PATIENT EVALUATION FLOW SHEET

Visits	**Screening Visit**	**Randomization Visit**	**Control Visits**	**Conclusion Visit of Randomized Treatment Period**	**Follow-up Assessments**
Time	≤ 21 days prior to end of Randomization Visit	≤ 21 days after Screening Visit	q 3 or 4 weeks depending on standard treatment	12 months after first dose or at premature termination of protocol treatment (eg if PD)	2 to 4 weeks after Conclusion Visit, then q 3 months
Periods	**Pre-Treatment Evaluation Period**		**Randomized Treatment Period**		**Follow-Up Period**
Informed consent - part 1 in blood sampling for CTC count and HER2 status on CTC[1]	X				
Informed consent - part 2 in study participation[1]		X			
Informed consent - part 3 in blood sampling for translational medical investigations[1,2]		X			
Allocation of the patient identification number	X				
Demography (YOB)*	X				
Date of primary tumor diagnosis*	X				
Information on primary breast cancer (TNM*, histology*, grading*, localisation**, surgery**)	X				
Information on metastases (date of diagnosis*, localization*, surgery**)	X				
HER2 status on primary tumor tissue and/or biopsies from metastatic sites	X				
Hormone receptor status on primary tumor tissue and/or biopsies from metastatic sites*	X				
Adjuvant/Neoadjuvant Therapy**	X				
Number of prior chemotherapy lines for metastatic disease*, type of therapies for metastatic disease**	X				
Blood sampling for CTC count and assessment of HER2 status on CTC	X[5] *Screening Kit*		X *Analysis Kit* Only at visits scheduled every 8-12 weeks[20] after 1st dose or at premature discontinuation of protocol treatment (eg if PD)		
Blood sampling for translational medical investigations	X[6] (part of Screening Kit)	X *Analysis Kit*			
Patient height + weight		X			
Medical/surgical history		X			
Concomitant diseases		X			
Ongoing toxicities attributed to prior anticancer therapies[3]		X			
Hormone receptor status in solid tumor tissue[4]	X				
Prior anticancer medication, other relevant		X			

Visits	Screening Visit	Randomization Visit	Control Visits	Conclusion Visit of Randomized Treatment Period	Follow-up Assessments
prior medication					
Concomitant medication		X	X	X	X
Documentation of and check for compatibility of planned standard chemo- or endocrine therapy with lapatinib		X[17]			
Protocol treatment (standard chemo- or endocrine therapy +/-lapatinib)		X[18]	X	X[19]	
Vital signs (heart rate, blood pressure, temperature)		X	X	X	
Physical examination		X	X	X	
Adverse Events		X	X	X	X
Hematology[7]		X[9]	X	X	
Biochemistry[8]		X[9]	X	X	
Coagulation parameters[15]		X[9]			
Serum or urine pregnancy test		X[9]			
Tumor evaluation according to RECIST guidelines (version 1.1) (see protocol section 10.2.1.)		X[16]	X[11]		
Tumor markers[21]		X	X		
12-lead ECG		X[10]			
UCG (including LVEF assessment)		X[10]	X[14]	X	
Quality of life (EORTC QLQ-C30 and -BR23)		X[13]	X	X	
Intensity of pain (NRS)		X	X	X	
Review of inclusion and exclusion criteria		X			
Randomization		X			
Application of denosumab			X[22]		
Dispense of lapatinib		X			
Additional supply of lapatinib if necessary			X		
Tablet count			X	X	
Collection of unused lapatinib				X	
Reminding the patient of the follow-up procedures planned				X	
Survival			X	X	X

[1]Cf. section 16.4

[2] Patient may participate in the study if this consent was not granted. However, in this case body material must not be sampled for the purpose of translational medical investigations

[3] Cf. section 11.1

[4] Estrogen and progesterone status each graded positive or negative

[5] Results must be obtained prior randomization visit. Blood sampling for CTC count and assessment of their HER2 status should be scheduled at least one week after last application of investigational agents of any type or anticancer therapy.

[6] If applicable: additional blood sampling in patients who consent to participate in translational research (part of patient information and consent form – part 1). If a patient objects to blood sampling for this purpose, she may nevertheless participate in the study.

[7] Must include: hemoglobin, hematocrit, red blood cell count, differential white blood cell count, platelet count

[8] Must include: total and direct bilirubin, ALT, AST, alkaline phosphatase, albumin, serum creatinine, BUN or urea, glucose, sodium, potassium, calcium

[9] Results obtained within the preceding 7 days may be employed

[10] Results obtained within the 3 preceding weeks may be employed
[11] Every 8 to 12 weeks after initiation of palliative treatment based on the individual treatment schedule or if medically indicated. In case of endocrine treatment therapy response evaluation should be performed every 3 months or if medically indicated. Treatment response evaluation should be performed together with the determination of CTCs
[12] The same method should be used on every assessment
[13] Results obtained within the preceding week may be employed
[14] Only if medically indicated
[15] Must include: INR and PTT or aPTT
[16] Results obtained within the 6 preceding weeks may be employed
[17] No administration of therapy, but documentation of planned standard therapy and check whether combination with lapatinib is either approved (see SPC of Tyverb® 250 mg tablets) or has been investigated in prior clinical trials.
[18] Initiation of protocol treatment, i.e. standard therapy +/- lapatinib within one week after randomization
[19] Documentation of end of protocol treatment (standard therapy +/-lapatinib therapy) and documentation of planned therapy after end of protocol treatment
[20] In case of endocrine treatment therapy CTC count should be performed every 3 months. Generally treatment response evaluation should be performed together with the determination of CTCs.
[21] Tumor markers are assessed on each tumor evaluation: CA15-3 is mandatory, CA125 and CEA are optional
[22] Only in Patients with bone metastases: Xgeva®120 mg s.c. q4w; Administer calcium (at least 500 mg p.o. daily) and vitamin D (at least 400 I.E. p.o. daily) to treat or prevent hypocalcemia.

*Data must be obtained before screening
**Patients may be screened without obtaining this additional information. Documentation of these data will be reimbursed additionally.