CI 0.27-0.47; $p<0.001$), although the median PFS in both groups was longer (10.6 vs. 4.1 months) than in the investigator-determined analysis. This is because for the central assessment data were censored on the date of the last valid radiologic assessment, also leading to fewer PFS events (218) for the central analysis. Subgroup analyses including patient characteristics as well as tumour parameters and previous treatment showed consistent PFS results across all groups. The two update analyses based on 457 PFS events at a median follow-up of 12.5 months and on 510 PFS events at 18 months follow-up showed quite similar PFS differences between the intervention group and control group (for details see table 1).

consistent across all subgroups

similar PFS results in updated analysis

data on OS yet immature

Only preliminary results have been available for the key secondary end point OS at 18 months (HR = 0.77, 95%CI 0.57 - 1.04). The authors stated that in all analyses up to now OS results were immature, with a total of 83, 138 and 200 deaths, respectively. Fewer deaths occurred in the intervention group (interim analysis 10.7% vs. 13.0%; updated analysis at 12.5 months 17.3% vs. 22.6%; updated analysis at 18 months 25.4% vs. 32.2%), but information on the statistical significance of these results is missing.

fewer deaths

ORR significantly better

Detailed information on tumour response and progression was only available in the interim analysis with significantly more patients in the intervention group having a complete or partial response (see table 1). In all 3 analyses, the ORR was significantly better in favour of the intervention group (local assessment at 7.5 months: 9.5% vs. 0.4%, $p<0.001$; at 12.5 months 12.0% vs. 1.3%, $p<0.0001$; at 18 months 12.6% vs. 1.7%, $p<0.0001$). Also the reported clinical benefit rates were significantly better in the intervention group (about 51% vs. about 26%, $p<0.0001$ at 12.5 months and 18 months follow-up, respectively). Further predefined efficacy outcomes were not reported in detail. Based on the global health status (GHS, the primary QoL variable of interest) the analysis of the TTD in QoL showed no significant group difference at 7.5 and 12.5 months follow-up but was statistically significant in favour of the intervention group at 18 months (8.3 vs 5.8 months). The TTD in ECOG performance status was only reported for the 7.5 months interim analysis with no difference between the groups.

QoL differs depending on the time of analysis

more SAEs

More patients in the everolimus-exemestane group had serious adverse events (SAEs) compared to the placebo-exemestane group (interim analysis 23% vs. 12%; updated analysis at 12.5 months 26.8% vs. 13.9%). Also a clearly higher proportion of SAEs was attributed to the study treatment in the intervention group (interim analysis 11% vs. 1%; updated analysis at 12.5 months 11.2% vs. 1.7%) and more deaths were also related to study treatment in the intervention group (interim analysis: 1.4% (n=7) vs. 0.4% (n=1)) .

AEs reason for discontinuation of treatment

In the intervention group, adverse events (AEs) were more often the reason, why patients discontinued their study treatment (8% vs. 3%) or particularly discontinued everolimus/placebo (19% vs. 4%).

more AEs when treatment included everolimus

AEs of grade 3 or 4 affecting more than 1% of patients in at least one treatment arm were stomatitis, anaemia, dyspnoea, hyperglycaemia, fatigue, pneumonitis, increased aspartate or alanine aminotransferase levels, diarrhoea, thrombocytopenia and asthenia. All of them occurred more often in the everolimus-exemestane group than in the placebo-exemestane group (for details see table 2). The reported proportions of patients with AEs of grade 3 or 4 in the updated analyses were quite similar.

The study authors concluded that, at the moment, patients' benefit in terms of survival is unknown, but results show a clinical benefit. However, adding everolimus to exemestane increased the toxicity of the treatment, which has to be weighed against the benefit.

6.2 Efficacy and safety - further studies

no phase II trials

No phase II trials investigating the effect of everolimus in combination with exemestane for the treatment of postmenopausal women with HR-positive locally advanced or metastatic breast cancer were identified.

7 Estimated costs

monthly treatment costs € 3,600

The price for one package Afinitor® 10 mg containing 30 tablets and thus for one month of therapy is € 3,600 [46, 47]. According to the summary of product characteristics (SPC) and the BOLERO-2 study protocol the recommended dose is 10mg daily for advanced breast cancer. Since the BOLERO-2 study is ongoing, final data on the median duration of treatment with everolimus are still missing. At the 18 months analysis the median duration of exposure in the everolimus-exemestane group was 29.5 weeks. Based on these data the overall costs for the treatment with Afinitor® per patient would result in about € 25,000. One can expect the actual costs being even higher, because 16.7% of the patients were still on study treatment at the time of analysis. As everolimus is approved only as add-on therapy to exemestane, these expenses occur in addition to the costs of the aromatase inhibitor.

8 Ongoing research

2 further ongoing phase III trials for everolimus + exemestane

Beside the ongoing BOLERO-2 trial, whose interim results are presented in this report, 2 additional ongoing phase III studies evaluating everolimus for the investigated indication and intervention were found on www.clinicaltrials.gov or on www.clinicaltrialsregister.eu:

- NCT01626222 (EudraCT 2011-006111-62): 4Ever – A multi-centre, open-label, single-arm study evaluating the efficacy and safety, QoL and health resources utilization in postmenopausal women with HR-positive BC progressing following prior therapy with non-steroidal aromatase inhibitors (NSAI) treated with the combination of everolimus and exemestane. The estimated study completion date is May 2014.
- EurdaCT 2012-000073-23: An open-label, multi-centre, expanded access study evaluating the safety of everolimus (RAD001) in combination with exemestane in postmenopausal women with estrogen receptor positive locally advanced or metastatic BC that is refractory to NSAIs. The estimated study completion date is not reported.

2 ongoing phase III trials for everolimus + trastuzumab and 1 for everolimus + letrozole

Furthermore 2 ongoing phase III trials currently investigate everolimus in combination with trastuzumab for locally advanced or metastatic HER2-*positive* BC:

- NCT00876395 (BOLERO-1): to confirm the value of adding everolimus as first-line therapy to weekly paclitaxel and trastuzumab as treatment of HER2-overexpressing metastatic BC. The estimated study completion date is December 2013.
- NCT01007942 (BOLERO-3): will assess the combination everolimus, vinorelbine, and trastuzumab compared to the combination vinorelbine and trastuzumab with respect to progressive-free survival and over survival in HER2-positive women with locally advanced or metastatic BC who are resistant to trastuzumab and have been pretreated with a taxane for second/third-line therapy) The estimated study completion date is May 2013.

Another trial investigates everolimus in combination with letrozole as first-line therapy for advanced BC (EudraCT 2004-000849-38).

no ongoing phase II trial for everolimus + exemestane

No ongoing phase II trial was found for everolimus in combination with exemestane. There are various phase II studies investigating everolimus in combination with other agents (e.g. trastuzumab, carboplatin, lapatinib) or as mono-therapy for the treatment of BC.

plenty phase III and phase II studies for other indications

In addition everolimus is under investigation in phase III and phase II trials for primary BC and other cancer types including prostate cancer, colorectal cancer, thyroid cancer or non-small cell lung cancer.

9 Commentary

approved for treatment of HR-positive advanced BC since July 2012

In July 2012, based on the results of the BOLERO-2 trial, both FDA and EMA extended the approval of everolimus (Afinitor®) to the treatment of HR-positive, HER2-negative advanced BC, in combination with exemestane, in postmenopausal women after recurrence or progression following a non-steroidal aromatase inhibitor as a new indication [2, 7].

PFS increase by about 4 months in HR-positive HER2-negative postmenopausal women

This phase III trial compared everolimus in combination with exemestane versus placebo plus exemestane in postmenopausal women with ER-positive and HER2-negative advanced BC. As the study is expected to be completed in June 2014, only results from the preplanned interim analysis and some updated results have been published until now. PFS, as determined by the local investigators, was the primary endpoint of this study. So far, analyses have shown a statistically significant absolute gain in PFS of 4 months for patients treated with everolimus. Supportive secondary analyses centrally assessed by an independent radiology committee but based on fewer events resulted in even longer PFS. Also, in all analyses the ORR was significantly higher in favour of the everolimus-exemestane group, almost all of these being partial responses.

more AEs in the everolimus group, most common stomatitis, anaemia, hyperglycaemia, dyspnoea, and pneumonitis

Overall AEs occurred more often in the everolimus group. This held also true for SAEs (23% vs. 12%) and AEs of grade 3 or 4 with clearly more patients in the intervention group suffering from stomatitis, anaemia, hyperglycaemia, dyspnoea, and pneumonitis. Consequently AEs leading to a discontinuation of the whole study treatment were more frequent in this group (8% vs. 3%). These proportions were even higher when it comes to the discontinuation of everolimus or placebo alone (19% vs. 4%).

questions still remaining to be answered:

no published results on OS yet,

QoL unclear

Despite the results of the BOLERO-2 trial some issues on everolimus as a treatment option for postmenopausal women with locally advanced or metastatic BC still remain unanswered. For instance, although fewer deaths were noted in the intervention group, information regarding the statistical significance is missing. Because data on OS was immature, the final analysis has to show whether longer PFS and fewer deaths in the everolimus group still translate into a statistically beneficial OS. Moreover, improving QoL is an important aim for any therapy of advanced BC. In the BOLERO-2 trial, QoL results were different depending on the time of analysis. Only for the 18 months follow-up recently published in a conference poster [41] a statistically significant benefit for everolimus was shown. As results are inconsistent, the final analysis has to proof the potential benefit.

everolimus monotherapy

appropriate comparators

In addition, BOLERO-2 does not address the question on safety and efficacy of everolimus alone in comparison to everolimus in combination with aromatase inhibitors or in comparison to chemotherapy, the preferred regimen for women with more aggressive tumours (i.e. with symptomatic visceral disease). The EMA has therefore, and in contrast to the FDA, restricted the indication to patients without visceral involvement. Furthermore, efficacy of everolimus in HER2-*positive* BC has not been evaluated yet, but is currently being tested in two phase III trials (BOLERO-1, BOLERO-3).

Due to the post marketing commitments between the manufacturer and the FDA answers to some of these questions can be expected in the near future [7]. These include submission of final OS results to the authorities by June 2015 at the latest, but also the undertaking of a further RCT that will compare everolimus in combination with exemestane versus everolimus alone versus capecitabine in women with ER-positive metastatic BC after recurrence or progression on letrozole or anastrozole (BOLERO-6). The completion of this study is scheduled for August 2016.

post marketing commitments:

final results

further 3-arm RCT

In summary, the interim results of the BOLERO-2 study indicate that everolimus in combination with exemestane can extend PFS when compared to exemestane alone. Overall, fewer women died in the everolimus group although there was a higher rate of adverse events, serious adverse events and on-treatment deaths. Final data on QoL and the OS can be expected in 2015. These as well as the results of the upcoming BOLERO-6 trial will be helpful in deciding on the use of everolimus for the therapy in postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic BC.

References

1. National Horizon Scanning Centre (NHSC). *Everolimus (Afinitor) in combination with exemestane for oestrogen receptor-positive, HER2-negative locally advanced or metastatic breast cancer*. 2011 2012 10.August]; Available from: http://www.nhsc-healthhorizons.org.uk/files/downloads/1552/2011.eabcb48a.EverolimusAfinitor_BreastCancer.pdf.
2. European Medicines Agency (EMA). *Afinitor: EPAR - Product Information* 2012 07.August 2012 10.August]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001038/WC500022814.pdf.
3. U.S. Food and Drug Administration (FDA). *Drugs@FDA - Afinitor; Summary Review*. 2009 2012 10.August]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022334s000_SumR.pdf.
4. U.S. Food and Drug Administration (FDA). *Drugs@FDA - Afinitor; Label Information*. 2012 2012 10.August]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s016lbl.pdf.
5. European Medicines Agency (EMA). *Votubia: EPAR - Product Information* 2012 10.July 2012 10.August]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002311/WC500112238.pdf.
6. European Medicines Agency (EMA). *Committee for Medicinal Products for Human Use (CHMP) - Summary of opinion for Afinitor*. 2012 21.June 2012 10.August]; Available from: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129092.
7. U.S. Food and Drug Administration (FDA). *Drugs@FDA - Afinitor; Supplemental Approval*. 2012 20.July 2012 10.August]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022334Orig1s016ltrRepl.pdf.
8. Zielonke, N. *Krebsinzidenz und Krebsmortalität in Österreich*. 2012 2012 10.August]; Available from: http://www.statistik.at/web_de/static/krebsinzidenz_und_krebsmortalitaet_in_oesterreich_2012_065928.pdf.
9. Statistik Austria. *Brust (C50) - Krebsmortalität, Jahresdurchschnitt (2007/2009)*. 2012 2012 10.August]; Available from: http://www.statistik.at/web_de/static/brust_c50_-_krebsmortalitaet_nach_bundeslaendern_jahresdurchschnitt_200720_021699.pdf.
10. Leitner, B. *Jahrbuch der Gesundheitsstatistik 2010*. 2011 2012 10.August]; Available from: http://www.statistik.at/web_de/Redirect/index.htm?dDocName=059824.
11. Howlader, N., et al. *SEER Cancer Statistics Review 1975-2009*. 2011 2012 10.August]; Available from: http://seer.cancer.gov/csr/1975_2009_pops09/results_merged/sect_04_breast.pdf.
12. National Cancer Institute. *Breast Cancer Treatment (PDQ®) - Genetic Characteristics and Risk Factors*. 2012 2012 10.August]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional#Section_551.

13. National Cancer Institute. *Breast Cancer Treatment (PDQ®) - Stage Information for Breast Cancer*. 2012 2012 10.August]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/page3.
14. Edge, S., D. Byrd, and C. Compton, *Breast*, in *AJCC Cancer Staging Manual*. 2010, Springer: New York. p. 347-76.
15. Statistik Austria. *Brust (C50) - Krebsinzidenz nach Stadium, Jahresdurchschnitt (2007/2009)*. 2012 2012 10.August]; Available from: http://www.statistik.at/web_de/static/brust_c50_-_krebsinzidenz_nach_stadium_jahresdurchschnitt_20072009_021700.pdf
16. Statistik Austria. *Überlebesrate von Krebserkrankten in Österreich von 1985 bis 2009*. 2012 2012 20.August]; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/ueberleben_mit_krebs/index.html.
17. Hayes, D. *Systemic treatment for metastatic breast cancer: General principles*. 2012 2012 10.August]; Available from: http://www.uptodate.com/contents/systemic-treatment-for-metastatic-breast-cancer-general-principles.
18. Giordano, S.H., *Update on locally advanced breast cancer.* Oncologist, 2003. **8**(6): p. 521-30.
19. Dobrescu, A., et al., *Study of Estrogen Receptor and Progesterone Receptor Expression in Breast Ductal Carcinoma In Situ by Immunohistochemical Staining in ER/PgR-Negative Invasive Breast Cancer.* ISRN Oncol, 2011. **2011**: p. 673790.
20. National Cancer Institute. *What You Need to Know About Advanced Breast Cancer*. 2009 2012 10.August]; Available from: http://www.cancer.gov/cancertopics/wyntk/breast/WYNTK_breast.pdf.
21. National Cancer Institute. *Breast Cancer Treatment (PDQ®) - Prognostic and Predictive Factors*. 2012 2012 10.August]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional#Section_639.
22. National Comprehensive Cancer Network (NCCN). *Practice Guidelines in Oncology, Breast Cancer*. 2012 2012 10.August]; 2.2012:[Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
23. Taghian, A. *Clinical features and management of locally advanced breast cancer*. 2012 2012 10.August]; Available from: http://www.uptodate.com/contents/clinical-features-and-management-of-locally-advanced-breast-cancer?view=print.
24. National Institute for Health and Clinical Excellence (NICE). *NICE guideline CG81 - Advanced breast cancer: diagnosis and treatment*. 2009 2012 10.August]; Available from: http://guidance.nice.org.uk/CG81/Guidance/pdf/English.
25. Pritchard, K. *Adjuvant endocrine therapy for postmenopausal women with early stage breast cancer*. 2012 2012 10.August]; Available from: http://www.uptodate.com/contents/adjuvant-endocrine-therapy-for-postmenopausal-women-with-early-stage-breast-cancer?view=print.
26. Massarweh, S. and R. Schiff, *Resistance to endocrine therapy in breast cancer: exploiting estrogen receptor/growth factor signaling crosstalk.* Endocr Relat Cancer, 2006. **13 Suppl 1**: p. S15-24.

27. Yamauchi, H. *HER2 and predicting response to therapy in breast cancer* 2012 2012 27.August]; Available from: http://www.uptodate.com/contents/her2-and-predicting-response-to-therapy-in-breast-cancer.
28. Harris, L., et al., *American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer.* J Clin Oncol, 2007. **25**(33): p. 5287-312.
29. National Cancer Institute. *Breast Cancer Treatment (PDQ®) - Stage IIIB, Inoperable IIIC, IV, Recurrent, and Metastatic Breast Cancer.* 2012 2012 10.August]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/page7.
30. National Cancer Institute. *Breast Cancer Treatment (PDQ®) - Stage I, II, IIIA, and Operable IIIC Breast Cancer.* 2012 2012 10.August]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/page6.
31. Gnant, M., *Late Breaking Abstracts EBCC8 - European Breast Cancer Conference 2012.* European Journal of Cancer, 2012. **48**.
32. Baselga, J., et al., *Everolimus in combination with exemestane for postmenopausal women with advanced breast cancer who are refractory to letrozole or anastrozole: Results of the BOLERO-2 phase III trial.* European Journal of Cancer, 2011. **47**: p. 6-7.
33. Campone, M., et al., *Bolero-2: Everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor-positive advanced breast cancer refractory to letrozole or anastrozole.* Breast, 2011. **20**: p. S30.
34. Kasprowicz, N., et al., *Evaluation of RAD001 (everolimus) in the setting of resistance to letrozole or anastrozole in postmenopausal ER-positive breast cancer patients: BOLERO-2 trial.* Archives of Gynecology and Obstetrics, 2010. **282**: p. S126.
35. Baselga, J., et al., *Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.* New England Journal of Medicine, 2012. **366**(6): p. 520-9.
36. Beaver, J.A. and B.H. Park, *The BOLERO-2 trial: the addition of everolimus to exemestane in the treatment of postmenopausal hormone receptor-positive advanced breast cancer.* Future Oncology, 2012. **8**(6): p. 651-7.
37. Rugo, H., et al., *Everolimus (EVE) for postmenopausal women with advanced breast cancer (ABC) refractory to letrozole or anastrozole: Long-term efficacy and safety results of the bolero-2 trial.* European Journal of Cancer, 2012. **48**: p. S116.
38. Rugo, H., et al., *Updated results of the BOLERO-2 phase III trial evaluating Everolimus (EVE) for postmenopausal women with advanced breast cancer (ABC).* Annals of Oncology, 2012. **23**(Supplement 2): p. 46.
39. Hortobagyi, G.N., et al., *Everolimus for Postmenopausal Women with Advanced Breast Cancer: Updated Results of the BOLERO-2 Phase III Trial.* Cancer Research, 2011. **71**(24 Supplement): p. 105.
40. Massarweh, S., J. Croley, and H. Weiss, *Everolimus in HR-Positive Advanced Breast Cancer.* New England Journal of Medicine, 2012. **366**(18): p. 1738.

41. Beck, J.T., H.S. Rugo, and H.A. Burris, *BOLERO-2: Health-Related Quality-of-Life in Metastatic Breast Cancer Patients Treated With Everolimus and Exemestane Versus Exemestane.* ASCO Annual Meeting, 2012. **abstract # 539**.
42. Piccart, M., et al., *Everolimus for Postmenopausal Women With Advanced Breast Cancer: Updated Results of the BOLERO-2 Phase III Trial.* ASCO Annual Meeting, 2012. **abstract # 559**.
43. Gnant, M., J. Baselga, and H. Rugo, *Effects of Everolimus on Disease Progression in Bone and Bone Markers in Patients With Bone Metastases.* ASCO Annual Meeting, 2012. **abstract # 512**.
44. Noguchi, S., N. Masuda, and Y. Ito, *BOLERO-2: Everolimus With Exemestane Versus Exemestane Alone in Asian Patients With HER2-Negative, Hormone-Receptor–Positive Breast Cancer.* ASCO Annual Meeting, 2012. **abstract # 540**.
45. Pritchard, K., H. Burris, and H. Rugo, *Safety of Everolimus for Women Over 65 Years of Age With Advanced Breast Cancer (BC): 18-Month Follow-up of BOLERO-2.* ASCO Annual Meeting, 2012. **abstract # 551**.
46. Novartis Oncology, *Afinitor Infofolder*. 2009.
47. Anstaltsapotheke LKI-Universitätskliniken Innsbruck, 2012.