

Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation

### CASE REPORT FORM

Protocol number BIG 1-06 / EGF 106903

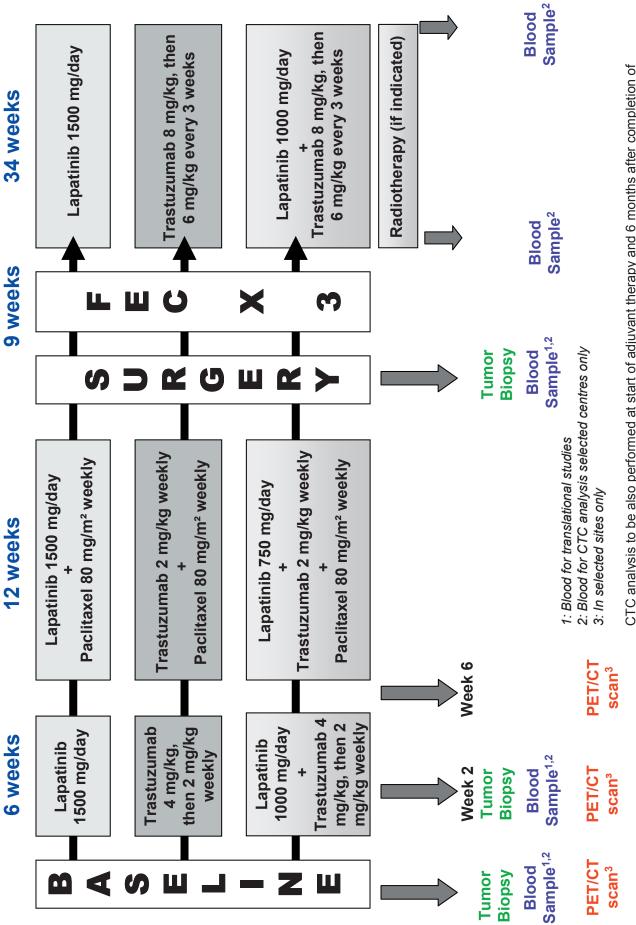
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### Case Report Form (CRF) index and timelines for completion and faxing

Form	Page	Completion and faxing timelines
Advice to the investigator	, 490	Completion and lexing unleaded
Schedule of assessments		
Study design		
Screening (see also page 170)	1-18	Within 2 weeks from visit
Week 2	19-23	Within 2 weeks from visit
Week 4 (see also page 171)	24-25	Within 2 weeks from visit
Week 6 (see also page 171)	26-31	Within 2 weeks from visit
Weeks 8-9	32	Within 2 weeks from visit
Week 10 (see also page 173)	33-34	Within 2 weeks from visit
Weeks 11-12	35	Within 2 weeks from visit
Week 13 (see also page 174)	36-37	Within 2 weeks from visit
Weeks 14-15	38	Within 2 weeks from visit
Week 16 (see also page 175)	39-40	Within 2 weeks from visit
Weeks 17-18	41	Within 2 weeks from visit
Pre-surgery visit (see also page 176)	42-44	Within 2 weeks from visit
Surgery	45-48	Within 2 weeks from surgery completion
Neo-adjuvant treatment completion	49-50	Within 2 weeks from neo-adjuvant treatment completion
Week 1 - Day 1 FEC cycle 1 (see also page 177)	51	Within 2 weeks from visit
Week 4 - Day 1 FEC cycle 2 (see also page 178)	52	Within 2 weeks from visit
Week 7 - Day 1 FEC cycle 3 (see also page 179)	53	Within 2 weeks from visit
Week 10 - Week 1 of targeted therapy (see also page 180)	54-55	Within 2 weeks from visit
Week 16 - Week 7 of targeted therapy	181	Within 2 weeks from visit
Week 22 - Week 13 of targeted therapy-FU M3 (see also page 182)	56-57	Within 2 weeks from visit
Week 28 - Week 19 of targeted therapy	183	Within 2 weeks from visit
Week 34 - Week 25 of targeted therapy-FU M6 (see also page 184)	58-59	Within 2 weeks from visit
Week 40 - Week 31 of targeted therapy-FU M3	185	Within 2 weeks from visit
Week 43 - Week 34 of targeted therapy-FU M9 (see also page 186)	60-62	Within 2 weeks from visit
Follow-up Month 12 (see also page 187)	63-66	Within 2 weeks from visit
Follow-up Month 15 (see also page 188)	67	Within 2 weeks from visit
Follow-up Month 18 (see also page 189)	68-69	Within 2 weeks from visit
Follow-up Month 21	70	Within 2 weeks from visit
Follow-up Month 24 (see also page 190)	71-74	Within 2 weeks from visit
Follow-up Month 30	75	Within 2 weeks from visit
Follow-up Month 36 (see also page 191)	76-79	Within 2 weeks from visit
Follow-up Month 42	80	Within 2 weeks from visit
Follow-up Month 48 (see also page 192)	81-84	Within 2 weeks from visit
Follow-up Month 54	85	Within 2 weeks from visit
Follow-up Month 60 (see also page 193)	86-89	Within 2 weeks from visit
Follow-up Year 6 (see also page 194)	90-93	Within 2 weeks from visit
Follow-up Year 7 (see also page 195)	94-97	Within 2 weeks from visit
Follow-up Year 8 (see also page 196)	98-101	Within 2 weeks from visit
Follow-up Year 9 (see also page 197)	102-105	Within 2 weeks from visit
Follow-up Year 10 (see also page 198)	106-109	Within 2 weeks from visit

### Case Report Form (CRF) index and timelines for completion and faxing (Cont.)

Form	Page	Completion and faxing timelines
Hormonotherapy	110	Within 2 weeks from treatment start
Radiotherapy	111	Within 2 weeks from radiotherapy treatment completion
Concomitant treatments	112-114	Any time a new treatment is started
Administration of study drug: Paclitaxel	115-116	Within 2 weeks from start and within 2 weeks from treatment completion
FEC adjuvant treatment	117-118	Within 2 weeks from start and within 2 weeks from treatment completion
Administration of study drug: Lapatinib	119	Within 2 weeks from starting lapatinib and each time there is change in dose or an interruption and within 1 week of treatment completion
Investigational product compliance	120	Within 2 weeks from treatment completion
Administration of study drug: Trastuzumab	121-125	Within 2 weeks from starting treatment, then every 12 weeks and within 1 week of treatment completion
Adverse event	126-132	Within 1 week from each AE start
Unscheduled EKG	133-134	Within 2 weeks of each assessment
Unscheduled LVEF	135-137	Within 2 weeks of each assessment
Unscheduled radiological exams	138-142	Within 2 weeks of each assessment
Adjuvant Treatment completion	143	Within 1 week from study treatment completion
Adjuvant Treatment completion (comments and signature page)	144	Every time a new comment is reported.  NOTE: the date and signature should be added <u>only</u> after request from data management
Recurrence of disease: local/regional	145	Within 1 week from occurrence
Recurrence of disease: distant	146	Within 1 week from occurrence
Second primary malignancy and CBC	147	Within 1 week from occurrence
Post event treatments	148-149	Within 2 weeks from start and within 2 weeks from completion
Additional comments	150	Every time a new comment is reported after the collection of page 144
Survival follow up	151-165	Yearly starting from 1 year after recurrence of disease. Within 2 weeks from visit
Death	166	Within 1 week from occurrence
Additional signature page	167-169	Upon request from data management
Liver function tests (scheduled visits)	170-198	Within 2 weeks from visit
Unscheduled liver function tests	199-204	Within 2 weeks of each assessment



CTC analysis to be also performed at start of adjuvant therapy and 6 months after completion of adjuvant therapy (W1 and Month15 FU), and at relapse

### Advice to the investigator on the completion of a Case Report Form (CRF)

### **Completion of questions**

- Please write legibly, only use **black** ink.
- All <u>text</u> and explanatory comments should be <u>brief</u>, in <u>English</u> and, if possible in <u>CAPITAL</u> letters.
- All dates should be in the format dd/mmm/yyyy, example: 12FEB2008 (see the list of month abbreviations on the right)
- Answer every question clearly, do not use ditto marks/commas (").
- Only enter results in the fields provided.
- If the answer is zero, do not leave the field blank; write '0'.
- If the answer to a question is unknown, or not available, write 'not known' or 'NK'.
- If a requested test has not been done, write 'not done' or 'ND'.
- If a question is not applicable, write 'not applicable' or 'NA'.
- Avoid abbreviations other than the above

Month #	Abb
1	JAN
2	FEB
3	MAR
4	APR
5	MAY
6	JUN
7	JUL
8	AUG
9	SEP
10	OCT
11	NOV
12	DEC

### **Additional pages**

An additional page is a copy of a numbered CRF page which is used to carry over data that cannot be entered on the original page, for example due to lack of space.

To create an additional page photocopy the relevant page that requires more data from the unbarcoded CRF in the Investigator File, write the Centre no. and Subject no. on the top of the page and please, be careful to number such pages correctly with a "-" and a sequential number after the printed page number, as shown in the examples on the right.

112-1 112-2

### **Correction of errors**

If an error occurs please correct in the following way:

① Cross through with a single straight line

② 2 2/A P R/2 0 0 7 ① |1.8|A,P,R|2,0,0,7|

Write the correct value above or to the side
 Initial and date the correction. In case of error in a date

Initial and date the correction. In case of error in a date, please make sure that we can clearly distinguish the date of correction from the corrected date

Please do not use White-out.

### Completion and sign-off of a CRF

A CRF should be completed for every randomised patient participating in the trial, including those who do not complete the trial.

A CRF should not be completed for screen failures.

Completion and sign off of a CRF should only be done after request from data management.

Only authorized investigators can sign a CRF.

For reasons of patient confidentiality, names or initials of patients must not appear on a CRF or on any other document.

### Schedule of assessments

Follow-up starting point is day 1 of adjuvant biological targeted therapy or date of surgery for patients who don't receive biological therapy for any reason.

A		Within 2				-	PRIOR	TO S	PRIOR TO SURGERY	۲										ADJU	ADJUVANT TREATMENT	EATME	۲		
Table   Tabl		weeks prior to																		FOL	LOW-UP	PERIO	0		
*** *** *** *** *** *** *** *** *** **		rando- misation													>	VEEK	S								
*** Section 1						NEO	-ADJU	VANT	TREA <sup>-</sup>	MENT				Su	RGERY		=EC				TAR	GETED	THERAP		
			2 Day 14	4 Day 28	6 Day 42		o	10		73					.0-22	- 2	4 C2	C3		16 W7	22 W13 FU M3	28 W19	34 W25 FU M6	40 W31	43 W34 FU M9^^
X	Informed consent	×							_																
x x x x x x x x x x x x x x x x x x x	Physical examination†† - Weight - Menstrual status/Pregn. Test**	**	×	×	×			×		×		×				×	×	×	×		×		×		×
X X X X X X X X X X X X X X X X X X X	Medical History	×																							
x	Vital signs	×	×	×	×			×		×		×			×	×	×	×	×		×		×		×
	Performance Status	×	×	×	×			×		×		×			×	×	×	×	×		×		×		×
	ErbB2 status	×																							
	ER/PgR expression	×																							
X       X	Breast palpation with tumor measurements and nodal status	×	×	×	*			×		×		×			×										
x x x x x x x x x x x x x x x x x x x	Prior/Concomitant medication	×	×	×	×			×		×		×			×	×	×	×	×		×		×		×
	Bilateral Mammography	×			××										×										
x       x	Bilateral breast echography	**×			**×										**×										
x       x	Chest X-ray or CT scan	×																							
x x x x x x x x x x x x x x x x x x x	Haematology	×		×	×	×		$\vdash$				-	×	×	×	×	×	×	×		×		×		×
x         x           x         x	Blood chemistry	×		×	×			×		×		×			×	×	×	×	×	×	×	×	×	×	×
x	Cardiac Monitoring - LVEF - FCG	××			×										×				×		×		×		×
value         X***         X†         X           Study         Xs         X         X           Xs         X         X         X           Xs         X         X         X           Ned         X         X         X	- Signs and symptoms	×			×										×				×		×		×		×
study Xs Xt Xtt Xtt Xtt Xtt Xtt Xtt Xtt Xtt X	Tumor biopsy for translational studies	***	×												×										
study Xs X X X X X X X X X X X X X X X X X X	PET (selected centres)	Xs	#		##						-														
x x x x pel	Blood collection for translational study	Xs	×												×										
x x x peu	Blood PGx	Xs							-		$\perp$			<u> </u>			T								
×	Blood sample for CTC (selected centres)	Xs	×												×				×						
	Feasibility / type of surgery planned	×																							
	Type of surgery performed														×										
AE and SAE (NCI-CTCAE) X X	AE and SAE (NCI-CTCAE)	×														×									

1 On day 14 Σ ε αιτεί μεσαιπείτη Απτεί surgery physical examination includes πιοίαχ wail and axilia assessment. Twitnin 3 days prior to the first infusion of pacifiaxel;
\*\* Only for women of childbearing potential; \*\*\* tumor biopsy for translational studies can be up to 4 weeks prior to randomisation; ^ Of the breast containing tumor only; ^APlease note that the 9 months FU visit will be done at week 34 of targeted therapy; # If applicable only; s To be performed after randomisation only; ‡ Prior to 2 weeks biopsy; ‡‡ Prior to paclitaxel administration

# Schedule of assessments (Continued)

Follow-up starting point is day 1 of adjuvant biological targeted therapy or date of surgery for patients who don't receive biological therapy for any reason.

						F	FOLLOW-UP	-UP					
					_	MONTHS	S S					YEARS	
	12	15	18	21	24	30	36	42	48	24	09	6 to 10	
Physical examination - Vital signs - Weight - Performance Status	×	×	×	×	×	×	×	×	×	×	×	×	
Haematology	×		×		×		×		×		×	×	
Blood chemistry	×	×	×		×		×		×		×	×	
Radiologic Exam:	;								3		Ş		
Chest X-ray/CT Scan	8				8		8		8		8	8	
Bone scan / X-ray Bilateral Mammography	×				×.		×(×		€×		×(×	×(×	
Liver imaging	8				8		8		8		8	8	
Concomitant medication	×	×	×	×	×	×	×	×	×	×	×		
Cardiac Monitoring	;		;		;		;		;		;	;	
LVEF 1770°	× >		× >		× >		× >		× >		× >	××	
- ENG Signs and exemptoms	< >		< >		< >		< >		< >		< >	< >	
	<	>	<		<		<		<		<	<	Т
(selected centres)		<											
AE and SAE (NCI-CTCAE)							×						Т
/- :													7

<sup>a</sup> Plain films (CT scan or MRI in case of vertebral abnormalities) are required to exclude metastatic disease if a bone scan is positive <sup>b</sup> Unilateral for patients with mastectomy <sup>c</sup> To be performed at any time if symptoms or clinical suspicion are present <sup>d</sup> See section 9.1.2 for requirements and timeframes on AE and SAEs reporting

## Study design: treatment schedule

Treatment schedule

Neoadjuvant Treatment (weeks)
17 18
Surgery
Lapatinib + Trastuzumab
As above color indication + weekly Paclitaxel

 $\boxed{2}$  Visit weeks

N FEC

Pro	otocol number BIG 1-06 / EGF106903	reeni	ing	J
	Centre No. Subject No.	Page 1		
		YES	NC	)
Eli	gibility screening form	0		
Inc	lusion criteria (Note that if any box is marked "NO", the patient is not eligible for enrollment.)			
1.	Female gender			
2.	Age ≥ 18 years			
3.	Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1;			
4.	Histologically confirmed invasive breast cancer:			
	<ul> <li>Primary tumor greater than 2 cm diameter, measured by clinical examination and mammography or echography;</li> </ul>			
	- Any N,			
	- No evidence of metastasis (M0) (isolated supraclavicular node involvement allowed);			
5.	Overexpression and/or amplification of HER2 in the invasive component of the primary tumor according to one of the following definitions and confirmed by certified laboratory before randomisation:			
	<ul><li>- 3+ over expression by IHC (&gt; 30% of invasive tumor cells);</li></ul>			
	<ul> <li>2+ or 3+ (in 30% or less neoplastic cells) over expression by IHC AND in situ hybridization (FISH/CISH) test demonstrating HER2 gene amplification;</li> </ul>			
	<ul> <li>HER2 gene amplification by FISH/CISH ( &gt; 6 HER2 gene copies per nucleus, or a FISH ratio [HER2 gene copies to chromosome 17 signals] of &gt; than 2.2.).</li> </ul>	)		
	Equivocal local results may be submitted for a final determination by the certified laboratory			
6.	Hormone receptor (HR) status:			
	- Oestrogen Receptor (ER) status must be known			
	- Progesterone (PR) status must be known			
7.	Haematopoietic status:			
	- Absolute Neutrophil count ≥ 1.5 x 10 <sup>9</sup> /L,			
	- Platelet count ≥ 100 x 10 <sup>9</sup> /L,			
	- Hemoglobin at least 9 g/dL			
8.	Hepatic status:			
	- Bilirubin $\leq$ 1.5 x upper limit of normal (ULN). In the case of known Gilbert's syndrome, a high serum total bilirubin (< 2 X ULN) is allowed,	er 🔲		
	- AST and ALT ≤ 2.5 times ULN,			
	- Alkaline phosphatase ≤ 2.5 times ULN,			
9.	Renal Status:			
	- Creatinine ≤ 2.0 mg/dL,			
10.	Baseline LVEF $\geq$ 50% measured by echocardiography (ECHO) or Multiple Gate Acquisition (MUGA) scan,			NΙΛ
11.	Negative serum pregnancy test, within 2-weeks (preferably 7 days) prior to randomisation (Forword of childbearing potential);			NA
				I



Pro	otocol number BIG 1-06 / EGF106903	ree	nin	ıg
	Centre No. Subject No.	Page	2	
		YES	NO	N
12.	Fertile patients must use effective contraception (barrier method - condoms, diaphragm - also in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not allowed);			
13.	Signed written informed consent (approved by an Independent Ethics Committee [IEC] and obtained prior to any study specific screening procedures);			
14.	Patient accepts to make available tumors samples for submission to central laboratory to conduct translational studies as part of this protocol			
Ex	clusion criteria (Note that if any box is marked "YES", the patient is not eligible for enrollment.)			
1.	Received any prior treatment for primary invasive breast cancer;			
2.	Previous (less than 10 years) or current history of malignant neoplasms. However, subjects with a past or current history of completely resected basal and squamous cell carcinoma of the skin or successfully treated in situ carcinoma of the cervix are eligible*;			
3.	Diagnosis of inflammatory breast cancer;			
4.	Bilateral cancer;			
5.	This exclusion criterion has been removed as of protocol amendment 1;			
6.	Known history of uncontrolled or symptomatic angina, clinically significant arrhythmias, congestive heart failure, transmural myocardial infarction, uncontrolled hypertension (≥ 180/110), unstable diabetes mellitus, dyspnoea at rest, or chronic therapy with oxygen;			
7.	Concurrent disease or condition that would make the subject inappropriate for study participation or any serious medical disorder that would interfere with the subject's safety;			
8.	Unresolved or unstable, serious adverse events from prior administration of another investigational drug;			
9.	Active or uncontrolled infection;			
10.	Dementia, altered mental status, or any psychiatric condition that would prevent the understanding or rendering of ICF;			
11.	Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel. Subjects with ulcerative colitis are also excluded;			
12.	Concurrent neoadjuvant cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy other than the trial therapies);			
13.	Concurrent treatment with an investigational agent or participation in another therapeutic clinical trial;			
14.	Known immediate or delayed hypersensitivity reaction or idiosyncrasy or contraindication to drugs chemically related to any of the study treatment or their excipients;			
15.	Pregnant or lactating women;			
16.	Concomitant use of CYP3A4 inhibitors or inducers (see protocol section 7.2 for list of prohibited medications).			

Protocol number BIG 1-06 / EGF106903	Screening
Centre No. Subject No.	Page 3
Randomisation	
Date of randomisation DD MMM YYYY	
Assigned treatment arm  Lapatinib alone  Trastuzumab alone  Lapatinib in combination with Trastuzumab	
Informed consents	
Date informed consent signed  DD MMM YYYY	
	No Yes □ □
Participate in CTC analysis	
Participate in Pharmacogenetic research	
Date of birth  DD MMM YYYY	
Race	
American Indian or Alaska Native: a person having origins in any of the original peoples of North and South America (including Central America) and who maintains affiliation or community attachment	s tribal
☐ Asian: Central/South Asian Heritage - a person having origins in Central Asia (Kaza Kyrgystan, Tajikstan, Turkmenistan and Uzbekistan) and Indian Subcontinent (India Pakistan, Bangladesh and Sri Lanka)	
☐ Asian: East Asian Heritage - a person having origins in China, Korea	
<ul> <li>☐ Asian: Japanese Heritage - a person having origins in Japan</li> <li>☐ Asian: South East Asia Heritage - a person having origins in Malaysia, the Philippin</li> </ul>	nes,
Indonesia, Thailand, Vietnam, Laos, Burma or Cambodia  Black or African American/African Heritage: a person having origins in any of the	e black
racial group of Africa.	
■ Native Hawaiian or other Pacific Islander: a person having origins in any of the opeoples of Hawaii, Guam, Samoa or other Pacific Islands, Australia (Aborigines), P	
New Guinea, New Zealand, Marshalls and other island groups west and south of Jawhite: Arabic/North African Heritage - a person having origins in any of the original peoples of Middle East or North Africa.	apan
☐ White: White/Caucasian European Heritage - a person having origins in any of the	
original peoples of Europe  Other, specify:	
Ethnicity (only for North American sites)	
☐ Hispanic or Latino	

Protocol nui	nber BIG 1-	06 / EGF	1069	903						Sc	reenin
Centr	Centre No. Subject No.										Page 4
			'		•						
Menopausal	Status (chec	ck one)									
bilateral	pausal (<6 mo ovariectomy Al of premenopa	ND not on o	oestro	gen repl	acen	nent; OR bio	•	nical			
since las	opausal (prior t menstrual pe postmenopau	riod with no	prio	r hystere	ctom	y; OR bioch					
☐ Above ca	itegories not a	pplicable A	ND a	ge < 50							
☐ Above ca	itegories not a	pplicable A	ND a	ge >= 50							
Date of last r	nenstrual perio	od L	<u> </u>	I I MMM		I I I	J	and Ye	ar. If LN		more than
									s prior to at least		nisation,
Pregnancy t	est										
Date of pregi	nancy test	LI DI	 D	MMM		YYYY	]				
☐ Negative	→ Patient			tial)							
Has the patie	nt had:										
Hysterectomy	∕ □ No	☐ Yes	$\rightarrow$	☐ Total	or	☐ Partial		DD DD	MMM	Y	YYY
	ariectomy/oop	horectomy,									
specify side:	□No	☐ Yes	<b>→</b>	☐ Left	or	□ Right		DD DD	MMM	Y	YYY
	ariectomy/oopl										therapy
tor primary bi	east cancer", p	page 110, e	even i	т рептопт	еа в	erore diagn	OSIS (	or breas	st cance	r.	

### **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

### New York Heart Association (NYHA) Functional Classification

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Protocol number BIG 1-	06 / EGF106903 Screening	g
Centre No.	Subject No. Page 5	
Vital signs and physical	measurements	
Date of physical exam	□ Normal □ Abnormal - Not clinically significant □ Abnormal - Clinically significant □ Specify abnormality in "Previous	
Height (cm)	or current diseases" page 13	
Weight (Kg)		
Blood pressure	systolic / Lata mmHg	
Heart rate (beats/min)		
ECOG performance status		
EKG		
Date of EKG	DD MMM YYYY	
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Specify in "Previous or current cardiovascular diseases" page 12</li> </ul>	
LVEF	cardiovasculai diseases page 12	
Date of LVEF	DD MMM YYYY	
LVEF (patient value)		
Method of Evaluation	☐ Echocardiogram ☐ MUGA scan	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Specify in "Previous or current cardiovascular diseases" page 12</li> </ul>	
Symptomatic CHF	□ No □ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the question above) ☐ Class II ☐ Class IV	ı

Protocol number BIG 1-06 / EGF106903			Scr	eening
Centre No. Subject No.			F	Page 6
HER2/neu status Was local laboratory certified according to Neo-ALTT criteria?	O Pathologist Board	For IHC For FISH For CISH	□ No □ No □ No	☐ Yes ☐ Yes ☐ Yes
Results from Certified Local Lab or Central L (Please transcribe the data analysed by the local cert Lab requisition form")	•	ata as reporte	ed on the	"Central
Material ID number:				
Certified Immunohistochemistry (IHC) result Sample  Antibody used: DAKO Herceptest □ No □		MMM	YYYY	│ □ Not done
Result Positive Equivocal	Negative ☐ Not inte	erpretable		
Percentage of invasive tumor cells with complete	membrane staining (3+	) []		
Certified FISH result Sample test date DD r	MMM YYYY	☐ Not don	ie	
Kit or Test Type: ☐ Vysis/PathVysion ☐ ☐ Other:	│ Dako Probe   □ Ve ────	entana/Oncor	probe	
Fish Result ☐ Amplified (>2.2) ☐ Equivocal (	(≥1.8; ≤ 2.2) □ Not a	amplified (<1.	8) 🗆 Not	t interpretable
FISH Her2/neu Chromosome 17 ratio				
Chromosome 17 copy number	<ul><li>□ Not evaluated</li><li>□ Polysomy (3 or moderate)</li><li>□ Monosomy (60% of large)</li><li>□ Normal</li></ul>	_		
Certified CISH result Sample test date	MMM YYYY	☐ Not do	one	
Kit or Test Type:	☐ Zymed ☐ C	Other:		
CISH Result ☐ Amplified (>6 gene ☐ Equiv copies/nucleus)		ot amplified 4 copies)	□ Not in	nterpretable
Chromosome 17 copy number	☐ Not evaluated ☐ Polysomy (3 or moderal) ☐ Monosomy (60% of ☐ Normal)	_		
	Study: Ne	o-ALTTO v. 6	.0 (19Mar	 09)

Contro No. Subject No.	
Centre No. Subject No.	Page 7
HER2/neu status (Continued)	
Results from Non Certified Local Labs only	
If your lab was not certified, please provide below the local IHC assessment   No	ot done
Staining antibody   DAKO A0485I  NCL-c-erbB2-316  CB-11/Ventana Kit  Other, specify:  TAB-250	
IHC Result ☐ Positive ☐ Equivocal ☐ Negative	
Percentage of invasive tumor cells with complete membrane staining (3+)	
If your lab was not certified, please provide below the local FISH assessment   No	ot done
Kit or Test Type: ☐ Vysis/PathVysion ☐ Dako Probe ☐ Ventana/Oncorp	probe
Fish Result $\square$ Amplified (>2.2) $\square$ Equivocal ( $\ge$ 1.8; $\le$ 2.2) $\square$ Not amplified (<1.8)	☐ Not interpretable
FISH Her2/neu Chromosome 17 ratio	
Chromosome 17 copy number  ☐ Not evaluated ☐ Polysomy (3 or more signals in ≥ 30 ☐ Monosomy (60% of cells with 1 or n ☐ Normal	,
If your lab was not certified, please provide below the local CISH assessment □ No	ot done
Kit or Test Type: ☐ Ventana INFORM ☐ Zymed ☐ Other:	<del> </del>
CISH Result	☐ Not interpretable
Chromosome 17 copy number  ☐ Not evaluated ☐ Polysomy (3 or more signals in ≥ 30 ☐ Monosomy (60% of cells with 1 or r ☐ Normal	*

Protocol number BIG 1-06 / EGF10690	3 Screening
Centre No. Subject	t No. Page 8
History of primary breast cancer	
Date of initial pathological diagnosis*	DD MMM YYYY
Method of evaluation	☐ Fine Needle Aspiration ☐ Core biopsy
Tumor laterality	☐ Left ☐ Right
Clinical tumor size by calliper: MD (mm) X LPI	D (mm)**
<ul> <li>N2a (metastasis in ipsilater structures)</li> <li>N2b (metastasis only in clir absence of clinically e</li> <li>N3a (metastasis in ipsilater</li> </ul>	e ipsilateral axillary lymph nodes) ral axillary lymph nodes fixed to one another (matted) or to other nically apparent ipsilateral internal mammary nodes and in the vident axillary lymph node metastasis ral infraclavicular lymph nodes) ral internal mammary lymph nodes and axillary lymph node)
· · · · ·	gical, specify type of test:
Invasive histologic type (tick all that apply)	
☐ Lobular ☐ C ☐ Mixed ductal and lobular ☐ N ☐ Tubular ☐ In ☐ Apocrine ☐ N	Aicropapillary Cribriform Aucinous nvasive NOS Aedullary Other, specify:
* date when a sample allowing conclusive only be a biopsy (tru-cut or core biopsy of ** MD: maximal diameter, LPD: largest pe	e diagnosis of invasive carcinoma is taken, and this may or mammotome biopsy)

Protocol number BIG 1-06 / EGF10	6903	Screening
Centre No. Sub	oject No.	Page 9
History of primary breast cancer (Co	ontinued)	
Is carcinoma in situ present?	□ No □ Yes → □ DCIS □ LCIS □ Mixed DCIS and LCIS	
Is there lymphovascular invasion?	☐ No ☐ Yes ☐ Unknown	
Is Paget's disease of the nipple present?	□ No □ Yes	
Histologic Grade  Gx		
	□ No □ Yes → Are the different lesions showing (tice □ Same HER2 and ER/PgR status □ Different HER2 status □ Different ER status □ Different PgR status □ Other lesions were not assessed	

rotocol number BIG 1-06 / E	EGF106903			Screenin
Centre No.	Subject No	).		Page 10
istory of primary breast can	cer (continued)			
ocal Lab hormonal receptor status	,			
very effort should be made to obtospital.		esult of the I	normonal receptors, eve	en if done in another
_aboratory Name				
City			stal Code	
		1 0.	otal 00dc	<del> </del>
ER status	<ul><li>☐ Positive</li><li>☐ Negative</li></ul>			
	☐ Unknown			
s oestrogen receptor analysis res	sult available?			
□ No				
☐ Yes —> Specify be	elow			
fmol/mg protei	n L			
ER % cells stained positiv	e			
H-score (0-300	))			
Allred score (0-8	, I I			
Remmele score (0-12	, I I			
Othe		specify		( )
		op 00)	Method	Range
PgR status	☐ Positive			
	☐ Negative			
	☐ Unknown			
s progesterone receptor analysis	result available?			
□ No	Jan			
☐ Yes —> Specify be	1 1			
fmol/mg protei				
PgR % cells stained positiv	1 1			
H-score (0-300	))			
Allred score (0-8	3)			
Remmele score (0-12	2)			
Othe	er L	specify	Mothed	()
			Method	Range –
			Study: Neo-ALTTO v.	6.0 (19Mar09)

### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln 1500="" mm<sup="" –="">3 <lln 1.5="" 10<sup="" x="" –="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903	Screening
Centre No.	Subject No.	Page 11
Feasibility of surgery diagnosis (check one	and type of <u>planned</u> breast cancer surgery at the time	of initial
☐ Not operable →	Specify below	
	☐ Locally advanced	
	☐ T4a-c	
	☐ T4d → Patient is not eligible	
☐ Lumpectomy		
☐ Quadrantectomy / S	egmentectomy	
☐ Partial mastectomy		
☐ Modified radical mass	•	
☐ Radical mastectomy		
☐ Other, specify:	<del></del>	
Haematology and biod	hemistry	
	tests that should be done within 14 days prior to randomisation, G3-4 or significant abnormality in the "Previous or current dise	
Date blood drawn	DD MMM YYYY	
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Specify abnormality or current diseases"</li> </ul>	

Centre No. Subject I	No.				Page 12
Previous or current cardiovascular diseas					
Does the patient have a history of cardiovascula					
□ No □ Yes →	Specify be	elow			
Medical condition (record only one per line)	Resolved		CTCAE Grade		equired?** Yes
Llynortonoion	<b>√</b>	✓ →	Grade	→ No	
Hypertension					
Hypotension Sinus technologies					
Sinus tachycardia					
Atrial tachycardia					
Palpitation					
Arrhythmia Atrial fibrillation					
Valvular heart disease					
Restrictive cardiomyopathy					
Cardiac ischemia					
Thrombosis/thrombus/embolism					
Cardiac infarction					

Protocol number BIG 1-06 / EGF106903

Study: Neo-ALTTO v. 6.0 (19Mar09)

**Screening** 

<sup>\*</sup> Report grade and treatments only for diseases current at time of randomisation. Grade using NCI CTCAE v.3

<sup>\*\*</sup>Report all ongoing treatments on the "Concomitant treatment" pages 112-114

Protocol number BIG 1-06 / EGF106903				Scr	eening
Centre No. Subject N	lo.			Р	age 13
Previous or current diseases other than pr	imary brea	ast cancer a	nd cardi	ovascular o	diseases
Any clinically significant diseases currently or at a	any time pre	viously?			
	Specify belo	-			
Medical condition (record only one per line)	Resolved	Current*	CTCAE	Treat. req	uired?**
, , , , ,	✓	✓ →	Grade		Yes
Osteoporosis					
Hot flashes/flushes					
Thyroid function, low (hypothyroidism)					
Thyroid function, high (hyperthyroidism)					
Insomnia					
Mood alteration - Anxiety					
Mood alteration - Depression					
Bronchospasm, wheezing					
Pain - Back					
Arthritis (non-septic)					
Cholesterol, serum-high (hypercholesteremia)					
Fatigue					
Diabetes					
			Щ		

 $<sup>^{*}</sup>$  Report grade and treatments only for diseases current at time of randomisation. Grade using NCI CTCAE v.3  $^{**}$ Report all ongoing treatments on the "Concomitant treatment" pages 112-114

Page 14

Protocol number BIG 1-06	EGF106903
	Subject No.

Type of radiological examination

	Not done	ne Date of test (DD/MMM/YYYY)	Are there any <u>clinically significant</u> abnormalities? (Please report a short description)
Abdominal CT-scan		-	□ No □ Yes → Specify ──────────────
Chest X-ray*			□ No □ Yes → Specify ──────────────
Chest CT-scan*			□ No □ Yes → Specify
Bone scan (scintigraphy)	□ \$		□ No □ Yes → Specify
Bone X-ray			□ No □ Yes → Specify ────────
Bone CT-scan			

\* Mandatory tests

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	00	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
cs	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
$\prec$	Kidney	SP	Spleen
PT	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

Protocol nu	Protocol number BIG 1-06 / EGF106903	-06 / EGF	F106903			Screening
Cent	Centre No.		Subject No.			Page 15
Type of radi	Type of radiological examination (continued)	ımination	(continued)			
	Not done	Date (DD/MI	Date of test tur (DD/MMM/YYYY)	tumor measurement	Are there any <u>clinically significant</u> abnormalities? (Please report a short description)	ities?
Left breast mammogram*	ram*			       	] mm	
Right breast mammogram*	gram* 🔲 📙	-		×	mm	
Left breast echography	\rangle h	-		×	mm	
Right breast echography	phy	-		   X   -	mm	
MRI		-		×	J mm ☐ No	
ogical	₹	Side	Date of test (DD/MMM/YYYY)		Are there any <u>clinically significant</u> abnormalities?	
examination				% D N Nes	No Yes → Specify	
]					No Yes —➤ Specify ——————	

\*\*BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

\*\*\* See facing page for anatomical site codes

\*Mandatory tests

rotocol number BIG 1-06 / EGF10	6903	Screening
Centre No. Su	bject No.	Page 16
PET/CT scan (only in selected site  Date of assessment	es)	□ Not done
Date of assessment	DD MMM	YYYY
Subject preparation		
Weight (Kg)		
Injection site		
Pre-injection blood glucose (mg/dL)		Time (hh:mm)
Amount of FDG in syringe pre-injection	(mCi)	Time (hh:mm)
Amount of FDG injected (mCi)		Time (hh:mm)
Amount of FDG in syringe post-injection	n (mCi)	Time (hh:mm)
<ul><li>Please describe any clinically sig event" page</li><li>Data acquisition protocol</li></ul>	nificant problem which occure	ed during injection on "Adverse
Start Time (hh:mm)		
End Time (hh:mm)		
FOV Time (mm)		
Number of FOVS		
Technical CT parameter (kV)		
Technical CT parameter (mA)		
PET	□2D □3D	
Please describe any problem which occ	curred during data acquisition	protocol (delay, etc.)

Screening

Page 17

EGF106903	Subject No.	
Protocol number BIG 1-06 / EGF106903	Centre No.	

PET/CT scan (cont.)

u	ŋ
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7	5
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7	5
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>	•
>	ζ
y	3
y	2
Description of Jacions	1

SUV <sub>mean</sub> (g/ml)										
SUV <sub>max</sub> (g/ml)										
Uptake No Yes										
Metabolic L volume N (cc)										
CT Largest bidimensional measurement of lesion (2 major axis) (mm) *	  -    - 	  -    -    - 	  -      - 	       	       	  -      - 	       		  -      - 	
Localization within this organ Right (quadrant, lymphatic region, etc.)										
Side Right										
Si Left										
Site (organ)	Breast	Breast	Breast	Lymphnode	Lymphnode	Lymphnode	Lymphnode	Specify:		
Targeted lesion number								Ø		

\* Report the structural measurement of the lesion, not the measurement showing metabolic activity

Pro	toco	ı nu	mbe	er Bi	IG 1	-06	/ EC	5F 1	069	03				Scre	enin
	С	entr	re N	Ο.				Sı	ubje	ct N	lo.			Pa	ige 18

# **Biological samples**

Type of tissue		sample ained?	Date of specimen collection
	No	Yes →	(dd/mmm/yyyy)
FFPE* tumor core biopsy			
Blood sample for PGx**			
Blood sample for proteomics: - serum			
Blood sample for proteomics: - plasma			
Additional blood sample for CTC*** (only in selected centres)			
Snap frozen tumor sample (2 cores)			

Formalin Fixed Paraffin Embedded.

\*\* PGx: Pharmacogenetics
\*\*\* CTC: Circulating tumor cells

# **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

## **WHO Criteria**

Response	Measurable disease
Complete response	The disappearance of all known disease.
Partial response	50% or more decrease in total tumor size, i.e. the sum of the products of the maximal diameter (MD) and the corresponding largest perpendicular diameter (LPD) of the lesions which have been measured to determine the effect of therapy. In addition, there can be no appearance of new lesions or progression of any lesion.
Progressive disease	At least a 25% increase in total tumor size, i.e. the sum of the products MD*LPD of lesions, and/or the appearance of one or more new lesion/s.
No change	A 50% decrease in total tumor size, i.e. the sum of the products MD*LPD of lesions cannot be established nor a 25% increase in the size of one or more measurable lesions has been determined.

Protocol number	er BIG 1-06 / EGF106903	Week 2
Centre N	lo. Subject No.	Page 19
Patient status		
Date of physical	exam  DD MMM YYYY  Normal Abnormal - Not clinically significant Abnormal - Clinically significant event" page	on "Adverse
Vital signs and	physical measurements	
Weight (Kg)		
Blood pressure	systolic / diastolic mmHg	
Heart rate (beats	/min)	
ECOG performar	nce status	
Breast palpation	n with tumor measurements and nodal status	
Clinical tumor siz	ze by calliper: MD (mm) X LPD (mm)*	
New lesion(s)	□ No □ Yes	
Clinical N stage	☐ N0 (no regional lymph nodes metastasis)	
	<ul> <li>N1 (metastasis to movable ipsilateral axillary lymph nodes)</li> <li>N2a (metastasis in ipsilateral axillary lymph nodes fixed to one another (matter structures)</li> </ul>	d) or to other
	☐ N2b (metastasis only in clinically apparent ipsilateral internal mammary nodes absence of clinically evident axillary lymph node metastasis	and in the
	☐ N3a (metastasis in ipsilateral infraclavicular lymph nodes)	
	☐ N3b (metastasis in ipsilateral internal mammary lymph nodes and axillary lymp	oh node)
	□ N3c (metastasis in ipsilateral subclavicular lymph nodes)	
	□ Nx (not assessed)	
Overall clinica	ll tumor response (WHO criteria) using physical measurem	ents
☐ Complete re	sponse	
Partial respo	onse	
Progressive	disease	
☐ No change		
	D5	
* MD: maxim	nal diameter, LPD: largest perpendicular diameter	
	Study: Neo-ALTTO v. 6.0 (1	9Mar09)

otocol number BIG 1-06 / EGF106	903	Week 2
Centre No. Sub	ject No.	Page 20
PET/CT scan (only in selected sites	5)	
Date of assessment	DD MMM YYY	Not done
Subject preparation		
Weight (Kg)		
njection site		
Pre-injection blood glucose (mg/dL)	Т	ime (hh:mm)
Amount of FDG in syringe pre-injection (	mCi)T	ime (hh:mm)
Amount of FDG injected (mCi)		ime (hh:mm)
Amount of FDG in syringe post-injection	(mCi)	ime (hh:mm)
<ul> <li>Please describe any clinically sign event" page</li> <li>Data acquisition protocol</li> </ul>	ificant problem which occured durin	ng injection on "Adverse
Start Time (hh:mm)	B	
End Time (hh:mm)		
FOV Time (mm)		
Number of FOVS		
Technical CT parameter (kV)		
Technical CT parameter (mA)		
PET	□2D □3D	
Please describe any problem which occu	rred during data acquisition protoc	ol (delay, etc.)

mCR: complete metabolic response would be complete resolution of [18F]-FDG uptake within the tumor volume so that it was indistinguishable from surrounding normal tissue. mPR: partial metabolic response would be classified as a reduction greater than 25% of [18F]-FDG uptake. Reporting would need to be accompanied by adequate and disclosed reproducibility measurements from each centre. An empirical 25% was found to be a useful cut-off point, for statistical significance. A reduction in th extent of the tumor [<sup>18</sup>F]-FDG uptake is not a but there is a need for a reproducibility analysis to determine the appropriate cutt-offs requirement for partial metabolic response. mSD: stable metabolic disease would be classified as an increase in tumor [<sup>18</sup>F]-FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of [18F]-FDG tumor uptake (>20% in the longest dimension).

in the extent of [18F]-FDG tumor uptake (>20% in the longest dimension) or the appearance mPD: progressive metabolic disease would be classified as an increase in [18F]-FDG tumor SUV of greater than 25% within the tumor region defined on the baseline scan, visible increase of new [<sup>18</sup>F]-FDG uptake in metastatic lesions.

Protocol number BIG 1-06 / EGF106903	3 / EGF106903	Week 2
Centre No.	Subject No.	
		Page 21
PET/CT scan (cont.)		
Description of lesions		

Lesion Metabolic response**	E	E	 	 E	E	E	E	
SUV <sub>mean</sub> (g/ml)								
SUV <sub>max</sub> (g/ml)								
Uptake No Yes								
J 8								
Metabolic volume (cc)								
CT Largest bidimensional measurement of lesion (2 major axis) (mm)**	X	×	×		×	×		
Localization (within this organ)								
Side Left Right								
Si Left								
Site (organ)	Breast	Breast	Breast	Lymphnode	Lymphnode	Lymphnode	Lymphnode	
Targeted lesion number*								

<sup>\*</sup> The same lesion should carry the same lesion number throughout the 3 PET/CT scan assessments (see page 17) \*\* Report the structural measurement of the lesion, not the measurement showing metabolic activity \*\*\* See facing page for metabolic response definitions

mCR: complete metabolic response would be complete resolution of [18F]-FDG uptake within the tumor volume so that it was indistinguishable from surrounding normal tissue. mPR: partial metabolic response would be classified as a reduction greater than 25% of [18F]-FDG uptake. Reporting would need to be accompanied by adequate and disclosed reproducibility measurements from each centre. An empirical 25% was found to be a useful cut-off point, for statistical significance. A reduction in th extent of the tumor [<sup>18</sup>F]-FDG uptake is not a but there is a need for a reproducibility analysis to determine the appropriate cutt-offs requirement for partial metabolic response. mSD: stable metabolic disease would be classified as an increase in tumor [<sup>18</sup>F]-FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of [18F]-FDG tumor uptake (>20% in the longest dimension).

in the extent of [18F]-FDG tumor uptake (>20% in the longest dimension) or the appearance mPD: progressive metabolic disease would be classified as an increase in [18F]-FDG tumor SUV of greater than 25% within the tumor region defined on the baseline scan, visible increase of new [<sup>18</sup>F]-FDG uptake in metastatic lesions.

k 2	8			Lesion Metabolic response***	E		m m		
Week 2	Page 22			SUV <sub>mean</sub> (g/ml)					
				SUV <sub>max</sub> (g/ml)					
				Uptake No Yes					
				Metabolic volume (cc)					
				CT Largest bidimensional measurement of lesion (2 major axis) (mm)**	×	×	×	×	×
Protocol number BIG 1-06 / EGF106903	Subject No.		lesions	Localization within this organ (quadrant, lymphatic region, etc.)					
er BIG	o O	ont.)	Description of distant lesions	Side t Right					
numbe	Centre No.	can (c	ption of	Si Left					
Protocol	ŭ	PET/CT scan (cont.)	Descri	Site (organ)					
				Targeted lesion number*					

\* The same lesion should carry the same lesion number throughout the 3 PET/CT scan assessments (see page 17) \*\* See facing page for metabolic response definitions

Pro	otocc	ol nu	mbe	er B	IG 1	-06	/ E(	<i>5</i> 11€	069	03						١	week
	С	enti	re N	0.				Sı	ubje	ct N	lo.					Р	age 23

## **Translational research**

Type of tissue		s sample ained?	Date of specimen collection			
	No	Yes →	(dd/mmm/yyyy)			
FFPE* tumor core biopsy						
Blood sample for proteomics: - serum						
Blood sample for proteomics: - plasma						
Additional blood sample for CTC** (only in selected centres)						
Snap frozen tumor sample (2 cores)						

<sup>\*</sup> Formalin Fixed Paraffin Embedded.\*\* CTC: Circulating tumor cells

# **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

# **WHO Criteria**

Response	Measurable disease
Complete response	The disappearance of all known disease.
Partial response	50% or more decrease in total tumor size, i.e. the sum of the products of the maximal diameter (MD) and the corresponding largest perpendicular diameter (LPD) of the lesions which have been measured to determine the effect of therapy. In addition, there can be no appearance of new lesions or progression of any lesion.
Progressive disease	At least a 25% increase in total tumor size, i.e. the sum of the products MD*LPD of lesions, and/or the appearance of one or more new lesion/s.
No change	A 50% decrease in total tumor size, i.e. the sum of the products MD*LPD of lesions cannot be established nor a 25% increase in the size of one or more measurable lesions has been determined.

Protocol number B	IG 1-06 / EGF106903	Week 4
Centre No.	Subject No.	Page 24
Patient status		
Date of physical exar	m	fy abnormality on "Adverse
Vital signs and phy	rsical measurements	
Weight (Kg)		
Blood pressure	systolic / Lastolic mmHg	
Heart rate (beats/min	)	
ECOG performance s	status	
Breast palpation wi	ith tumor measurements and nodal status	
Clinical tumor size by	calliper: MD (mm) X LPD (mm)*	x
New lesion(s)	□ No □ Yes	
	<ul> <li>N0 (no regional lymph nodes metastasis)</li> <li>N1 (metastasis to movable ipsilateral axillary lymph nodes)</li> <li>N2a (metastasis in ipsilateral axillary lymph nodes fixed to one structures)</li> </ul>	e another (matted) or to other
	N2b (metastasis only in clinically apparent ipsilateral internal in absence of clinically evident axillary lymph node metastal N3a (metastasis in ipsilateral infraclavicular lymph nodes)	nammary nodes and in the sis
	N3b (metastasis in ipsilateral internal mammary lymph nodes N3c (metastasis in ipsilateral subclavicular lymph nodes) Nx (not assessed)	and axillary lymph node)
Overall clinical tu	mor response (WHO criteria) using physica	l measurements
Complete response Partial response Progressive dise No change Not evaluated		
* MD: maximal d	liameter, LPD: largest perpendicular diameter	
	Study: Neo-A	ALTTO v. 6.0 (19Mar09)

# NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln 1500="" mm<sup="" –="">3 <lln 1.5="" 10<sup="" x="" –="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number	BIG 1-	-06 / EG	F106903
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Week 4

Centre No.				Sı	ubje	ct N	0.				

Page 25

# Haematology and biochemistry Please check the blood tests that should be done at this visit, as per protocol, and report any clinically significant (NCI CTCAE G3-4) abnormality on the "Adverse event" page. Date blood drawn DD MMM YYYY Result Normal Abnormal - Not clinically significant Abnormal - Clinically significant (G3-4) → Report on Adverse Event page

# **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

# **WHO Criteria**

Response	Measurable disease	
Complete response	The disappearance of all known disease.	
Partial response	50% or more decrease in total tumor size, i.e. the sum of the products of the maximal diameter (MD) and the corresponding largest perpendicular diameter (LPD) of the lesions which have been measured to determine the effect of therapy. In addition, there can be no appearance of new lesions or progression of any lesion.	
Progressive disease	At least a 25% increase in total tumor size, i.e. the sum of the products MD*LPD of lesions, and/or the appearance of one or more new lesion/s.	
No change	A 50% decrease in total tumor size, i.e. the sum of the products MD*LPD of lesions cannot be established nor a 25% increase in the size of one or more measurable lesions has been determined.	

Protocol number BIG 1	-06 / EGF106903	Week 6
Centre No.	Subject No.	Page 26
Patient status		
Date of physical exam	DD MMM YYYY  ☐ Normal ☐ Abnormal - Not clinically significant ☐ Abnormal - Clinically significant → Spe	ecify abnormality on "Adverse nt" page
Vital signs and physical	measurements	
Weight (Kg)		
Blood pressure	systolic / diastolic mmHg	
Heart rate (beats/min)		
ECOG performance status		
Breast palpation with tu	mor measurements and nodal status	
Clinical tumor size by callip	per: MD (mm) X LPD (mm)*	x
New lesion(s)	□ No □ Yes	
□ N1 ( □ N2a ( □ N2b ( □ N3a ( □ N3b ( □ N3c ( □ N3c ( □ N3c (	no regional lymph nodes metastasis) metastasis to movable ipsilateral axillary lymph nodes metastasis in ipsilateral axillary lymph nodes fixed to structures) metastasis only in clinically apparent ipsilateral internationals of clinically evident axillary lymph node metastastasis in ipsilateral infraclavicular lymph nodes) metastasis in ipsilateral internal mammary lymph nod metastasis in ipsilateral subclavicular lymph nodes) of assessed)	one another (matted) or to other al mammary nodes and in the stasis
Overall clinical tumor	response (WHO criteria) using physic	cal measurements
Complete response Partial response Progressive disease No change Not evaluated * MD: maximal diamet	er, LPD: largest perpendicular diameter	

## **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

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Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903	Week
Centre No.	Subject No.	Page 27
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the page.</li> </ul>	"Adverse even
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the question Class II ☐ Class III (study treatment should be interrupted) ☐ Class IV (study treatment should be interrupted)	on above)
EKG should be perform the "Unscheduled EKG	ned at any time if symptoms or clinical suspicion are present and re " page	eported on
Haematology and biod	hemistry	
	d tests that should be done at this visit, as per protocol, and report CI CTCAE G3-4) abnormality on the "Adverse event" page.	any
Date blood drawn	DD MMM YYYY	
Result [	<ul> <li>Normal</li> <li>Abnormal - Not clinically significant</li> <li>Abnormal - Clinically significant (G3-4) → Report on Adverse</li> </ul>	Event page

Week 6	Page 28		normalities?					
3 / EGF106903	Subject No.	ination	Date of test tumor measurement Are there any <u>clinically significant</u> abnormalities? (DD/MMM/YYYY) (Please report a short description)	No	ON ☐ MM ☐ I ☐ X ☐ I ☐ I ☐ I ☐ I ☐ I ☐ I ☐ I ☐ I	No	No   No   No   No   No   No   No   No	N ☐ mm ☐ NoN ☐ NoN ☐ Yes →
r BIG 1-06		jical exami	Not done					
Protocol number BIG 1-06 / EGF106903	Centre No.	Type of radiological examination	Ň	Left breast mammogram	Right breast mammogram	Left breast echography	Right breast echography	MRI

rotocol number BIG 1-06 / EGF1	06903 <b>Week</b>
Centre No. S	ubject No. Page 29
PET/CT scan (only in selected si	es)
Date of assessment	□ Not done  DD MMM YYYY
Subject preparation	
Weight (Kg)	
Injection site	
Pre-injection blood glucose (mg/dL)	Time (hh:mm)
Amount of FDG in syringe pre-injection	n (mCi) Time (hh:mm)
Amount of FDG injected (mCi)	Time (hh:mm)
Amount of FDG in syringe post-injection	n (mCi)
event" page  Data acquisition protocol	gnificant problem which occured during injection on "Adverse
Start Time (hh:mm)	
End Time (hh:mm)	
FOV Time (mm)	
Number of FOVS	
Technical CT parameter (kV)	
Technical CT parameter (mA)	
PET	□2D □3D
D	
Please describe any problem which of	curred during data acquisition protocol (delay, etc.)

mCR: complete metabolic response would be complete resolution of [18F]-FDG uptake within the tumor volume so that it was indistinguishable from surrounding normal tissue. mPR: partial metabolic response would be classified as a reduction greater than 25% of [18F]-FDG uptake. Reporting would need to be accompanied by adequate and disclosed reproducibility measurements from each centre. An empirical 25% was found to be a useful cut-off point, for statistical significance. A reduction in th extent of the tumor [<sup>18</sup>F]-FDG uptake is not a but there is a need for a reproducibility analysis to determine the appropriate cutt-offs requirement for partial metabolic response. mSD: stable metabolic disease would be classified as an increase in tumor [<sup>18</sup>F]-FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of [18F]-FDG tumor uptake (>20% in the longest dimension).

in the extent of [18F]-FDG tumor uptake (>20% in the longest dimension) or the appearance mPD: progressive metabolic disease would be classified as an increase in [18F]-FDG tumor SUV of greater than 25% within the tumor region defined on the baseline scan, visible increase of new [<sup>18</sup>F]-FDG uptake in metastatic lesions.

8 8	0			Lesion Metabolic response***				 E	
Week 6	Page 30			SUV <sub>mean</sub> (g/ml)					
				SUV <sub>max</sub> (g/ml)					
				ake Yes					
				Uptake No Yes					
				Metabolic volume (cc)					
				CT Largest bidimensional measurement of lesion (2 major axis) (mm)**		       	   X	       	       
Protocol number BIG 1-06 / EGF106903	Subject No.			Localization within this organ (quadrant, lymphatic region, etc.)					
r BIG		int.)	esions	de Right					
numbe	Centre No.	san (cc	otion of	Side Left Ri					
Protocol r	Ğ — Cē	PET/CT scan (cont.)	Description of lesions	Site (organ)	Breast	Breast	Breast	Lymphnode	Lymphnode
				Targeted lesion number*					

Jm | | | | | | | | | | |

Lymphnode

Lymphnode

<sup>\*</sup> The same lesion should carry the same lesion number throughout the 3 PET/CT scan assessments (see pages 17, 21 and 22)

<sup>\*\*</sup> Report the structural measurement of the lesion, not the measurement showing metabolic activity

<sup>\*\*\*</sup> See facing page for metabolic response definitions

mCR: complete metabolic response would be complete resolution of [18F]-FDG uptake within the tumor volume so that it was indistinguishable from surrounding normal tissue. mPR: partial metabolic response would be classified as a reduction greater than 25% of [18F]-FDG uptake. Reporting would need to be accompanied by adequate and disclosed reproducibility measurements from each centre. An empirical 25% was found to be a useful cut-off point, for statistical significance. A reduction in th extent of the tumor [<sup>18</sup>F]-FDG uptake is not a but there is a need for a reproducibility analysis to determine the appropriate cutt-offs requirement for partial metabolic response. mSD: stable metabolic disease would be classified as an increase in tumor [<sup>18</sup>F]-FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of [18F]-FDG tumor uptake (>20% in the longest dimension).

in the extent of [18F]-FDG tumor uptake (>20% in the longest dimension) or the appearance mPD: progressive metabolic disease would be classified as an increase in [18F]-FDG tumor SUV of greater than 25% within the tumor region defined on the baseline scan, visible increase of new [<sup>18</sup>F]-FDG uptake in metastatic lesions.

ဖ			Lesion Metabolic response**	- - -	E	E	E	E	E	
Week 6 Page 31			SUV <sub>mean</sub> (g/ml)	- - -						
			SUV <sub>max</sub> (g/ml)	- - -						
			Uptake No Yes	l	_					
			PET volume (cc)	- - - -						
			CT Largest bidimensional measurement of lesion (2 major axis) (mm)	-		×		×	  -    - 	
Protocol number BIG 1-06 / EGF106903  Centre No. Subject No.		lesions	Localization (within this organ)							
er BIG	ont.)	Description of distant lesions	Side t Right	[						
Centre No.	can (c	iption o	Si Left	[						
Protocol Ce	PET/CT scan (cont.)	Descr	Site (organ)							
			Targeted lesion number	-						

\* The same lesion should carry the same lesion number throughout the 3 PET/CT scan assessments (see pages 17, 21 and 22)
\*\* See facing page for metabolic response definitions

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Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol	number	RIG 1	-06 /	FGF1	06903

Week 8 and 9

Centre No.				Sı	ubje	ct N	lo.				Page 32

Haematology						
Please check the blood tests that should be done at these visits, as per protocol, and report any clinically significant (NCI CTCAE G3-4) abnormality on the "Adverse event" page.						
Date blood drawn week 8	DD MMM YYYY					
Result	Normal Abnormal - Not clinically significant Abnormal - Clinically significant (G3-4) -> Report on Adverse Event page					
Date blood drawn week 9	DD MMM YYYY					
Result	Normal Abnormal - Not clinically significant Abnormal - Clinically significant (G3-4) -> Report on Adverse Event page					

# ECOG performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

## **WHO Criteria**

Response	Measurable disease
Complete response	The disappearance of all known disease.
Partial response	50% or more decrease in total tumor size, i.e. the sum of the products of the maximal diameter (MD) and the corresponding largest perpendicular diameter (LPD) of the lesions which have been measured to determine the effect of therapy. In addition, there can be no appearance of new lesions or progression of any lesion.
Progressive disease	At least a 25% increase in total tumor size, i.e. the sum of the products MD*LPD of lesions, and/or the appearance of one or more new lesion/s.
No change	A 50% decrease in total tumor size, i.e. the sum of the products MD*LPD of lesions cannot be established nor a 25% increase in the size of one or more measurable lesions has been determined.

Pro	COCC	oi nui	mbe	er Bi	IG 1	-06 /	EGF	1069	03									VV	eek 10
	C	entr	e N	0.		Subject No.							Р	age 33					
Pati	ent	statı	ıs																
Date of physical exam		า		Abnormal - Not clinically significant						lverse									
Vita	l siç	gns a	nd	phy	sical	mea	sure	ment	S										
We	ight	(Kg)					Ш												
Blood pressure					L	systolic	/	dia	astolic	;	mmŀ	Нg							
He	art ra	ate (b	eats/	min)	)		Ш												
EC	OG	perfor	man	ice s	tatus		]												
Bre	ast	palpa	atior	ı wi	th tu	mor	meas	uren	nents	and	l no	dal s	tatu	s					
Clir	nical	tumo	r siz	e by	callip	er: M	ID (mn	n) X L	PD (m	m)*	L					ι L			<b> </b> -
Ne	w les	sion(s	)						□No	)		Yes							
Clii	nical	N sta	ige		N1 ( N2a ( S N2b ( a N3a ( N3b (	metas metas structu metas absend metas metas	res) tasis or ce of cli tasis in	mova ipsilat nly in c nically ipsilat ipsilat	ble ipsi eral ax clinically eviden eral inf	ilatera illary y app nt axil racla rernal	al axi lymp aren lary l vicula	illary ly t ipsila ymph ar lymp nmary	es fix iteral node ph no lymp	internate metas odes)	one and	mary i	matted nodes a y lymph	and in	the
Ove	eral	l clin	ica	l tui	mor	resp	onse	e (W⊦	HO cr	riter	ia)	usin	g pl	hysid	cal m	eası	ıreme	∍nts	i
	Pa Pro No No	mplet rtial re ogress chan t eval	espo sive ge uate	nse disea	ase	er I C	PD: lar	nest n	ernen	dicul	ar di	amete	۵r						
	IV	ווו .עו	axiii	ıaı ül	amel	.cı, Lf	D. اها ا	<del>υσ</del> οι β	e hall	uicul	aı Ul	amele	<del>C</del> I						

NCI CTCAE v. 3: haematology and biochemistry toxicity scale

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WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Week 10

С	entr	e N	0.		Sı	ubje	ct N	0.	

Page 34

Haematology and biochemistry

Please check the blood tests that should be done at this visit, as per protocol, and report any clinically significant (NCI CTCAE G3-4) abnormality on the "Adverse event" page.

Date blood drawn

DD MMM YYYY

Result

Normal

Abnormal - Not clinically significant

Abnormal - Clinically significant (G3-4) → Report on Adverse Event page

NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

F	Protocol	number	RIG 1	1-06 /	FGF1	06903
	LOLOGOL	HUHHIOGE	DICJ	1-00/		TOO SOLD

Week 11 and 12

Centre No.						Sı	ubje	ct N	lo.		Pa	age 35

Haematology							
Please check the blood tests that should be done at these visits, as per protocol, and report any clinically significant (NCI CTCAE G3-4) abnormality on the "Adverse event" page.							
Date blood drawn week 11  DD MMM YYYY							
Result □ Normal □ Abnormal - Not clinically significant □ Abnormal - Clinically significant (G3-4) → Report on Adverse Event page							
Date blood drawn week 12 DD MMM YYYY							
Result ☐ Normal ☐ Abnormal - Not clinically significant ☐ Abnormal - Clinically significant (G3-4) → Report on Adverse Event page							

## **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

### **WHO Criteria**

Response	Measurable disease
Complete response	The disappearance of all known disease.
Partial response	50% or more decrease in total tumor size, i.e. the sum of the products of the maximal diameter (MD) and the corresponding largest perpendicular diameter (LPD) of the lesions which have been measured to determine the effect of therapy. In addition, there can be no appearance of new lesions or progression of any lesion.
Progressive disease	At least a 25% increase in total tumor size, i.e. the sum of the products MD*LPD of lesions, and/or the appearance of one or more new lesion/s.
No change	A 50% decrease in total tumor size, i.e. the sum of the products MD*LPD of lesions cannot be established nor a 25% increase in the size of one or more measurable lesions has been determined.

Protocol number BIG 1	-06 / EGF106903	Week 13
Centre No.	Subject No.	Page 36
Patient status		
Date of physical exam	DD MMM YYYY  ☐ Normal ☐ Abnormal - Not clinically significant ☐ Abnormal - Clinically significant → Spec	t done cify abnormality on "Adverse at" page
Vital signs and physica	I measurements	
Weight (Kg)		
Blood pressure	systolic / diastolic mmHg	
Heart rate (beats/min)		
ECOG performance status		
Breast palpation with tu	umor measurements and nodal status	
Clinical tumor size by callip	per: MD (mm) X LPD (mm)*	x
New lesion(s)	□ No □ Yes	
☐ N1 (☐ N2a (☐ N2b (☐ N3a (☐ N3c (☐	(no regional lymph nodes metastasis) (metastasis to movable ipsilateral axillary lymph nodes (metastasis in ipsilateral axillary lymph nodes fixed to ostructures) (metastasis only in clinically apparent ipsilateral internal absence of clinically evident axillary lymph node metast (metastasis in ipsilateral infraclavicular lymph nodes) (metastasis in ipsilateral internal mammary lymph nodes) (metastasis in ipsilateral subclavicular lymph nodes) (metastasis in ipsilateral subclavicular lymph nodes) (metastasis in ipsilateral subclavicular lymph nodes)	one another (matted) or to other all mammary nodes and in the stasis
Overall clinical tumor	response (WHO criteria) using physic	al measurements
Complete response Partial response Progressive disease No change Not evaluated * MD: maximal diame	ter, LPD: largest perpendicular diameter	

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number	BIG 1-06	6 / EGF106903
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Week 13

С	entr	e N	0.		Subject No.						

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Haematology and biochemistry

Please check the blood tests that should be done at this visit, as per protocol, and report any clinically significant (NCI CTCAE G3-4) abnormality on the "Adverse event" page.

Date blood drawn

DD MMM YYYY

Result

Normal

Abnormal - Not clinically significant

Abnormal - Clinically significant (G3-4) → Report on Adverse Event page

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln 1500="" mm<sup="" –="">3 <lln 1.5="" 10<sup="" x="" –="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

F	Protocol	number	RIG 1	1-06 /	FGF1	06903
	LOLOGOL	HUHHIOGE	DICJ	1-00/		TOO SOLD

Week 14 and 15

С	entr	e N	0.		Sı	ubje	ct N	lo.			Page 38

Haematology Please check the blood tests that should be done at these visits, as per protocol, and report any clinically significant (NCI CTCAE G3-4) abnormality on the "Adverse event" page.
Date blood drawn week 14
Result
Date blood drawn week 15  DD MMM YYYY
Result ☐ Normal ☐ Abnormal - Not clinically significant ☐ Abnormal - Clinically significant (G3-4) → Report on Adverse Event page

### **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

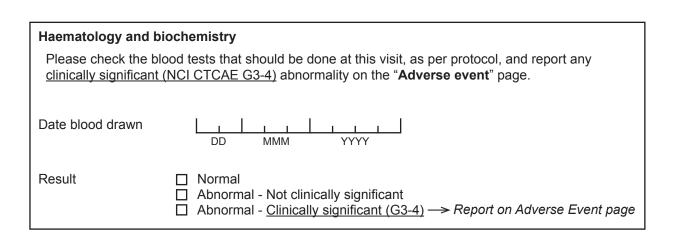
### **WHO Criteria**

Response	Measurable disease
Complete response	The disappearance of all known disease.
Partial response	50% or more decrease in total tumor size, i.e. the sum of the products of the maximal diameter (MD) and the corresponding largest perpendicular diameter (LPD) of the lesions which have been measured to determine the effect of therapy. In addition, there can be no appearance of new lesions or progression of any lesion.
Progressive disease	At least a 25% increase in total tumor size, i.e. the sum of the products MD*LPD of lesions, and/or the appearance of one or more new lesion/s.
No change	A 50% decrease in total tumor size, i.e. the sum of the products MD*LPD of lesions cannot be established nor a 25% increase in the size of one or more measurable lesions has been determined.

Protocol number	er BIG 1-06 / EGF106903	vveek 16
Centre N	o. Subject No.	Page 39
Patient status		
Date of physical of	exam  DD MMM YYYY  Normal Abnormal - Not clinically significant Abnormal - Clinically significant event" page	า "Adverse
Vital signs and	physical measurements	
Weight (Kg)		
Blood pressure	systolic / Later mmHg	
Heart rate (beats	/min)	
ECOG performar	nce status	
Breast palpation	n with tumor measurements and nodal status	
Clinical tumor siz	re by calliper: MD (mm) X LPD (mm)*	<b>□-</b> □
New lesion(s)	□ No □ Yes	
Clinical N stage	<ul> <li>N0 (no regional lymph nodes metastasis)</li> <li>N1 (metastasis to movable ipsilateral axillary lymph nodes)</li> <li>N2a (metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) structures)</li> <li>N2b (metastasis only in clinically apparent ipsilateral internal mammary nodes a absence of clinically evident axillary lymph node metastasis</li> <li>N3a (metastasis in ipsilateral infraclavicular lymph nodes)</li> <li>N3b (metastasis in ipsilateral internal mammary lymph nodes and axillary lymph</li> <li>N3c (metastasis in ipsilateral subclavicular lymph nodes)</li> <li>Nx (not assessed)</li> </ul>	and in the
_	Il tumor response (WHO criteria) using physical measureme	ents
☐ Complete re☐ Partial response		
Progressive		
☐ No change		
☐ Not evaluate	ed .	
* MD: maxim	nal diameter, LPD: largest perpendicular diameter	
	Study: Neo-ALTTO v. 6.0 (19	Mar09)

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Pro	Protocol number BIG 1-06 / EGF106903											Week 16			16				
	С	entr	e N	0.				Sı	ubje	ct N	lo.						Pag	je 40	0



Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

F	Protocol	number	RIG 1	1-06 /	FGF1	06903
	LOLOGOL	HUHHIOGE	DICJ	1-00/		TOO SOLD

Week 17 and 18

Centr	re No.		Sı	ubje	ct N	Ο.			Page 41

Haematology					
Please check the blood tests that should be done at these visits, as per protocol, and report any clinically significant (NCI CTCAE G3-4) abnormality on the "Adverse event" page.					
Date blood drawn week 17  DD MMM YYYY					
	Normal Abnormal - Not clinically significant Abnormal - Clinically significant (G3-4) -> Report on Adverse Event page				
Date blood drawn week 18 DD MMM YYYY					
	Normal Abnormal - Not clinically significant Abnormal - Clinically significant (G3-4) -> Report on Adverse Event page				

Note: The pre-surgery visit should take place within a few days prior to surgery. Surgery will take place at 2-4 weeks after the last dose of paclitaxel.

### **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

### **WHO Criteria**

Response	Measurable disease
Complete response	The disappearance of all known disease.
Partial response	50% or more decrease in total tumor size, i.e. the sum of the products of the maximal diameter (MD) and the corresponding largest perpendicular diameter (LPD) of the lesions which have been measured to determine the effect of therapy. In addition, there can be no appearance of new lesions or progression of any lesion.
Progressive disease	At least a 25% increase in total tumor size, i.e. the sum of the products MD*LPD of lesions, and/or the appearance of one or more new lesion/s.
No change	A 50% decrease in total tumor size, i.e. the sum of the products MD*LPD of lesions cannot be established nor a 25% increase in the size of one or more measurable lesions has been determined.

Protocol number BIG	1-06 / EGF106903	Pre-surgery visit
Centre No.	Subject No.	Page 42
Patient status		
Date of physical exam		□ Not done  nt  → Specify abnormality on "Adverse event" page
Vital signs and physic	al measurements	
Weight (Kg)		
Blood pressure	systolic / diastolic mmH	g
Heart rate (beats/min)		
ECOG performance state	us	
Breast palpation with	tumor measurements and nodal sta	atus
Clinical tumor size by cal	lliper: MD (mm) X LPD (mm)*	X
New lesion(s)	□ No □ Yes	
<ul><li>□ N2t</li><li>□ N3t</li><li>□ N3t</li><li>□ N3c</li><li>□ Nx</li></ul>	(no regional lymph nodes metastasis) (metastasis to movable ipsilateral axillary lyra (metastasis in ipsilateral axillary lymph node structures) o (metastasis only in clinically apparent ipsilate absence of clinically evident axillary lymph note (metastasis in ipsilateral infraclavicular lymph of (metastasis in ipsilateral internal mammary loc (metastasis in ipsilateral subclavicular lymph (not assessed) or response (WHO criteria) using	eral internal mammary nodes and in the node metastasis h nodes)  ymph nodes and axillary lymph node)
☐ No change	;	
☐ Not evaluated		
* MD: maximal diam	neter, LPD: largest perpendicular diamete	r
	S	study: Neo-ALTTO v. 6.0 (19Mar09)

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903	Pre-surgery visit
Centre No.	Subject No.	Page 43
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluation	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ P</li> </ul>	Please complete the "Adverse event" age.
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, t☐ Class II ☐ Class III (study treatment should be inte	errupted)
EKG should be perform the "Unscheduled EKG	ed at any time if symptoms or clinical suspicio " page	n are present and reported on
Haematology and biod	hemistry	
	d tests that should be done at this visit, as per CI CTCAE G3-4) abnormality on the " <b>Adverse</b>	• • • • • • • • • • • • • • • • • • • •
Date blood drawn	DD MMM YYYY	
	☐ Normal ☐ Abnormal - Not clinically significant ☐ Abnormal - Clinically significant (G3-4) —>	Report on Adverse Event page

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Subject No.

Centre No.

Protocol number BIG 1-06 / EGF106903

Page 44

Type of radiological examination	ogical exa	mination		
	Not done	Date of test (DD/MMM/YYYY)	tumor measurement	Are there any <u>c</u> (Please report a
Bilateral mammogram*			×	
Left breast echography			×	on mm

Are there any clinically significant abnormalities?

(Please report a short description)

No	NO MW NO Yes Yes	No   Mm
Left breast echography	Right breast echography	MRI

\* Mandatory test

Centre No. Subject No. Page 45
Sentinel node(s) sampling
Was sentinel node sampling performed? ☐ No ☐ Yes
Sentinel node biopsy date  DD MMM YYYY  Right
Axillary sentinel node biopsy
□ Negative □ Positive → Total sampled □ □ □ □  Total positive □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □
Internal sentinel mammary nodes biopsy → □ Negative □ Positive □ Not done
Pathological N status
<ul> <li>□ pNX (Regional lymph nodes cannot be assessed)</li> <li>□ pN0 (i-): (No regional lymph node metastasis histologically, negative IHC)</li> <li>□ pN0 (i+): (No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2mm)</li> </ul>
<ul> <li>□ pN0 (mol-): (No regional lymph node metastasis histologically, negative molecular findings (RT-PCR))</li> <li>□ pN0 (mol+): (No regional lymph node metastasis histologically, positive molecular findings (RT-PCR))</li> </ul>
<ul><li>□ pN1mi: Micrometastasis (larger than 0.2 mm but not larger than 2.0 mm)</li><li>□ pN1a: Metastasis in one to three axillary lymph nodes</li></ul>
□ pN1b: Metastasis in one to three axillary lymph nodes □ pN1b: Metastasis in internal mammary nodes with microscopic disease detected by SLN dissection but not clinically apparent
pN1c: Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by SLN dissection but not clinically apparent
□ pN2a: Metastasis in four to nine axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
□ pN2b: Metastasis in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis
□ pN3a: Metastasis in 10 or more axillary lymph nodes (at least 1 tumor deposit larger than 2.0 mm); or, metastasis to the infraclavicular lymph nodes
pN3b: Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph node(s); or, in more than three axillary lymph nodes and in interna mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
□ pN3c: Metastasis in ipsilateral supraclavicular lymph nodes
Pathological measurement of largest lymph node (mm)  Study: Neo-ALTTO v. 6.0 (19Mar09)

ro	tocol	num	ıbe	r B	IG 1	-06	3 / I	EG	F10	69	903												,	Su	rg	ery	/
	Ce	entre	No	٥.					Sul	bje	ect N	lo.												Pa	ge	46	
											,																
A	killary	noc	de (	diss	secti	on																					
D	ate of	axilla	ary	diss	ectic	n	L	D	<u>                                     </u>		II MMM		YY	L YY	Ш		l Lef ] Rig				[	□N	lot	dor	ne		
N	lumbe	r of ly	/mp	h n	odes	exa	<u>amiı</u>	<u>ned</u>					L	L													
Ν	lumbe	r of p	<u>osi</u>	<u>tive</u>	lymp	h no	ode	:S					L														
Priı	mary	brea	ıst	car	ncer	sui	rge	ry																			
Wa	s surg	jery d	lone	€?									No	I	□ Yes												
Ту	pe of s	surge	ery (	che	eck a	all th	nat	арі	oly)				Later	alit	у	ı	Date	: (E	D/I	ММ	M/Y	ΥY	Y)				
Lu	mpect	tomy											Left		□Right	Į											]
Qι	uadran	ntecto	my	/ S	egme	ente	cto	my					] Left		□Right	Į				1	1						
Pa	artial m	naste	ctor	ny									] Left		□Right	Į							_				]
Mo	odified	radio	cal	mas	tecto	my							] Left	1	□Right	Į					ı						
Ra	adical ı	maste	ecto	my	(Hal	stec	1)						] Left		□Right	Į											]
Ot	her, sp	pecify	/: _										] Left		□Right	l					ı						

Protocol number BIG 1-06 / E	GF106903	Surgery								
Centre No.	Subject No.	Page 47								
Tumor characteristics										
Largest bidimensional measureme	ent of invasive lesion (mm)									
Invasive histologic type (tick all that	at apply)									
<ul><li>☐ Ductal Not Otherwise Specified</li><li>☐ Lobular</li><li>☐ Mixed ductal and lobular</li><li>☐ Tubular</li></ul>	(NOS) ☐ Micropapillary ☐ Cribriform ☐ Mucinous ☐ Invasive Not Otherwise Specified (NOS)									
☐ Apocrine	☐ Medullary									
☐ Tubulolobular	☐ Other, specify:									
Is carcinoma in situ present?	<ul> <li>No</li> <li>Yes → □ DCIS</li> <li>□ LCIS</li> <li>□ Mixed</li> </ul>									
Is Paget's disease present?	□ No □ Yes									
Margin involvement?	<ul> <li>□ No</li> <li>□ Yes → □ Involved with invasive disease</li> <li>□ Involved with DCIS only</li> <li>□ Non-resectable deep margins</li> </ul>									
Histologic Grade										
Gx ☐ Differentiation cannot be assessed G1 ☐ Well differentiated G2 ☐ Moderately differentiated G3 ☐ Poorly differentiated / Undifferentiated										
Breast pathological response (p  □ No □ Yes → □ pT0 □ pTIS	oathological complete response (pT0 or pTIS))									

Protocol number BIG 1-06 / EGF106903												Sui	rge	L.				
	Cent	re N	lo.				Sı	ubje	ct N	lo.						Pag	e 48	

#### **Translational research**

Type of tissue		s sample ained?	Date of specimen collection				
	No	Yes →	(dd/mmm/yyyy)				
FFPE* tumor core biopsy							
Blood sample for proteomics: - serum							
Blood sample for proteomics: - plasma							
Additional blood sample for CTC** (only in selected centres)							
Snap frozen tumor sample (2 cores)							

<sup>\*</sup> Formalin Fixed Paraffin Embedded.\*\* CTC: Circulating tumor cells

Neo-adjuvant treatment completion
Page 49
Lapatinib (L)?
specify below
pechy below
- · · · · · · · · · · · · · · · · · · ·
<u>Trastuzumab (<b>T</b>)</u> ?
specify below
poonly below
Dealitaval (B)2
Paclitaxel (P)?
specify below
•
T P**
□ □ → Complete "Adverse event" page
□ □ → Specify:
Ц Ц
□ □ → Complete "Death" page
□ → Specify:
DD MMM YYYY
plete the planned preoperative [therapy]?', if the study
plete the planned preoperative [therapy]?', if the study e protocol specified treatment duration.

-1010C0111	ullibel bi	G 1-00/E	GF 10090	JS	neo-aujuva	nt treatment completion
Cen	tre No.		Subje	ct No.		Page 50
	-1			·		
		ts and Inve				the neo-adjuvant treatment
CRF page number	Commen	ts				
		s case report		been er	ntered under my au	uthority and to the best of
Investigator's signature					(A medically qualified sub- investigator is allowed to sign the	
Date DD MMM YYYY						CRF if he/she is listed on the form FDA 1572)
Please date	e and sign	<u>ONLY</u> after r	equest fror	m data m	anagement	

## **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln 1500="" mm<sup="" –="">3 <lln 1.5="" 10<sup="" x="" –="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG 1	-06 / EGF106903	Week 1 - Day 1 FEC cycle
Centre No.	Subject No.	Page 51
Patient status		
Date of physical exam	DD MMM YYYY	☐ Not done
Vital signs and physica	measurements	
Weight (Kg)		
BSA (m²)	<b>□.</b> □□	
Blood pressure	systolic / diastolic mm	Hg
Heart rate (beats/min)		
ECOG performance status		
	emistry tests that should be done at this visit, I CTCAE G3-4) abnormality on the "Ad	
Date blood drawn	DD MMM YYYY	
	Abnormal - Not clinically significant	4)> Report on Adverse Event nage

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln 1500="" mm<sup="" –="">3 <lln 1.5="" 10<sup="" x="" –="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903	Week 4 - Day 1 FEC cycle 2
Centre No.	Subject No.	Page 52
Patient status		
Date of physical exam	DD MMM YYYY	☐ Not done
Vital signs and physic	cal measurements	
Weight (Kg)		
BSA (m²)		
Blood pressure	systolic / diastolic mi	mHg
Heart rate (beats/min)		
ECOG performance state	rus []	
Haematology and bio		
	od tests that should be done at this visiting the state of the state o	
Date blood drawn	DD MMM YYYY	
Result	<ul><li>☐ Normal</li><li>☐ Abnormal - Not clinically significan</li><li>☐ Abnormal - Clinically significant (G</li></ul>	t 3-4) —> Report on Adverse Event page

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln 1500="" mm<sup="" –="">3 <lln 1.5="" 10<sup="" x="" –="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Pr	otoco	ol numb	er BIG	G 1-06 / EGF106903	Week 7 - Day 1 FEC cycle
	- C	entre l	No.	Subject No.	Page 53
Pa	atient	status			
С	ate of	physical	l exam	DD MMM YYY	Not done
Vi	tal sig	ıns and	l physi	cal measurements	
٧	Veight	(Kg)			
E	BSA (m	<sup>2</sup> )			
В	Blood p	ressure		systolic / Lastolic	mmHg
H	leart ra	ate (beat	s/min)		
E	COG	performa	ance sta	atus	
Г					
				ochemistry	
				od tests that should be done at the NCI CTCAE G3-4) abnormality o	nis visit, as per protocol, and report any n the "Adverse event" page.
	Date b	lood dra	iwn	DD MMM YYY	Y
	Result			<ul><li>□ Normal</li><li>□ Abnormal - Not clinically sig</li><li>□ Abnormal - Clinically significant</li></ul>	nificant cant (G3-4) -> Report on Adverse Event page

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Protocol number BIG 1-06 / EGF10	06903 <b>W</b>	eek 10 (Week 1 targe	ted therapy)
Centre No. Su	ubject No.		Page 54
Patient status			
Date of physical exam	MMM YYYY	□ Not done	
Vital signs and physical measurem	ents		
Weight (Kg)			
Blood pressure systolic	/ L diastolic		
Heart rate (beats/min)			
ECOG performance status			
Translational research			
Type of tissue	Was sample obtained?	Date of specimen collection	
	No Yes	(dd/mmm/yyyy)	
Additional blood sample for CTC* (only		1 . 1 1 1	

<sup>\*</sup>Circulating tumor cells

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln 1500="" mm<sup="" –="">3 <lln 1.5="" 10<sup="" x="" –="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	Week 10 (Week 1 targeted the	erapy)
Centre No.	Subject No.	age 55
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│ │ │ │ │ │	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the "Advers page.</li> </ul>	e event"
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the question abo ☐ Class II ☐ Class III ☐ Class IV	ve)
EKG should be performe the "Unscheduled EKG"	ed at any time if symptoms or clinical suspicion are present and reported or " page	า
Haematology and bio	ochemistry	
	od tests that should be done at this visit, as per protocol, and report any NCI CTCAE G3-4) abnormality on the "Adverse event" page.	
Date blood drawn	DD MMM YYYY	
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant (G3-4) → Report on Adverse Event p</li> </ul>	page

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Protocol number BIG 1-	06 / EGF106903	Week 22 (W13 targeted therapy)-	FU Month 3
Centre No.	Subject No	Э.	Page 56
Patient status			
Date of physical exam	DD MMM	Not done	
Vital signs and physical	measurements		
Weight (Kg)	L		
Blood pressure	systolic / dia	astolic	
Heart rate (beats/min)			
ECOG performance status			
Are there any changes since	e the previous assessme □ No □ Yes → Specify be		
<ul><li>☐ Recurrence of disease (a</li><li>☐ Second primary maligna and contralateral BC" pa</li></ul>	ncy or contralateral bre	nce of disease" page) east cancer (complete the "Second primary	malignancy
☐ Significant cardiac disea	se (complete the "Adve	erse event" page)	
☐ Adverse event (complete	the "Adverse event" p	age)	
☐ Death (complete the "De	eath" page)		
<ul><li>☐ Lost to follow-up</li><li>☐ Patient withdrew study c</li></ul>	onsent	ast contact (or date	YYYY
☐ Patient withdrew treatme	ent but remains on follo	w-up	
alive.	s known to be alive cou	ntact should be the last date the patient wa lld either be the same as the previous repor .)	

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
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- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903 Week 22 (W13 targeted therapy)-FU Month	3
Centre No.	Subject No. Page 57	
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│ │ │ │ │ │ │ │ │ │ │ │ │	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the "Adverse event" page.</li> </ul>	,,
Symptomatic CHF	<ul> <li>□ No</li> <li>□ Yes → Specify below</li> </ul>	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the question above) ☐ Class II ☐ Class IV	
EKG should be performe the "Unscheduled EKG"	d at any time if symptoms or clinical suspicion are present and reported on page	
Haematology and biod	chemistry	
1	d tests that should be done at this visit, as per protocol, and report any CI CTCAE G3-4) abnormality on the "Adverse event" page.	
Date blood drawn	DD MMM YYYY	
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant (G3-4) → Report on Adverse Event page</li> </ul>	

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Protocol number BIG 1-06 / EGF106903 Week 34 (W25 targeted therapy)-FU Mor	ith 6
Centre No. Subject No. Page	58
Patient status	
Date of physical exam  DD MMM YYYY  Not done	
Vital signs and physical measurements	
Weight (Kg)	
Blood pressure	
Heart rate (beats/min)	
ECOG performance status	
Are there any changes since the previous assessment?  ☐ No ☐ Yes → Specify below	
<ul> <li>□ Recurrence of disease (complete the "Recurrence of disease" page)</li> <li>□ Second primary malignancy or contralateral breast cancer (complete the "Second primary malignan</li> </ul>	O1/
and contralateral BC" page)	Cy
☐ Significant cardiac disease (complete the "Adverse event" page)	
Adverse event (complete the "Adverse event" page)	
Death (complete the "Death" page)	
☐ Lost to follow-up ☐ Patient withdrew study consent ☐ DD MMM YYYY ☐ Date of last contact (or date ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Ш
☐ Patient withdrew treatment but remains on follow-up	
(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known alive.  The last date the patient was known to be alive could either be the same as the previous reported visit or any date between the previous visit and this one.)	

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

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- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903 Week 34 (W25 targeted therapy)-FU Month	ւ 6
Centre No.	Subject No. Page 59	ı
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the "Adverse ever page.</li> </ul>	าt"
Symptomatic CHF	□ No □ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the question above) ☐ Class II ☐ Class III ☐ Class IV	
EKG should be performed the "Unscheduled EKG" p	d at any time if symptoms or clinical suspicion are present and reported on page	
Haematology and biod	hemistry	
	I tests that should be done at this visit, as per protocol, and report any CI CTCAE G3-4) abnormality on the "Adverse event" page.	
Date blood drawn	DD MMM YYYY	
Result [	☐ Normal ☐ Abnormal - Not clinically significant ☐ Abnormal - <u>Clinically significant (G3-4)</u> —> Report on Adverse Event page	

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Protocol number BIG 1-06 / EGF106903 Week 43 (W34 targeted therapy)-FU Month
Centre No. Subject No. Page 60
Patient status
Date of physical exam  DD MMM YYYY  Not done
Vital signs and physical measurements
Weight (Kg)
Blood pressure
Heart rate (beats/min)
ECOG performance status
Are there any changes since the previous assessment?
☐ No ☐ Yes → Specify below
Recurrence of disease (complete the "Recurrence of disease" page)
Second primary malignancy or contralateral breast cancer (complete the "Second primary malignancy and contralateral BC" page)
☐ Significant cardiac disease (complete the "Adverse event" page)
Adverse event (complete the "Adverse event" page)
Death (complete the "Death" page)
☐ Lost to follow-up ☐ Patient withdrew study consent ☐ Date of last contact (or date study consent withdrawn) ☐ DD MMM YYYY
☐ Patient withdrew treatment but remains on follow-up
(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.  The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

#### New York Heart Association (NYHA) Functional Classification

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- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903 Week 43 (W34 targeted therapy)-FU Mor	ıth 9
Centre No.	Subject No. Page	61
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the "Adverse en page.</li> </ul>	vent"
Symptomatic CHF	□ No □ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the question above) ☐ Class II ☐ Class IV	
EKG should be performe the "Unscheduled EKG" p	d at any time if symptoms or clinical suspicion are present and reported on page	
Haematology and biod	chemistry	
	d tests that should be done at this visit, as per protocol, and report any CI CTCAE G3-4) abnormality on the "Adverse event" page.	
Date blood drawn	DD MMM YYYY	
Result [	<ul> <li>Normal</li> <li>Abnormal - Not clinically significant</li> <li>Abnormal - Clinically significant (G3-4) → Report on Adverse Event page</li> </ul>	,

Pro	otocc	ol nu	mbe	er B	IG 1	-06	/ E(	GF1	069	03	VV	eek	43 (۷۷34	targete	a tnera	оу)-г	) Wonth 9
	C	enti	re N	lo.				Sı	ubje	ct N	lo.						Page 62

This page has been deleted from CRF version 4.0 due to changed timelines for CTC blood collection

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be

➤ Date of last contact (or date study consent withdrawn)

☐ Death (complete the "Death" page)

☐ Patient withdrew study consent

☐ Lost to follow-up

alive.

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln 1500="" mm<sup="" –="">3 <lln 1.5="" 10<sup="" x="" –="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903	Follow-up month 12
Centre No.	Subject No.	Page 64
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluation Ec	hocardiogram JGA scan
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please page.</li> </ul>	e complete the "Adverse event"
Symptomatic CHF	<ul><li>□ No</li><li>□ Yes → Specify below</li></ul>	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick III☐ Class III☐ Class IV	No for the question above)
EKG should be performe the "Unscheduled EKG"	d at any time if symptoms or clinical suspicion are រុ page	present and reported on

Haematology and b	piochemistry					
Please check the blood tests that should be done at this visit, as per protocol, and report any clinically significant (NCI CTCAE G3-4) abnormality on the "Adverse event" page.						
Date blood drawn	DD MMM YYYY					
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant (G3-4) → Report on Adverse Event page, if related to study drug</li> </ul>					

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Protocol number BIG 1-06 / EGF106903	1-06 /		Follow-up month 1
Centre No.		Subject No.	Page 65
Type of radiological examination	amina	lon	
ž	Not done	Date of test  Are there any <u>clinically significant</u> abnormalities?  (DD/MMM/YYYY)  (Please report a short description)	
Abdominal CT-scan			
Chest X-ray			
Chest CT-scan			
Bone scan (scintigraphy)			
Bone X-ray			
Bone CT-scan			
Bilateral mammography			
Left mammography, only			

Study: Neo-ALTTO v. 6.0 (19Mar09)

」□ No □ Yes —➤ Specify-

Right mammography, only

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

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Type of radiological examination (continued)

Are there an <u>y clinically significant</u> abnormalities? (Please report a short description)	□ No □ Yes → Specify □ □ · · · · · · · · · · · · · · · · ·	□ No □ Yes —> Specify ————————————————————————————————————
Date of test A		D NMM DD D
Side (L or R)		
ype of Anatomical Side adiological site** (L or R) xamination*		
ype of adiological xamination*	$\exists$	7

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Protocol number BIG 1-06 / EGF106903	Follow-up month 1
Centre No. Subject No.	Page 67
Patient status	
Date of physical exam  DD MMM YYYY	ot done
Vital signs and physical measurements	
Weight (Kg)	
Blood pressure systolic / diastolic	
Heart rate (beats/min)	
ECOG performance status	
Are there any changes since the previous assessment?  ☐ No ☐ Yes → Specify below	
☐ Recurrence of disease (complete the "Recurrence of disease" page)	
<ul> <li>Second primary malignancy or contralateral breast cancer (complete the and contralateral BC" page)</li> </ul>	e "Second primary malignancy
☐ Significant cardiac disease (complete the "Adverse event" page)	
Adverse event (complete the "Adverse event" page)	

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

> Date of last contact (or date study consent withdrawn)

☐ Death (complete the "Death" page)

☐ Patient withdrew study consent

☐ Lost to follow-up

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

Study: Neo-ALTTO v. 6.0 (19Mar09)

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ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

➤ Date of last contact (or date study consent withdrawn)

☐ Death (complete the "Death" page)

☐ Patient withdrew study consent

☐ Lost to follow-up

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln 1500="" mm<sup="" –="">3 <lln 1.5="" 10<sup="" x="" –="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903	Follow-up month 18
Centre No.	Subject No.	Page 69
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluation	Echocardiogram MUGA scan
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>→ Pleading</li> </ul>	
Symptomatic CHF	<ul><li>□ No</li><li>□ Yes → Specify below</li></ul>	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tic ☐ Class II ☐ Class III ☐ Class IV	k No for the question above)
EKG should be performe the "Unscheduled EKG" p	d at any time if symptoms or clinical suspicion ar page	e present and reported on
Haematology and biod	chemistry	

Haematology and bi	iochemistry
	ood tests that should be done at this visit, as per protocol, and report any (NCI CTCAE G3-4) abnormality on the "Adverse event" page.
Date blood drawn	DD MMM YYYY
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant (G3-4) → Report on Adverse Event page, if related to study drug</li> </ul>

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Pro	otocol number BIG 1-06 / EGF106903	Follow-up month 2
	Centre No. Subject No.	Page 70
Ра	tient status	
D	ate of physical exam  DD MMM YYYY	□ Not done
Vit	tal signs and physical measurements	
W	/eight (Kg)	
ВІ	lood pressure / diastolic	
Н	eart rate (beats/min)	
E	COG performance status	
Are	e there any changes since the previous assessment?  ☐ No ☐ Yes → Specify below	
	Recurrence of disease (complete the "Recurrence of disease" page	e)
	Second primary malignancy or contralateral breast cancer (compleand contralateral BC" page)	ete the "Second primary malignancy
	Significant cardiac disease (complete the "Adverse event" page)	
	Adverse event (complete the "Adverse event" page)	
	Death (complete the "Death" page)	

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

➤ Date of last contact (or date study consent withdrawn)

☐ Lost to follow-up

☐ Patient withdrew study consent

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Protocol number BIG 1	I-06 / EGF106903	Follow-up month 24
Centre No.	Subject No.	Page 71
Patient status		
Date of physical exam	DD MMM YYYY	☐ Not done
Vital signs and physica	ıl measurements	
Weight (Kg)		
Blood pressure	systolic diastolic	
Heart rate (beats/min)		
ECOG performance status	s 🔲	
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluati	ion ☐ Echocardiogram ☐ MUGA scan
	<ul><li>□ Normal</li><li>□ Abnormal - Not clinically significan</li><li>□ Abnormal - Clinically significant</li></ul>	t  Please complete the "Adverse event" page.
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic C☐ Class II☐ Class III☐ Class IV	CHF, tick No for the question above)

EKG should be performed at any time if symptoms or clinical suspicion are present and reported on the "Unscheduled EKG" page

# NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils			<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Follow-u	month	24
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Protocol number E	BIG 1-06 / EGF106903	Follow-up month 2
Centre No.	Subject No.	Page 72
	piochemistry  plood tests that should be done at this visit  t (NCI CTCAE G3-4) abnormality on the "A	· · · · · · · · · · · · · · · · · · ·
Result	DD MMM YYYY  ☐ Normal ☐ Abnormal - Not clinically significant ☐ Abnormal - Clinically significant (G3	I

### **Translational research**

Type of tissue		s sample ained?	Date of specimen collection
	No	Yes	(dd/mmm/yyyy)
Additional blood sample for CTC* (only in selected centres)			

<sup>\*</sup>Circulating tumor cells

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Page 73		<u>nificant</u> abnormalities? ption)									
		<mark>clinically sic</mark> a short descr	→ Specify -	→ Specify -	→ Specify -	→ Specify -	→ Specify -	→ Specify -	→ Specify -	→ Specify-	→ Specify-
Subject No.	ıation	Date of test (DD/MMM/YYYY)	No	No	No	No	No	No	No	No	No
Centre No.	Type of radiological examin≀	Not don	Abdominal CT-scan	Chest X-ray □	Chest CT-scan	Bone scan (scintigraphy)	Bone X-ray	Bone CT-scan	Bilateral mammography	Left mammography, only	Right mammography, only
	Subject No.	Subject No.	Subject No.  Date of test  Are there any clinically significant abnormalities?  (Please report a short description)	Subject No.  Date of test  Are there any clinically significant abnormalities?  DD/MMM/YYYY)  (Please report a short description)	Subject No.  Date of test Are there any clinically significant abnormalities?  DD/MMM/YYYY) (Please report a short description)	Subject No.	Subject No.  Date of test Are there any clinically significant abnormalities?  Downwhy YYYY) (Please report a short description)	Subject No.		Date of test   Are there any clinically significant abnormalities?	

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

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Protocol number BIG 1-06 / EGF106903		Follow-up
Centre No.	Subject No.	
Type of radiological examination (continued)	nation (continued)	

Are there any clinically significant abnormalities? (Please report a short description) □ No □ Yes —➤ Specify □ No □ Yes → Specify Date of test (LorR) Anatomical site\*\* examination\* radiological Type of

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Protocol num	ber BIG 1	-06 / EGF106903	Follow-up month 3
Centre	No.	Subject No.	Page 75
Patient status			
Date of physica	al exam	DD MMM YYYY	☐ Not done
Vital signs an	d physica	ıl measurements	
Weight (Kg)			
Blood pressure	<b>:</b>	systolic / diastolic	
Heart rate (bea	its/min)		
ECOG perform	ance status	s	
Are there any ch	nanges sinc	the previous assessment? ☐ No ☐ Yes → Specify below	
☐ Recurrence	of disease	(complete the "Recurrence of disease" p	page)
☐ Second primand contrals	nary malign nteral BC" p	ancy or contralateral breast cancer <i>(con</i> age)	nplete the "Second primary malignancy
☐ Significant of	ardiac dise	ase (complete the "Adverse event" page	*)
☐ Adverse eve	ent (comple	te the "Adverse event" page)	

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be

> Date of last contact (or date study consent withdrawn)

☐ Death (complete the "Death" page)

☐ Patient withdrew study consent

☐ Lost to follow-up

alive.

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

➤ Date of last contact (or date study consent withdrawn)

☐ Significant cardiac disease (complete the "Adverse event" page)

☐ Adverse event (complete the "Adverse event" page)

☐ Death (complete the "Death" page)

□ Patient withdrew study consent

☐ Lost to follow-up

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

#### New York Heart Association (NYHA) Functional Classification

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

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Protocol number BIG	1-06 / EGF106903	Follow-up month 3
Centre No.	Subject No.	Page 77
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluation	Echocardiogram MUGA scan
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Ple pa</li> </ul>	ease complete the "Adverse event ge.
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tide)☐ Class II☐ Class III☐ Class IV	ck No for the question above)
EKG should be performed the "Unscheduled EKG" p	d at any time if symptoms or clinical suspicion a page	re present and reported on
	hemistry If tests that should be done at this visit, as per poly CI CTCAE G3-4) abnormality on the "Adverse of	
Date blood drawn	DD MMM YYYY	
Result [	<ul> <li>Normal</li> <li>Abnormal - Not clinically significant</li> <li>Abnormal - Clinically significant (G3-4) → F</li> </ul>	Report on Adverse Event

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-06 / EGF106903 Follow-up month 3	Subject No. Page 78	amination	Not done Date of test Are there any <u>clinically significant</u> abnormalities?  (DD/MMM/YYYY) (Please report a short description)	□	□	□	□	□	□	□	□	□
06 / EGF106903	Subject N	nination										
Protocol number BIG 1-06 / EGF106903	Centre No.	Type of radiological examination	Note	Abdominal CT-scan	Chest X-ray	Chest CT-scan	Bone scan (scintigraphy)	Bone X-ray	Bone CT-scan	Bilateral mammography	Left mammography, only	Right mammography, only

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

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Subject No.	
Centre No.	

Type of radiological examination (continued)

Are there an <u>y clinically significant</u> abnormalities? (Please report a short description)		
Date of test	Y MMM dd	DD MMM
Side (L or R)		
Type of Anatomical Side radiological site** (L or R examination*		
Type of radiological examination*		3

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Pro	otocol number BIG 1	-06 / EGF106903	Follow-up month 42
Г	Contro No	Cubiast Na	Page 80
	Centre No.	Subject No.	rage ou
Pa	tient status		
Da	ate of physical exam	DD MMM YYYY	☐ Not done
Vit	al signs and physica	measurements	
W	eight (Kg)		
ВІ	ood pressure	systolic / diastolic	
Н	eart rate (beats/min)		
E	COG performance status		
Are	there any changes since	e the previous assessment?  ☐ No ☐ Yes → Specify below	
	Recurrence of disease	complete the "Recurrence of disease	" page)
	Second primary maligna and contralateral BC" pa	ancy or contralateral breast cancer <i>(coage)</i>	omplete the "Second primary malignancy
	Significant cardiac disea	ase (complete the "Adverse event" pa	ge)
	Adverse event (complet	e the "Adverse event" page)	
	Death (complete the "De	eath" page)	
	Lost to follow-up Patient withdrew study of	Date of last contact (or study consent withdraw	

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

□ Patient withdrew study consent

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity.

  Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Follow-up	month	48
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Protocol number BIG	-06 / EGF106903	Follow-up month 48
Centre No.	Subject No.	Page 82
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluation	☐ Echocardiogram ☐ MUGA scan
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> </ul>	➤ Please complete the "Adverse event page.
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CH☐ Class II☐ Class III☐ Class IV	F, tick No for the question above)
EKG should be performed the "Unscheduled EKG" p	l at any time if symptoms or clinical suspici age	ion are present and reported on
Haematology and bioc	•	
	tests that should be done at this visit, as post CTCAE G3-4) abnormality on the "Adve	
Date blood drawn	DD MMM YYYY	
Result [	Normal Abnormal - Not clinically significant Abnormal - <u>Clinically significant (G3-4)</u> -	→ Report on Adverse Event page, if related to study drug

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Page 83		<b>Are there any <u>clinically significant</u> abnormalities?</b> (Please report a short description)									
		clinically s a short des	- ➤ Specify -	→ Specify	→ Specify	→ Specify	→ Specify	→ Specify	→ Specify	→ Specify-	-≯ Specify-
		<b>Are there any <u>clinically significa</u></b> (Please report a short description)	- Sey Yes -	- Sey	- Sey	- Sey	No D	No D	No D		- Sey
Subject No.	ou	Date of test (DD/MMM/YYYY)									
	aminati	Not done	_	_	_	_		_	_	_	_
Centre No.	Type of radiological examination	ON	Abdominal CT-scan	Chest X-ray	Chest CT-scan	Bone scan (scintigraphy)	Bone X-ray	Bone CT-scan	Bilateral mammography	Left mammography, only	Right mammography, only

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
cs	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
$\prec$	Kidney	SP	Spleen
PT	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

Protocol number BIG 1-06 / EGF106903	Follow-up month 4
Centre No. Subject No.	
	Page 84
Type of radiological examination (continued)	

Are there any clinically significant abnormalities?

Date of test

(LorR)

examination\* radiological Type of

Anatomical site\*\*

(Please report a short description)

□ No □ Yes —➤ Specify

□ No □ Yes → Specify

\* BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Pr	otocol number BIG 1-06 / EGF	-106903	Follow-up month 5
	Centre No.	Subject No.	Page 85
Pa	tient status		
D	ate of physical exam DD	MMM YYYY	☐ Not done
Vit	al signs and physical measure	ements	
V	reight (Kg)		
В	lood pressure	diastolic	
Н	eart rate (beats/min)		
Е	COG performance status		
Are	e there any changes since the previo ☐ No ☐ Yes —	ous assessment?  ➤ Specify below	
	Recurrence of disease (complete the	he "Recurrence of disease" p	age)
	Second primary malignancy or con and contralateral BC" page)	tralateral breast cancer (com	plete the "Second primary malignancy
	Significant cardiac disease (comple	ete the "Adverse event" page	)
	Adverse event (complete the "Adve	erse event" page)	
	Death (complete the "Death" page)	)	
	Lost to follow-up Patient withdrew study consent	→ Date of last contact (or destudy consent withdrawn	

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

study consent withdrawn)

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

Study: Neo-ALTTO v. 6.0 (19Mar09)

DD

MMM

YYYY

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

#### New York Heart Association (NYHA) Functional Classification

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Protocol number BIG	1-06 / EGF106903	Follow-up month 6
Centre No.	Subject No.	Page 86
Patient status		
Date of physical exam	DD MMM YYYY	☐ Not done
Vital signs and physic	al measurements	
Weight (Kg)		
Blood pressure	systolic diastolic	
Heart rate (beats/min)		
ECOG performance stat	us 🔲	
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluation	on ☐ Echocardiogram ☐ MUGA scan
	<ul><li>☐ Normal</li><li>☐ Abnormal - Not clinically significant</li><li>☐ Abnormal - Clinically significant</li></ul>	Please complete the "Adverse event page.
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic Cl☐ Class II ☐ Class III ☐ Class IV	HF, tick No for the question above)
EKG should be performe the "Unscheduled EKG"	ed at any time if symptoms or clinical suspic page	cion are present and reported on

## NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Follow-up	o month 60
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Protocol number BIG 1-06 / EGF106903			Follow-up month 6
	Centre No.	Subject No.	Page 87

Haematology and bi	ochemistry		
Please check the blood tests that should be done at this visit, as per protocol, and report any clinically significant (NCI CTCAE G3-4) abnormality on the "Adverse event" page.			
Date blood drawn	DD MMM YYYY		
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant (G3-4) → Report on Adverse Event page, if related to study drug</li> </ul>		

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Protocol	Į

Subject No.	
Centre No.	

Type of radiological examination

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

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Type of radiological examination (continued)

Are there any <u>clinically significant</u> abnormalities? (Please report a short description)	No     Specify	
Date of test	Y MMM GG	Y MMM dd
Side (L or R)		
Type of Anatomical Side radiological site** (L or R) examination*		
Type of radiological examination*		]

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

# **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity.

  Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903	Year 6
Centre No.	Subject No.	Page 91
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│ │	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the page.</li> </ul>	"Adverse event"
Symptomatic CHF	<ul><li>□ No</li><li>□ Yes → Specify below</li></ul>	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the questi ☐ Class II ☐ Class IV	on above)
EKG should be performe the "Unscheduled EKG"	d at any time if symptoms or clinical suspicion are present and rep page	orted on
Haematology and biod	chemistry d tests that should be done at this visit, as per protocol, and report	anv
	CI CTCAE G3-4) abnormality on the "Adverse event" page.	апу
Date blood drawn		

MMM

Result

□ Normal
 □ Abnormal - Not clinically significant
 □ Abnormal - Clinically significant (G3-4) → Report on Adverse Event page, if related to study drug

Protocol number BIG 1-06 / EGF106903	/ 90-	GF106903 Year
Centre No.		Subject No.
	_	
Type of radiological examination	amina	uo
ON	Not done	Date of test  Are there any <u>clinically significant</u> abnormalities? (DD/MMM/YYYY)  (Please report a short description)
Abdominal CT-scan		No
Chest X-ray		
Chest CT-scan		
Bone scan (scintigraphy)		No
Bone X-ray		
Bone CT-scan		
Bilateral mammography		
Left mammography, only		
Right mammography, only		

Study: Neo-ALTTO v. 6.0 (19Mar09)

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

Centre No.

Date of test  Are there any <u>clinically significant</u> abnormalities?  (Please report a short description)		
Date of test	-	-
Side (L or R)		
Anatomical Side site** (Lor R	]	]
Type of A radiological examination*	]	]

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

# **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity.

  Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903	Year 7
Centre No.	Subject No.	Page 95
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	☐ Echocardiogram ☐ MUGA scan	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the "Adv page.</li> </ul>	erse event"
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the question a☐ Class II☐ Class III☐ Class IV	bove)
EKG should be performe the "Unscheduled EKG" <sub>l</sub>	ed at any time if symptoms or clinical suspicion are present and reported page	d on
	chemistry d tests that should be done at this visit, as per protocol, and report any CI CTCAE G3-4) abnormality on the "Adverse event" page.	

Please check the blood tests that should be done at this visit, as per protocol, and report any clinically significant (NCI CTCAE G3-4) abnormality on the "Adverse event" page.

Date blood drawn

DD MMM YYYYY

Result

Normal

Abnormal - Not clinically significant

Abnormal - Clinically significant (G3-4) -> Report on Adverse Event page, if related to study drug

Protocol number BIG 1-06 / EGF106903	-06 / E		Yeal
Centre No.		Subject No.	Page 96
Type of radiological examination	aminati	uc	
°Z	Not done	Date of test  Are there any <u>clinically significant</u> abnormalities? (DD/MMM/YYYY)  (Please report a short description)	
Abdominal CT-scan			
Chest X-ray	_		
Chest CT-scan			
Bone scan (scintigraphy)		No	
Bone X-ray	_		
Bone CT-scan	_		
Bilateral mammography			
Left mammography, only	_		
Right mammography, only		No	

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

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Subject No.	
Centre No.	

Protocol number BIG 1-06 / EGF106903

Type of radiological examination (continued)

Are there an <u>y clinically significant</u> abnormalities? (Please report a short description)	□ No □ Yes → Specify □ Yes	□ No □ Yes → Specify
Date of test	DD MMM	DD MMM
Side (L or R)		
Anatomical Side site** (L or R		
Type of Anatomic radiological site** examination*	]	

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

# **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

Pro	otocol number BIG 1-06 / E0	GF106903	Year 8
	Centre No.	Subject No.	Page 98
Pat	ient status		
Da	ate of physical exam DD	MMM YYYY	☐ Not done
Vit	al signs and physical measu	rements	
W	eight (Kg)		
ВІ	ood pressure	colic diastolic	
Н	eart rate (beats/min)		
E	COG performance status		
Are	there any changes since the pre  No Yes	vious assessment?  -> Specify below	
	Recurrence of disease (complete	e the "Recurrence of disease" p	page)
	Second primary malignancy or c and contralateral BC" page)	ontralateral breast cancer <i>(con</i>	nplete the "Second primary malignancy
	Significant cardiac disease (com	plete the "Adverse event" page	a)
	Adverse event (complete the "Ad	dverse event" page)	
	Death (complete the "Death" pag	ge)	
	Lost to follow-up	Date of last contact (or o	late   ,   , .
	Patient withdrew study consent	> Date of last contact (or c study consent withdrawn	n) DD MMM YYYY

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

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- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln 1500="" mm<sup="" –="">3 <lln 1.5="" 10<sup="" x="" –="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Year	8
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Protocol number BIG	1-06 / EGF106903	Year
Centre No.	Subject No.	Page 99
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│ │	mı
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete page.</li> </ul>	the "Adverse event
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the qu☐ Class II ☐ Class III ☐ Class IV	uestion above)
EKG should be performe the "Unscheduled EKG"	ed at any time if symptoms or clinical suspicion are present and page	reported on
	chemistry d tests that should be done at this visit, as per protocol, and re CI CTCAE G3-4) abnormality on the "Adverse event" page.	port any
Date blood drawn	DD MMM YYYY	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant (G3-4) → Report on Adversary</li> <li>□ page, if related</li> </ul>	

Protocol number BIG 1-06 / EGF106903	/ 90-	EGF106903 Year 8	Ø
Centre No.		Subject No.	
		Page 100	0
	_		
Type of radiological examination	amina	ion	
O.	Not done	Date of test  Are there any <u>clinically significant</u> abnormalities?  (DD/MMM/YYYY)  (Please report a short description)	
Abdominal CT-scan			
Chest X-ray			
Chest CT-scan			
Bone scan (scintigraphy)			
Bone X-ray			
Bone CT-scan			
Bilateral mammography			
Left mammography, only			
Right mammography, only		No	

Study: Neo-ALTTO v. 6.0 (19Mar09)

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

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3 1-06
·BIG
number
Protocol

Subject No.	
Centre No.	

Type of radiological examination (continued)

Are there an <u>y clinically significant</u> abnormalities? (Please report a short description)	□ No □ Yes → Specify	□ No □ Yes —➤ Specify ————————————————————————————————————
Date of test	DD MMM YYYY	DD MMM YYYY
Side (L or R)		
Anatomical Side site** (Lor R		
ype of Ar adiological xamination*	7	$\exists$

\* BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

# **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Protocol number BIG	1-06 / EGF106903	Year 9
Centre No.	Subject No.	Page 103
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the "Advergage.</li> </ul>	erse event"
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the question all ☐ Class II ☐ Class III ☐ Class IV	ove)
EKG should be performed the "Unscheduled EKG" p	d at any time if symptoms or clinical suspicion are present and reported page	' on
Haematology and bioc	hemistry	
	d tests that should be done at this visit, as per protocol, and report any CI CTCAE G3-4) abnormality on the "Adverse event" page.	

MMM

□ Normal
 □ Abnormal - Not clinically significant
 □ Abnormal - Clinically significant (G3-4) → Report on Adverse Event page, if related to study drug

Date blood drawn

Result

Protocol number BIG 1-06 / EGF106903	/ 90-	EGF106903 Year
Centre No.		Subject No.
		Page 104
	_	
Type of radiological examination	amina	tion
Ŏ	Not done	Date of test  Are there any <u>clinically significant</u> abnormalities? (DD/MMM/YYYY)  (Please report a short description)
Abdominal CT-scan		
Chest X-ray		
Chest CT-scan		
Bone scan (scintigraphy)		
Bone X-ray		
Bone CT-scan		
Bilateral mammography		
Left mammography, only		
Right mammography, only		

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
cs	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
$\prec$	Kidney	SP	Spleen
PT	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

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1-06 / EGF106903	Subject No.	amination (continued)
Protocol number BIG 1-06 / EGF106903	Centre No.	Type of radiological examination (continued)

Are there any clinically significant abnormalities? (Please report a short description) □ No □ Yes → Specify □ No □ Yes → Specify Date of test (LorR) Anatomical site\*\* examination\* radiological Type of

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

#### **ECOG** performance status

ECOG	Performance status	Approximate Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	90 - 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70 - 80
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 - 60
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	30 - 40
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	10 - 20

☐ Adverse event (complete the "Adverse event" page)

☐ Death (complete the "Death" page)

☐ Lost to follow-up

□ Patient withdrew study consent

→ Date of last contact (or date study consent withdrawn)

(For patients "Lost to Follow-up", the date of last contact should be the last date the patient was known to be alive.

The last date the patient was known to be alive could either be the same as the previous reported visit date or any date between the previous visit and this one.)

#### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<lln -="" 1500="" mm<sup="">3 <lln -="" 1.5="" 10<sup="" x="">9/L</lln></lln>	<1500 – 1000/mm³ <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm³ <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm³ <0.5 x 10 <sup>9</sup> /L	Death
WBC	<lln -="" 3000="" mm<sup="">3 <lln -="" 10<sup="" 3.0="" x="">9/L</lln></lln>	<3000 – 2000/mm³ <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm³ <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm³ <1.0 x 10 <sup>9</sup> /L	Death
Haemoglobin	<lln -="" 10.0="" dl<br="" g=""><lln -="" 6.2="" l<br="" mmol=""><lln -="" 100="" g="" l<="" td=""><td>&lt;10.0 – 8.0 g/dL &lt;6.2 – 4.9 mmol/L &lt;100 – 80 g/L</td><td>&lt;8.0 – 6.5 g/dL &lt;4.9 – 4.0 mmol/L &lt;80-65 g/L</td><td>&lt;6.5 g/dL &lt;4.0 mmol/L &lt;65 g/L</td><td>Death</td></lln></lln></lln>	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Platelets	<lln -75,000="" mm<sup="">3 <lln-75.0 10<sup="" x="">9/L</lln-75.0></lln>	<75,000-50,000/mm³ <75.0-50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm³ <50.0-25.0 x 10 <sup>9</sup> /L	<25,000/mm³ <25.0 x 10 <sup>9</sup> /L	Death
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	
Serum creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death

Year	1	0
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Protocol number BIG	1-06 / EGF106903	Year 1
Centre No.	Subject No.	Page 107
Cardiac monitoring		
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│ │ │ │ │ │ │ │ │ │ │ │ │	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the "page.</li> </ul>	Adverse event
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the questic ☐ Class II ☐ Class III ☐ Class IV	on above)
EKG should be performed the "Unscheduled EKG" p	d at any time if symptoms or clinical suspicion are present and repo page	orted on
	hemistry It tests that should be done at this visit, as per protocol, and report a CI CTCAE G3-4) abnormality on the "Adverse event" page.	any
Date blood drawn	DD MMM YYYY	
Result [	☐ Normal ☐ Abnormal - Not clinically significant ☐ Abnormal - Clinically significant (G3-4) → Report on Adverse E page, if related to sta	

Year 10		Page 108
)6 / EGF106903	Subject No.	
Protocol number BIG 1-06 / EGF106903	Centre No.	

Type of radiological examination

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

Protocol number BIG 1-06 / EGF106903	3 / EGF106903	Year 1
Centre No.	Subject No.	
		Page 109
Type of radiological examination (continued)	ination (continued)	

Type

Are there an <u>y clinically significant</u> abnormalities? (Please report a short description)	□ No □ Yes → Specify □ Yes	□ No □ Yes → Specify ─────
Date of test	DD MMM TYYYY	DD MMM
Side (L or R)		
ype of Anatomical Side adiological site** (L or R) xamination*		
ype of adiological xamination*	7	$\exists$

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

Hormonotherapy

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Subject No. Centre No.

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### Hormone therapy for primary breast cancer

Has the patient received hormone therapy before or during the trial?

☐ Yes → Specify below **%**□

Name of treatment* or surgical procedure	Dose	Units	Adjuvant hormonal therapy start date (dd/mmm/yyyy)	Adjuvant hormonal therapy end date (dd/mmm/yyyy)	Ongoing at time of study completion
Tamoxifen		mg			
Anastrozole		mg			
Letrozole		mg			
Exemestane		mg			
Goserelin		mg			
Other LH-RH analogue:		mg			
Bilateral ovariectomy/oophorectomy	AN	NA		ΨZ	NA

<sup>\*</sup> generic name whenever possible, record only one per line

/6 / EGF106903	Subject No.	
Protocol number BIG 1-06 / EGF106903	Centre No.	

### Adjuvant radiotherapy for primary breast cancer

Specify below
$\uparrow$
∃Yes
<b>8</b> □
Radiation therapy

Radiation therapy site	Side		Total dose	_	Radiation therapy start date	Radiation therapy end date
	left r	right	of radiation therapy	1=Gy (100rads) 2=cGy 3=Rads	(dd/mmm/yyyy)	(dd/mmm/dd/)
Breast					-	-
Chest wall						
Axilla						
Supraclavicular area						
Internal mammary nodes						
Tumor bed, boost						

Note: in case of mastectomy, please report the site as chest wall instead of breast

In case of treatment given as study treatment pre-medication or any prophylaxis treatment given intermittently, please report only one line with start date of first administration and end date of last administration.

#### **Concomitant treatments**

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Protocol number BIG 1-06 / EGF106903

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Concomitant relevant treatments and/or surgical procedures (Please report here also <u>significant</u> treatments ongoing from screening or surgical procedures performed before screening)

Name of treatment (generic name whenever possible, record only one per line)	Indication for use	Date started (dd/mmm/yyyy)	Date stopped (dd/mmm/yyyy)	Ongoing (at time of study completion)
	5=Prophylactic 9=Curative			
Bisphosphonate, specify:				
Oestrogen replacement, specify:				
Prophylactic mastectomy ☐ Left or ☐ Right		-	ΑN	NA
Breast reconstruction ☐ Left or ☐ Right			ΥN	ΥN

In case of treatment given as study treatment pre-medication or any prophylaxis treatment given intermittently, please report only one line with start date of first administration and end date of last administration.

#### **Concomitant treatments**

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Protocol number BIG 1-06 / EGF106903

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Subject	
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Concomitant relevant treatments and/or surgical procedures (Please report here also <u>significant</u> treatments ongoing from screening or surgical procedures performed before screening)

News of treatment (see also <u>significant</u> treatments originally from screening of surgical procedures performed before screening).	ongoing none	Creening or surgical procedu		Ongoing (of time of
ne wnenever	for use	dd/mmm/yyyy)	dd/mmm/yyyy)	Study completion)
	5=Prophylactic 9=Curative			<b>&gt;</b>
		-	-	
		-	-	

In case of treatment given as study treatment pre-medication or any prophylaxis treatment given intermittently, please report only one line with start date of first administration and end date of last administration.

#### **Concomitant treatments**

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Protocol number BIG 1-06 / EGF106903

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Concomitant relevant treatments and/or surgical procedures (Please report here also <u>significant</u> treatments ongoing from screening or surgical procedures performed before screening)

<b>5</b> ~							
Ongoing (at time of study completion)	•						
Date stopped (dd/mmm/yyyy)							
Date started (dd/mmm/yyyy)							
Indication for use	5=Prophylactic 9=Curative						
Name of treatment (generic name whenever possible, record only one per line)							

Dose delay: please note that the delay of +/- 1 day from the planned cycle date is not considered as a delay

### Primary reason for dose delay or reduction

Code	Description	Examples
~	Haematologic adverse event (Report Adverse Event)	
2	Cardiac adverse event (Report Adverse Event)	
3	Adverse event other than haematologic or cardiac (Report Adverse Event)	
4	Dosing error	
	Subject non-compliance	- Patient's holiday - Patient's request - Personal reasons
6	Administrative reasons	<ul> <li>- Public holiday</li> <li>- Investigator or study staff error</li> <li>- Delivery of study medication delayed</li> </ul>
ОТ	Other	None of the above

### Administration of study drug

Protocol number BIG 1-06 / EGF106903

Centre No. Subject No.

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#### Administration of Paclitaxel

Date agent administered	Dose (mg/m²)	Total dose (mq)	Total dose   Was treatment delayed?	>	Vas do	Was dose reduced?
(dd/mmm/yyyy)	,		No Yes, specify code*		No Ye	Yes, specify code*
			□ □ If OT, specify			l lifOT, specify
				<u> </u>		
			☐ ☐ If OT, specify			l if OT, specify
			☐ ☐ If OT, specify			if OT, specify
			□ □ If OT, specify	-		□ If OT, specify
			□ □ If OT, specify			l L I if OT, specify
			□ □ If OT, specify			if OT, specify
			□ □ If OT, specify			l I if OT, specify
-						

\*See adjacent table for coding of primary reason for delay of treatment or dose reduction

Dose delay: please note that the delay of +/- 1 day from the planned cycle date is not considered as a delay

### Primary reason for dose delay or reduction

Code	Description	Examples
~	Haematologic adverse event (Report Adverse Event)	
2	Cardiac adverse event (Report Adverse Event)	
3	Adverse event other than haematologic or cardiac (Report Adverse Event)	
4	Dosing error	
	Subject non-compliance	- Patient's holiday - Patient's request - Personal reasons
6	Administrative reasons	<ul> <li>- Public holiday</li> <li>- Investigator or study staff error</li> <li>- Delivery of study medication delayed</li> </ul>
ОТ	Other	None of the above

### Administration of study drug

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Protocol number BIG 1-06 / EGF106903

Centre No.

Subject No.

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#### Administration of Paclitaxel

Date agent administered	Dose (mg/m²)	Total dose   Was treatment delayed?	Was	treatm	ent del	ayed?	>	Vas c	lose r	Was dose reduced?	d?	
(dd/mmm/yyyy)	)		Š		Yes, specify code*	ode*	Z	No	res, s	pecify	Yes, specify code*	
				_		j if OT, specify					☐ if OT, specify	pecify
							<u> </u> 					
						if OT, specify					If OT, specify	specify
						if OT, specify					if OT, specify	pecify
-							<u> </u> 					
						if OT, specify	<del>                                     </del>				If OT, specify	specify
-												
						if OT, specify	-				☐ if OT, specify	specify
						if OT, specify					☐ if OT, specify	pecify
				_		if OT, specify					If OT, specify     If O	pecify
							<u> </u>					

\*See adjacent table for coding of primary reason for delay of treatment or dose reduction

Primary reason for dose delay or reduction

Code	Description	Examples
-	Haematologic adverse event (Report Adverse Event)	
2	Cardiac adverse event (Report Adverse Event)	
8	Adverse event other than haematologic or cardiac (Report Adverse Event)	
4	Dosing error	
7	Subject non-compliance	- Patient's holiday - Patient's request - Personal reasons
6	Administrative reasons	<ul> <li>- Public holiday</li> <li>- Investigator or study staff error</li> <li>- Delivery of study medication delayed</li> </ul>
ОТ	Other	None of the above

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3 / EGF106903	Subject No.
Protocol number BIG 1-06 / EGF106903	Centre No.

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Name of treatment	Date agent administered	Dose (mg/m²)	Total dose (mg)	Was treatment delayed?	Was dose reduced?
	(dd/mmm/yyyy)		<u>,</u>	No Yes, specify code*	No Yes, specify code*
Fluorouracil				□ □   If OT, specify	□ □ If OT, specify
Epirubicin				□ □ If OT, specify	□ □ If OT, specify
Cyclophosphamide				□ □ If OT, specify	□ □ If OT, specify
Fluorouracil	-			□ □ If OT, specify	□ □ If OT, specify
Epirubicin				□ □ If OT, specify	□ □ If OT, specify
Cyclophosphamide				□ □ If OT, specify	□ □ If OT, specify

<sup>\*</sup>See adjacent table for coding of primary reason for delay of treatment or dose reduction

Primary reason for dose delay or reduction

Code	Description	Examples
-	Haematologic adverse event (Report Adverse Event)	
2	Cardiac adverse event (Report Adverse Event)	
8	Adverse event other than haematologic or cardiac (Report Adverse Event)	
4	Dosing error	
7	Subject non-compliance	- Patient's holiday - Patient's request - Personal reasons
6	Administrative reasons	<ul> <li>- Public holiday</li> <li>- Investigator or study staff error</li> <li>- Delivery of study medication delayed</li> </ul>
ОТ	Other	None of the above

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FEC adjuvant treatment

Subject No.

Centre No.

Protocol number BIG 1-06 / EGF106903

Vame of treatment	Date agent administered	Dose (ma/m²)	Total dose	Total dose   Was treatment delayed?	Was dose reduced?
	(dd/mmm/yyyy)		(8)	No Yes, specify code*	No Yes, specify code*
-Iuorouracil	- - - - - -			□ □ If OT, specify	□ □ If OT, specify
oirubicin				□ □ If OT, specify	□ □ If OT, specify
abimedusodaolox				□ □ If OT, specify	□ □ If OT, specify

\*See adjacent table for coding of primary reason for delay of treatment or dose reduction

# Completion instruction in case of Lapatinib interruption or dose reduction:

In case of interruption, please tick the checkbox "Yes" for "Was treatment interrupted?", report the stop date (last date of administration before interruption) and start a new line with the first day the treatment is restarted as the start date. If the dose is reduced, please enter the last date of administration (before the dose reduction) as the "Date stopped". In the next row, enter the reduced dose, the date treatment is restarted at the reduced dose and tick the checkbox "Yes" for "Was dose reduced?".the reduced dose.

## Primary reason for dose reduction or treatment interruption

Code	Description	Examples
1	Haematologic adverse event (Report Adverse Event)	
2	Cardiac adverse event (Report Adverse Event)	
3	Adverse event other than haematologic or cardiac (Report Adverse Event)	
4	Dosing error	
	Subject non-compliance	- Patient's holiday - Patient's request - Personal reasons
6	Administrative reasons	<ul> <li>- Public holiday</li> <li>- Investigator or study staff error</li> <li>- Delivery of study medication delayed</li> </ul>
ОТ	Other	None of the above

### Administration of study drug

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Protocol number BIG 1-06 / EGF106903

Centre No. Subject No.

#### Administration of Lapatinib

Date started	Date stopped	-	Was treatment interrupted?	Was dose reduced?
(dd/mmm/yyyy)	(dd/mmm/yyyy)	dose of agent (or drug) (mg)	No Yes, specify code*	No Yes, specify code*
		_	□ □ If OT, specify	□ □ If OT, specify
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\*See adjacent table for coding of primary reason for interruption of treatment or dose reduction

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Subject No. Centre No.

Investigational product compliance

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#### Investigational product compliance

Please record the data from the Lapatinib Dispensing Log on this form.

Agent Name	Date tablets dispensed (dd/mmm/yyyy)	Number of tablets dispensed	Date tablets returned (dd/mmm/yyyy)	Number of tablets returned
Lapatinib				

Dose delay: please note that the delays within the limits reported below are not considered as a delay - 3 weekly schedule: +/- 3 days from the planned cycle date - weekly schedule: +/- 1 day from the planned cycle date

Total dose received: if weight changes more than 10% from screening, it is recommended to recalculate the

If the trastuzumab infusion is interrupted and re-started on the same day, please enter the total of all trastuzumab doses given in the same day in one row of the table.

## Primary reason for treatment delay or dose interrupted

Code	Description	Examples
<b>←</b>	Haematologic adverse event (Report Adverse Event)	
2	Cardiac adverse event (Report Adverse Event)	
8	Adverse event other than haematologic or cardiac (Report Adverse Event)	
4	Dosing error	
7	Subject non-compliance	- Patient's holiday - Patient's request - Personal reasons
6	Administrative reasons	<ul> <li>Public holiday</li> <li>Investigator or study staff error</li> <li>Delivery of study medication delayed</li> </ul>
ОТ	Other	None of the above

### Administration of study drug

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Protocol number BIG 1-06 / EGF106903

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ate agent administered	Dose (mg/kg)	Total dose	Was tro	Total dose Was treatment delayed?	/ed?	Was d	Was dose interrupted?
dd/mmm/yyyy)	(By (B))	(B.III)	No Y	Yes, specify code*	*epo	N <sub>o</sub>	Yes, specify code*
					if OT, specify		□ I if OT, specify
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					if OT, specify		□ if OT, specify
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					if OT, specify		□ if OT, specify

\*See adjacent table for coding of primary reason for delay of treatment or dose interruption

Dose delay: please note that the delays within the limits reported below are not considered as a delay - 3 weekly schedule: +/- 3 days from the planned cycle date - weekly schedule: +/- 1 day from the planned cycle date

Total dose received: if weight changes more than 10% from screening, it is recommended to recalculate the

If the trastuzumab infusion is interrupted and re-started on the same day, please enter the total of all trastuzumab doses given in the same day in one row of the table.

## Primary reason for treatment delay or dose interrupted

Code	Description	Examples
<b>←</b>	Haematologic adverse event (Report Adverse Event)	
2	Cardiac adverse event (Report Adverse Event)	
8	Adverse event other than haematologic or cardiac (Report Adverse Event)	
4	Dosing error	
7	Subject non-compliance	<ul><li>- Patient's holiday</li><li>- Patient's request</li><li>- Personal reasons</li></ul>
6	Administrative reasons	<ul> <li>- Public holiday</li> <li>- Investigator or study staff error</li> <li>- Delivery of study medication delayed</li> </ul>
ОТ	Other	None of the above

### Administration of study drug

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Protocol number BIG 1-06 / EGF106903

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Administration of Trastuzumab (cont.)

Date agent administered	Dose (mg/kg)	Total dose (mg)	Was 1	Total dose   Was treatment delayed? (mg)		Was	dose	Was dose interrupted?	oted?	
(dd/mmm/yyyy)		<b>.</b>	No	Yes, specify code*		No	Yes, s	Yes, specify code*	code*	
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\*See adjacent table for coding of primary reason for delay of treatment or dose interruption

Dose delay: please note that the delays within the limits reported below are not considered as a delay - 3 weekly schedule: +/- 3 days from the planned cycle date - weekly schedule: +/- 1 day from the planned cycle date

Total dose received: if weight changes more than 10% from screening, it is recommended to recalculate the

If the trastuzumab infusion is interrupted and re-started on the same day, please enter the total of all trastuzumab doses given in the same day in one row of the table.

## Primary reason for treatment delay or dose interrupted

Code	Description	Examples
<b>←</b>	Haematologic adverse event (Report Adverse Event)	
2	Cardiac adverse event (Report Adverse Event)	
8	Adverse event other than haematologic or cardiac (Report Adverse Event)	
4	Dosing error	
7	Subject non-compliance	<ul><li>- Patient's holiday</li><li>- Patient's request</li><li>- Personal reasons</li></ul>
6	Administrative reasons	<ul> <li>- Public holiday</li> <li>- Investigator or study staff error</li> <li>- Delivery of study medication delayed</li> </ul>
ОТ	Other	None of the above

## Administration of study drug

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Administration of Trastuzumab (cont.)

Date agent administered	Dose (mg/kg)	Total dose (mg)	Total dose   Was treatment delayed?		Was c	Was dose interrupted?
(dd/mmm/yyyy)		<b>.</b>	No Yes, specify code*		No	Yes, specify code*
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\*See adjacent table for coding of primary reason for delay of treatment or dose interruption

Dose delay: please note that the delays within the limits reported below are not considered as a delay - 3 weekly schedule: +/- 3 days from the planned cycle date - weekly schedule: +/- 1 day from the planned cycle date

Total dose received: if weight changes more than 10% from screening, it is recommended to recalculate the

If the trastuzumab infusion is interrupted and re-started on the same day, please enter the total of all trastuzumab doses given in the same day in one row of the table.

# Primary reason for treatment delay or dose interrupted

Code	Description	Fxamples
_	Haematologic adverse event	
	(Report Adverse Event)	
2	Cardiac adverse event	
	(Report Adverse Event)	
3	Adverse event other than	
	haematologic or cardiac	
	(Report Adverse Event)	
4	Dosing error	
7	Subject non-compliance	- Patient's holiday
		- Patient's request
		- Personal reasons
6	Administrative reasons	- Public holiday
		<ul> <li>Investigator or study staff error</li> </ul>
		- Delivery of study medication delayed
OT	Other	None of the above

## Administration of study drug

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Date agent administered	Dose (mg/kg)	Total dose	Was treatment delayed?	ent delaye	d?	Was	Was dose interrupted?
-	ì	(G)	No Yes, sl	Yes, specify code*	* <b>o</b>	8 N	Yes, specify code*
					if OT, specify		□ I if OT, specify
					if OT, specify		□ If OT, specify
					if OT, specify		□ I If OT, specify
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					if OT, specify		□ if OT, specify
					if OT, specify		□ I if OT, specify
					if OT, specify		□ If OT, specify

\*See adjacent table for coding of primary reason for delay of treatment or dose interruption

Dose delay: please note that the delays within the limits reported below are not considered as a delay - 3 weekly schedule: +/- 3 days from the planned cycle date - weekly schedule: +/- 1 day from the planned cycle date

Total dose received: if weight changes more than 10% from screening, it is recommended to recalculate the

If the trastuzumab infusion is interrupted and re-started on the same day, please enter the total of all trastuzumab doses given in the same day in one row of the table.

## Primary reason for dose delay or reduction

Code	Description	Examples
<b>←</b>	Haematologic adverse event (Report Adverse Event)	
2	Cardiac adverse event (Report Adverse Event)	
3	Adverse event other than haematologic or cardiac (Report Adverse Event)	
4	Dosing error	
7	Subject non-compliance	- Patient's holiday - Patient's request - Personal reasons
6	Administrative reasons	- Public holiday - Investigator or study staff error - Delivery of study medication delayed
OT	Other	None of the above

## Administration of study drug

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Administration of Trastuzumab (cont.)

Date agent administered	Dose (mg/kg)	Total dose (mg)	Was 1	Total dose   Was treatment delayed? (mg)		Was	dose	Was dose interrupted?	oted?	
(dd/mmm/yyyy)		<b>.</b>	No	Yes, specify code*		No	Yes, s	Yes, specify code*	code*	
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\*See adjacent table for coding of primary reason for delay of treatment or dose interruption

AE name	<ul> <li>Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available then this must be entered instead.</li> <li>Pre-exisiting conditions, which worsen during the study are to be reported as Adverse Events</li> <li>Use medical terminology in English. Do not use abbreviations.</li> <li>Include the anatomical site.</li> <li>Recurrence of breast cancer must not be recorded as an Adverse Event. Second Primary Malignancy (SPM) must be reported as a Serious Adverse Event</li> </ul>
Serious	<ul> <li>Refer to Protocol 'Definition of a Serious Adverse Event'</li> <li>All deaths thought to be related to the study drug(s) at any time must be reported as an SAE</li> <li>All primary cardiac endpoints (symptomatic CHF and cardiac death) must be reported as an SAE</li> <li>All Grade 4 laboratory abnormalities must be reported as SAEs</li> <li>If the event meets the definition of 'serious', sites must submit the Serious Adverse Event Report to GSK with the exception of sites participating with the CTSU in the United States and Canada which must file an electronic report via the NCI Adverse Event Electronic Reporting System (AdEERS).</li> </ul>
CTCAE begin date	<ul> <li>Events that occur in intermittent episodes must be reported on one line. The start date will be the date of the first episode and the end date will be the date of resolution.</li> <li>If the exact Begin Date is not known, at a minimum record the month and year.</li> </ul>
CTCAE end date	<ul> <li>Complete the end date when the AE becomes 'Resolved' or 'Resolved with sequelae'</li> <li>Leave blank if the AE is 'Resolving' or 'Unresolved'</li> </ul>
Grade (maximum)	<ul> <li>Record the maximum grade that occurred over the duration of the event. Refer to the SPAM for more detail.</li> <li>National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 3.0 will be used for grading of events with the exception of congestive heart failure where the NYHA classification system; NYHA classes I, II, III, and IV replaces NCI-CTCAE v3.0 Grades 1, 2, 3, and 4 respectively.</li> </ul>
Outcome of the adverse event	Leave blank if the adverse event is not resolved. Tick 'Unresolved' or 'Resolving' only if the AE is still ongoing at time of: • Death, withdrawal of consent, recurrence of disease, lost to follow-up, or the end of the 10 year follow-up period. • EXCEPTION: where possible, cardiac, cardio-vascular or study drug-related AEs must be followed until resolution.
Action taken at time of adverse event	<ol> <li>Protocol treatment(s) discontinued: Administration of investigational product(s) was permanently discontinued</li> <li>Study Dose Reduced: Dose is reduced for one or more investigational product(s)</li> <li>None: Investigational product(s) continues even though an adverse event has occurred</li> <li>Protocol treatment(s) delayed (or interrupted): Administration of one or more investigational products was stopped temporarily but then restarted</li> <li>Not applicable: Subject was not receiving investigational product(s) when the event occurred. (e.g. pre- or post-dosing)</li> </ol>
relation to study drug(s)	It is a regulatory requirement for investigators to assess relationships to investigational products based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. Indicate if there was a reasonable possibility that the event was caused by an investigational product. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support a reasonable possibility include e.g. a temporal relationship, a pharmacologically predicted event or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness or relevant medical history, should also be considered.

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Adverse event (AE)
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Relation to study drug	No Yes							
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Action taken at time of adverse event 1=protocol treatment discontinued	2=Study dose reduced 4=None 5=protocol treatment delayed (or interrupted) X=Not applicable							
Outcome of adverse event 1=Resolved 2=Resolving	3=Unresolved 4=Resolved with sequelae 5=Death							
Grade (maximum) Outcome of 1=Mild adverse eve 2=Moderate 1=Resolved 3=Severe 2=Resolving	4=Life threatening 5=Death							
CTCAE end date (dd/mmm/yyyy)								
CTCAE begin date (dd/mmm/yyyy)								
Serious	o Yes			] [				
Ň	o Z							
AE Name								

In case of intermittent episodes, please report on one line with the start date of the first episode and the end date of the last

AE name	<ul> <li>Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available then this must be entered instead.</li> <li>Pre-exisiting conditions, which worsen during the study are to be reported as Adverse Events</li> <li>Use medical terminology in English. Do not use abbreviations.</li> <li>Include the anatomical site.</li> <li>Recurrence of breast cancer must not be recorded as an Adverse Event. Second Primary Malignancy (SPM) must be reported as a Serious Adverse Event</li> </ul>
Serious	<ul> <li>Refer to Protocol 'Definition of a Serious Adverse Event'</li> <li>All deaths thought to be related to the study drug(s) at any time must be reported as an SAE</li> <li>All primary cardiac endpoints (symptomatic CHF and cardiac death) must be reported as an SAE</li> <li>All Grade 4 laboratory abnormalities must be reported as SAEs</li> <li>If the event meets the definition of 'serious', sites must submit the Serious Adverse Event Report to GSK with the exception of sites participating with the CTSU in the United States and Canada which must file an electronic report via the NCI Adverse Event Electronic Reporting System (AdEERS).</li> </ul>
CTCAE begin date	<ul> <li>Events that occur in intermittent episodes must be reported on one line. The start date will be the date of the first episode and the end date will be the date of resolution.</li> <li>If the exact Begin Date is not known, at a minimum record the month and year.</li> </ul>
CTCAE end date	<ul> <li>Complete the end date when the AE becomes 'Resolved' or 'Resolved with sequelae'</li> <li>Leave blank if the AE is 'Resolving' or 'Unresolved'</li> </ul>
Grade (maximum)	<ul> <li>Record the maximum grade that occurred over the duration of the event. Refer to the SPAM for more detail.</li> <li>National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 3.0 will be used for grading of events with the exception of congestive heart failure where the NYHA classification system; NYHA classes I, II, III, and IV replaces NCI-CTCAE v3.0 Grades 1, 2, 3, and 4 respectively.</li> </ul>
Outcome of the adverse event	Leave blank if the adverse event is not resolved. Tick 'Unresolved' or 'Resolving' only if the AE is still ongoing at time of:  • Death, withdrawal of consent, recurrence of disease, lost to follow-up, or the end of the 10 year follow-up period.  • EXCEPTION: where possible, cardiac, cardio-vascular or study drug-related AEs must be followed until resolution.
Action taken at time of adverse event	<ol> <li>Protocol treatment(s) discontinued: Administration of investigational product(s) was permanently discontinued</li> <li>Study Dose Reduced: Dose is reduced for one or more investigational product(s)</li> <li>None: Investigational product(s) continues even though an adverse event has occurred</li> <li>Protocol treatment(s) delayed (or interrupted): Administration of one or more investigational products was stopped temporarily but then restarted</li> <li>Not applicable: Subject was not receiving investigational product(s) when the event occurred. (e.g. pre- or post-dosing)</li> </ol>
relation to study drug(s)	It is a regulatory requirement for investigators to assess relationships to investigational products based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. Indicate if there was a reasonable possibility that the event was caused by an investigational product. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support a reasonable possibility include e.g. a temporal relationship, a pharmacologically predicted event or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness or relevant medical history, should also be considered.

Adverse event (AE)		Page 127
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### Adverse events (AE)

AE Name	Serious	CTCAE begin date (dd/mmm/yyyy)	CTCAE end date (dd/mmm/yyyy)	Grade (maximum) Outcome of 1=Mild adverse eve 2=Moderate 1=Resolved 3=Severe 2=Resolving	Outcome of adverse event 1=Resolved 2=Resolving	Action taken at time of adverse event 1=protocol treatment discontinued	Relation to study drug
	No Yes			4=Life threatening 5=Death	3=Unresolved 4=Resolved with sequelae 5=Death	2=Study dose reduced 4=None 5=protocol treatment delayed (or interrupted) X=Not applicable	No Yes
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In case of intermittent episodes, please report on one line with the start date of the first episode and the end date of the last

AE name	<ul> <li>Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available then this must be entered instead.</li> <li>Pre-exisiting conditions, which worsen during the study are to be reported as Adverse Events</li> <li>Use medical terminology in English. Do not use abbreviations.</li> <li>Include the anatomical site.</li> <li>Recurrence of breast cancer must not be recorded as an Adverse Event. Second Primary Malignancy (SPM) must be reported as a Serious Adverse Event</li> </ul>
Serious	<ul> <li>Refer to Protocol 'Definition of a Serious Adverse Event'</li> <li>All deaths thought to be related to the study drug(s) at any time must be reported as an SAE</li> <li>All primary cardiac endpoints (symptomatic CHF and cardiac death) must be reported as an SAE</li> <li>All Grade 4 laboratory abnormalities must be reported as SAEs</li> <li>If the event meets the definition of 'serious', sites must submit the Serious Adverse Event Report to GSK with the exception of sites participating with the CTSU in the United States and Canada which must file an electronic report via the NCI Adverse Event Electronic Reporting System (AdEERS).</li> </ul>
CTCAE begin date	<ul> <li>Events that occur in intermittent episodes must be reported on one line. The start date will be the date of the first episode and the end date will be the date of resolution.</li> <li>If the exact Begin Date is not known, at a minimum record the month and year.</li> </ul>
CTCAE end date	<ul> <li>Complete the end date when the AE becomes 'Resolved' or 'Resolved with sequelae'</li> <li>Leave blank if the AE is 'Resolving' or 'Unresolved'</li> </ul>
Grade (maximum)	<ul> <li>Record the maximum grade that occurred over the duration of the event. Refer to the SPAM for more detail.</li> <li>National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 3.0 will be used for grading of events with the exception of congestive heart failure where the NYHA classification system; NYHA classes I, II, III, and IV replaces NCI-CTCAE v3.0 Grades 1, 2, 3, and 4 respectively.</li> </ul>
Outcome of the adverse event	Leave blank if the adverse event is not resolved. Tick 'Unresolved' or 'Resolving' only if the AE is still ongoing at time of:  • Death, withdrawal of consent, recurrence of disease, lost to follow-up, or the end of the 10 year follow-up period.  • EXCEPTION: where possible, cardiac, cardio-vascular or study drug-related AEs must be followed until resolution.
Action taken at time of adverse event	<ol> <li>Protocol treatment(s) discontinued: Administration of investigational product(s) was permanently discontinued</li> <li>Study Dose Reduced: Dose is reduced for one or more investigational product(s)</li> <li>None: Investigational product(s) continues even though an adverse event has occurred</li> <li>Protocol treatment(s) delayed (or interrupted): Administration of one or more investigational products was stopped temporarily but then restarted</li> <li>Not applicable: Subject was not receiving investigational product(s) when the event occurred. (e.g. pre- or post-dosing)</li> </ol>
relation to study drug(s)	It is a regulatory requirement for investigators to assess relationships to investigational products based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. Indicate if there was a reasonable possibility that the event was caused by an investigational product. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support a reasonable possibility include e.g. a temporal relationship, a pharmacologically predicted event or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness or relevant medical history, should also be considered.

Adverse event (AE)

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Adverse events (AE)					
AE Name	Serions	CTCAE begin date	CTCAE end date	Grade (maximum) Outcome of Action taken at time	Action taken at tin

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Relation to study drug  No Yes						
Action taken at time of adverse event 1=protocol treatment discontinued 2=Study dose reduced 4=None 5=protocol treatment delayed (or interrupted) X=Not applicable						7-1-17
Outcome of adverse event 1=Resolved 2=Resolving 3=Unresolved 4=Resolved with sequelae 5=Death						-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1
Grade (maximum) Outcome of 1=Mild adverse eve 2=Moderate 1=Resolved 2=Resolving 3=Unresolved 5=Death sequelae 5=Death						
CTCAE end date (dd/mmm/yyyy)						7 - 1 - 17 3 7 - 17 1 17 1 17 17 17 3 17 3 17 17 17 17 18 18 18 18 1
CTCAE begin date (dd/mmm/yyyy)						
Serious No Yes						1 - 1 - 1
AE Name						

In case of intermittent episodes, please report on one line with the start date of the first episode and the end date of the last

AE name	<ul> <li>Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available then this must be entered instead.</li> <li>Pre-exisiting conditions, which worsen during the study are to be reported as Adverse Events</li> <li>Use medical terminology in English. Do not use abbreviations.</li> <li>Include the anatomical site.</li> <li>Recurrence of breast cancer must not be recorded as an Adverse Event. Second Primary Malignancy (SPM) must be reported as a Serious Adverse Event</li> </ul>
Serious	<ul> <li>Refer to Protocol 'Definition of a Serious Adverse Event'</li> <li>All deaths thought to be related to the study drug(s) at any time must be reported as an SAE</li> <li>All primary cardiac endpoints (symptomatic CHF and cardiac death) must be reported as an SAE</li> <li>All Grade 4 laboratory abnormalities must be reported as SAEs</li> <li>If the event meets the definition of 'serious', sites must submit the Serious Adverse Event Report to GSK with the exception of sites participating with the CTSU in the United States and Canada which must file an electronic report via the NCI Adverse Event Electronic Reporting System (AdEERS).</li> </ul>
CTCAE begin date	<ul> <li>Events that occur in intermittent episodes must be reported on one line. The start date will be the date of the first episode and the end date will be the date of resolution.</li> <li>If the exact Begin Date is not known, at a minimum record the month and year.</li> </ul>
CTCAE end date	<ul> <li>Complete the end date when the AE becomes 'Resolved' or 'Resolved with sequelae'</li> <li>Leave blank if the AE is 'Resolving' or 'Unresolved'</li> </ul>
Grade (maximum)	<ul> <li>Record the maximum grade that occurred over the duration of the event. Refer to the SPAM for more detail.</li> <li>National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 3.0 will be used for grading of events with the exception of congestive heart failure where the NYHA classification system; NYHA classes I, II, III, and IV replaces NCI-CTCAE v3.0 Grades 1, 2, 3, and 4 respectively.</li> </ul>
Outcome of the adverse event	Leave blank if the adverse event is not resolved. Tick 'Unresolved' or 'Resolving' only if the AE is still ongoing at time of:  • Death, withdrawal of consent, recurrence of disease, lost to follow-up, or the end of the 10 year follow-up period.  • EXCEPTION: where possible, cardiac, cardio-vascular or study drug-related AEs must be followed until resolution.
Action taken at time of adverse event	<ol> <li>Protocol treatment(s) discontinued: Administration of investigational product(s) was permanently discontinued</li> <li>Study Dose Reduced: Dose is reduced for one or more investigational product(s)</li> <li>None: Investigational product(s) continues even though an adverse event has occurred</li> <li>Protocol treatment(s) delayed (or interrupted): Administration of one or more investigational products was stopped temporarily but then restarted</li> <li>Not applicable: Subject was not receiving investigational product(s) when the event occurred. (e.g. pre- or post-dosing)</li> </ol>
relation to study drug(s)	It is a regulatory requirement for investigators to assess relationships to investigational products based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. Indicate if there was a reasonable possibility that the event was caused by an investigational product. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support a reasonable possibility include e.g. a temporal relationship, a pharmacologically predicted event or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness or relevant medical history, should also be considered.

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Adverse event (AE)

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AE Name	Serious	CTCAE begin date (dd/mmm/yyyy)	CTCAE end date (dd/mmm/yyyy)	Grade (maximum) Outcome of 1=Mild adverse eve 2=Moderate 1=Resolved 3=Severe 2=Resolving	Outcome of adverse event 1=Resolved 2=Resolving	Action taken at time of adverse event 1=protocol treatment discontinued	Relation to study drug
	No Yes			4=Life threatening 5=Death	3=Unresolved 4=Resolved with sequelae 5=Death	2=Study dose reduced 4=None 5=protocol treatment delayed (or interrupted) X=Not applicable	No Yes
فيما بالمائم بغمار ليمن ملايمينين فمينة بالمائم مغمار فيمغم بالمائين مينا معم عم فيمعم بممايد ممادميني فيمكننسيمغينا غم محمد ما	10014 001		1+ 30 0+010 troto 04+ 4+in	ao opooido foris oc	0406 600 644 6	100 cdt 30	

In case of intermittent episodes, please report on one line with the start date of the first episode and the end date of the last

AE name	<ul> <li>Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available then this must be entered instead.</li> <li>Pre-exisiting conditions, which worsen during the study are to be reported as Adverse Events</li> <li>Use medical terminology in English. Do not use abbreviations.</li> <li>Include the anatomical site.</li> <li>Recurrence of breast cancer must not be recorded as an Adverse Event. Second Primary Malignancy (SPM) must be reported as a Serious Adverse Event</li> </ul>
Serious	<ul> <li>Refer to Protocol 'Definition of a Serious Adverse Event'</li> <li>All deaths thought to be related to the study drug(s) at any time must be reported as an SAE</li> <li>All primary cardiac endpoints (symptomatic CHF and cardiac death) must be reported as an SAE</li> <li>All Grade 4 laboratory abnormalities must be reported as SAEs</li> <li>If the event meets the definition of 'serious', sites must submit the Serious Adverse Event Report to GSK with the exception of sites participating with the CTSU in the United States and Canada which must file an electronic report via the NCI Adverse Event Electronic Reporting System (AdEERS).</li> </ul>
CTCAE begin date	<ul> <li>Events that occur in intermittent episodes must be reported on one line. The start date will be the date of the first episode and the end date will be the date of resolution.</li> <li>If the exact Begin Date is not known, at a minimum record the month and year.</li> </ul>
CTCAE end date	<ul> <li>Complete the end date when the AE becomes 'Resolved' or 'Resolved with sequelae'</li> <li>Leave blank if the AE is 'Resolving' or 'Unresolved'</li> </ul>
Grade (maximum)	<ul> <li>Record the maximum grade that occurred over the duration of the event. Refer to the SPAM for more detail.</li> <li>National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 3.0 will be used for grading of events with the exception of congestive heart failure where the NYHA classification system; NYHA classes I, II, III, and IV replaces NCI-CTCAE v3.0 Grades 1, 2, 3, and 4 respectively.</li> </ul>
Outcome of the adverse event	Leave blank if the adverse event is not resolved. Tick 'Unresolved' or 'Resolving' only if the AE is still ongoing at time of:  • Death, withdrawal of consent, recurrence of disease, lost to follow-up, or the end of the 10 year follow-up period.  • EXCEPTION: where possible, cardiac, cardio-vascular or study drug-related AEs must be followed until resolution.
Action taken at time of adverse event	<ol> <li>Protocol treatment(s) discontinued: Administration of investigational product(s) was permanently discontinued</li> <li>Study Dose Reduced: Dose is reduced for one or more investigational product(s)</li> <li>None: Investigational product(s) continues even though an adverse event has occurred</li> <li>Protocol treatment(s) delayed (or interrupted): Administration of one or more investigational products was stopped temporarily but then restarted</li> <li>Not applicable: Subject was not receiving investigational product(s) when the event occurred. (e.g. pre- or post-dosing)</li> </ol>
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Adverse event (AE)

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AE Name	Serions	CTCAE begin date (dd/mmm/yyyy)	CTCAE end date (dd/mmm/yyyy)	Grade (maximum) Outcome of 1=Mild adverse eve 1=Resolved	Outcome of adverse event	Action taken at time of adverse event	Relation to study
	No Yes			3=Severe 4=Life threatening 5=Death	2=Resolving 3=Unresolved 4=Resolved with sequelae 5=Death	discontinued discontinued discontinued along the discontinued disconti	No Yes
	00019 0019		فحاصل جاملة فيم اجفواته ليحيم اجاملة ليحيان اجلاء والمحادثين ومراية وم ومفوله لمسوفون جاملة والفندين جعدا المح	a opociac tonit o	of the base off to	to 0 1 4 to	

In case of intermittent episodes, please report on one line with the start date of the first episode and the end date of the last

AE name	<ul> <li>Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available then this must be entered instead.</li> <li>Pre-exisiting conditions, which worsen during the study are to be reported as Adverse Events</li> <li>Use medical terminology in English. Do not use abbreviations.</li> <li>Include the anatomical site.</li> <li>Recurrence of breast cancer must not be recorded as an Adverse Event. Second Primary Malignancy (SPM) must be reported as a Serious Adverse Event</li> </ul>
Serious	<ul> <li>Refer to Protocol 'Definition of a Serious Adverse Event'</li> <li>All deaths thought to be related to the study drug(s) at any time must be reported as an SAE</li> <li>All primary cardiac endpoints (symptomatic CHF and cardiac death) must be reported as an SAE</li> <li>All Grade 4 laboratory abnormalities must be reported as SAEs</li> <li>If the event meets the definition of 'serious', sites must submit the Serious Adverse Event Report to GSK with the exception of sites participating with the CTSU in the United States and Canada which must file an electronic report via the NCI Adverse Event Electronic Reporting System (AdEERS).</li> </ul>
CTCAE begin date	<ul> <li>Events that occur in intermittent episodes must be reported on one line. The start date will be the date of the first episode and the end date will be the date of resolution.</li> <li>If the exact Begin Date is not known, at a minimum record the month and year.</li> </ul>
CTCAE end date	<ul> <li>Complete the end date when the AE becomes 'Resolved' or 'Resolved with sequelae'</li> <li>Leave blank if the AE is 'Resolving' or 'Unresolved'</li> </ul>
Grade (maximum)	<ul> <li>Record the maximum grade that occurred over the duration of the event. Refer to the SPAM for more detail.</li> <li>National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 3.0 will be used for grading of events with the exception of congestive heart failure where the NYHA classification system; NYHA classes I, II, III, and IV replaces NCI-CTCAE v3.0 Grades 1, 2, 3, and 4 respectively.</li> </ul>
Outcome of the adverse event	Leave blank if the adverse event is not resolved. Tick 'Unresolved' or 'Resolving' only if the AE is still ongoing at time of: • Death, withdrawal of consent, recurrence of disease, lost to follow-up, or the end of the 10 year follow-up period. • EXCEPTION: where possible, cardiac, cardio-vascular or study drug-related AEs must be followed until resolution.
Action taken at time of adverse event	<ol> <li>Protocol treatment(s) discontinued: Administration of investigational product(s) was permanently discontinued</li> <li>Study Dose Reduced: Dose is reduced for one or more investigational product(s)</li> <li>None: Investigational product(s) continues even though an adverse event has occurred</li> <li>Protocol treatment(s) delayed (or interrupted): Administration of one or more investigational products was stopped temporarily but then restarted</li> <li>Not applicable: Subject was not receiving investigational product(s) when the event occurred. (e.g. pre- or post-dosing)</li> </ol>
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Adverse event (AE)

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### Adverse events (AE)

AE Name	Serious	CTCAE begin date (dd/mmm/yyyy)	CTCAE end date (dd/mmm/yyyy)	Grade (maximum) Outcome of 1=Mild adverse eve 1=Resolved	Outcome of adverse event	Action taken at time of adverse event	Relation to study
	No Yes			3=Severe 4=Life threatening 5=Death	2=Resolving 3=Unresolved 4=Resolved with sequelae 5=Death	discontinued 2=Study dose reduced 4=None 5=protocol treatment delayed (or interrupted) X=Not applicable	No Yes
	000/4 00/		فيما برطه قبي برفيولد ليمين برطه ليمين بالدينيين فيريته برطه قبي بفيرك فيرمفن برطة طفنين برمنا بري	ao opooido toris o	مؤمام المنام مطالم الم	100104130	

In case of intermittent episodes, please report on one line with the start date of the first episode and the end date of the last

AE name	<ul> <li>Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available then this must be entered instead.</li> <li>Pre-exisiting conditions, which worsen during the study are to be reported as Adverse Events</li> <li>Use medical terminology in English. Do not use abbreviations.</li> <li>Include the anatomical site.</li> <li>Recurrence of breast cancer must not be recorded as an Adverse Event. Second Primary Malignancy (SPM) must be reported as a Serious Adverse Event</li> </ul>
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Adverse event (AE)

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Relation to study drug No Yes	]	]	]	 ]	]	 	
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Action taken at time of adverse event 1=protocol treatment discontinued 2=Study dose reduced 4=None 5=protocol treatment delayed (or interrupted) X=Not applicable							
Outcome of adverse event 1=Resolved 2=Resolving 3=Unresolved 4=Resolved with sequelae 5=Death							
Grade (maximum) Outcome of adverse eve 2=Moderate 1=Resolved 3=Severe 2=Resolving 3=Unresolved 5=Death 5=Death							
CTCAE end date (dd/mmm/yyyy)							
CTCAE begin date (dd/mmm/yyyy)							
Serious No Yes							
S o							
AE Name							

In case of intermittent episodes, please report on one line with the start date of the first episode and the end date of the last

Protocol number BIG 1	-06 / EGF106903	Unscheduled EKG
Centre No.	Subject No.	Page 133
EKG		
Date of EKG	DD MMM YYYY	
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> </ul>	Please complete the "Adverse event" page
EKG		
Date of EKG	DD MMM YYYY	
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> </ul>	Please complete the "Adverse event" page
EKG		
Date of EKG	DD MMM YYYY	
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> </ul>	Please complete the "Adverse event" page

Protocol number BIG 1	-06 / EGF106903	Unscheduled EKG
Centre No.	Subject No.	Page 134
EKG		
Date of EKG	DD MMM YYYY	
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> </ul>	Please complete the "Adverse event" page
EKG		
Date of EKG	DD MMM YYYY	
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> </ul>	Please complete the "Adverse event" page
EKG		
Date of EKG	DD MMM YYYY	
Result	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> </ul>	Please complete the "Adverse event" page

### **New York Heart Association (NYHA) Functional Classification**

NOTE: If the patient does not have congestive heart failure (CHF), leave this field blank.

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Protocol number BIG 1-	-06 / EGF106903	Unscheduled LVEF
Centre No.	Subject No.	Page 135
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluation	chocardiogram UGA scan
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ → Please event</li> </ul>	e complete the "Adverse " page.
Symptomatic CHF	☐ No☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick II☐ Class II☐ Class III☐ Class IV	No for the question above)
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluation	chocardiogram UGA scan
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ → Please event</li> </ul>	e complete the "Adverse " page.
Symptomatic CHF	☐ No☐ Yes → Specify below	
NYHA classification	☐ Class I (in case of asymptomatic CHF, tick N	lo for the question above)

(complete only in

case of CHF)

☐ Class III☐ Class III

☐ Class IV

### **New York Heart Association (NYHA) Functional Classification**

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Protocol number BIG 1		
Centre No.	Subject No. Page	136
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the "Adverse event" page.</li> </ul>	
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CHF, tick No for the question above) ☐ Class II ☐ Class III ☐ Class IV	)
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	│ │ │	
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> <li>□ Please complete the "Adverse event" page.</li> </ul>	
Symptomatic CHF	□ No □ Yes → Specify below	
NYHA classification	☐ Class I (in case of asymptomatic CHE tick No for the guestion above)	)

(complete only in

case of CHF)

Class II
Class III
Class IV

### **New York Heart Association (NYHA) Functional Classification**

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Protocol number BIG 1	-06 / EGF106903	Unscheduled LVEF
Centre No.	Subject No.	Page 137
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluation	☐ Echocardiogram ☐ MUGA scan
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> </ul>	- Please complete the "Adverse event" page.
Symptomatic CHF	<ul><li>□ No</li><li>□ Yes → Specify below</li></ul>	
NYHA classification (complete only in case of CHF)	☐ Class I (in case of asymptomatic CH.☐ Class II☐ Class III☐ Class IV	F, tick No for the question above)
LVEF		
Date of LVEF	DD MMM YYYY	
LVEF (patient value)	Method of Evaluation	☐ Echocardiogram ☐ MUGA scan
	<ul> <li>□ Normal</li> <li>□ Abnormal - Not clinically significant</li> <li>□ Abnormal - Clinically significant</li> </ul>	- Please complete the "Adverse event" page.
Symptomatic CHF	☐ No ☐ Yes → Specify below	
NYHA classification (complete only in	☐ Class I (in case of asymptomatic CH	F, tick No for the question above)

☐ Class III ☐ Class IV

case of CHF)

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	00	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

Unscheduled radiological exams		Page 138
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Protocol number BIG 1-06 / EGF106903	Centre No.	

<b>Are</b> there any <u>clinically significant</u> abnormalities? (Please report a short description)	☐ No ☐ Yes —➤ Specify	☐ No ☐ Yes —> Specify	☐ No ☐ Yes —> Specify ————————————————————————————————————	☐ No ☐ Yes —> Specify ————————————————————————————————————	☐ No ☐ Yes —> Specify	☐ No ☐ Yes —> Specify ————————————————————————————————————
Date of test	DD MMM YYYYY	DD MMM YYYY	DD MMM YYYY	DD MMM YYYYY	DD MMM YYYYY	DD MMM DD
Side (L or R)						
Anatomical   site** 	]					]
Type of radiological examination*	]					

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

Unscheduled radiological exams		Page 139
6 / EGF106903	Subject No.	
Protocol number BIG 1-06 / EGF106903	Centre No.	

Are there any clinically significant abnormalities?	(Please report a short description)	No Specify   Yes → Specify	No Specify Specify Specify Specify	No	No Specify	No Specify	No □ No □ Yes → Specify − − − − − − − − − − − − − − − − − − −
Date of test		Y MMM QQ	Y MMM QQ	Y MMM QQ	Y MMM GG	Y MMM GG	X MWW QQ
Side	(LorR)						
Anatomical							
Type of	radiological examination*						

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
cs	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
$\prec$	Kidney	SP	Spleen
PT	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

Protocol nur	Protocol number BIG 1-06 / EGF106903	06 / EGF	106903	Unscheduled radiological exams
Centre No.	o No		Subject No.	Page 140
Type of radiological examination*	Anatomical site**	Side (L or R)	Date of test	<b>Are there an<u>y clinically significant</u> abnormalities?</b> (Please report a short description)
]			DD MMM YYYYY	」☐ No ☐ Yes —> Specify

☐ No ☐ Yes —> Specify

□ No □ Yes —> Specify	□ No □ Yes —> Specify	□ No □ Yes —> Specify	□ No □ Yes —➤ Specify
DD MMM YYYY	DD MMM YYYY	DD MMM YYYY	DD MMM dd

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
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CL	Colon	PM	Peritoneum
CR	Colorectal	PR	Prostate
cs	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
$\prec$	Kidney	SP	Spleen
PT	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

Unscheduled radiological exams Page 141 Subject No. Protocol number BIG 1-06 / EGF106903 Centre No.

•							
	Are there any <u>clinically significant</u> abnormalities? (Please report a short description)	➤ Specify	➤ Specify	➤ Specify	Specify ————————————————————————————————————	Specify	➤ Specify
	<b>Are there a</b> n (Please repo	l □ No Yes →	 S≥, □ □	 S≥, □ □	√ No	Ves →	l □ No □ Yes ─
	Date of test	DD MMM TYYY	DD MMM YYYY	DD MMM YYYY	DD MMM YYYY	DD MMM YYYY	DD MMM
	Side (L or R)						
	Anatomical site**						]
	Type of radiological examination*						

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

Anatomical site	Description	Anatomical site	Description
AB	Abdomen/abdominal wall	ΓΛ	Liver
AD	Adrenals	00	Oral cavity
BE	Bone	ОТ	Other
BR	Bladder	NO VO	Ovary
BT	Breast	PA	Pleura
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CR	Colorectal	PR	Prostate
CS	CNS (brain)	PS	Pancreas
CW	Chest	PV	Pelvis
X	Cervix	RC	Rectum
ЕО	Esophagus/Oesophagus	SH	Stomach
NH	Head and neck	SI	Small intestine
HT	Heart	SK	Skin
¥	Kidney	SP	Spleen
FG	Lung	TD	Thyroid
LN	Lymph nodes	WB	Whole body

Protocol number BIG 1-06 / EGF106903	mber BIG 1-	.06 / EGF	=106903	Unscheduled radiological exams
Centr	Centre No.		Subject No.	Page 142
Type of radiological examination*	Anatomical site**	Side (L or R)	Date of test	Are there an <u>y clinically significant</u> abnormalities? (Please report a short description)
			DD MMM YYYY	」☐ No ☐ Yes —➤ Specify
]			DD MMM YYYY	」☐ No ☐ Yes → Specify
]	]		- AAAA MWW	

□ No □ Yes → Specify

□ No □ Yes → Specify

□ No □ Yes ──➤ Specify

DD

MMM

<sup>\*</sup> BS=Bone scan (scintigraphy); C=CT scan; E=Endoscopy; L=Lymphangiogram; M=MRI; MA=Mammography; NS=Nuclear scan; PC=PET/CT Scan; PT=PET scan; TU=Transvaginal ultrasound; UL=Ultrasound (echography); XR=X-ray

<sup>\*\*</sup> See facing page for anatomical site codes

Protocol number BIG 1-06 / EG	F106903			<b>Adjuvant Treatment completion</b>
Centre No.	Subject No			Page 143
Adjuvant Treatment completion	*			
Did the patient complete Lapatinib (	<b>L</b> ) as per protoc	ol?		
	☐ Yes ☐ No → S ☐ NA	peci	fy be	elow
Did the patient complete <u>Trastuzum</u>	<u>ab (<b>T</b>)</u> as per pr	otoc	ol?	
	☐ Yes ☐ No → S	noci	fy b	olow
	□ NA	peci	IY D	EIOW
Did the patient complete <u>FEC</u> as pe	r protocol?			
	☐ Yes			
	<ul><li>□ No → S</li><li>□ NA</li></ul>	peci	fy be	elow
Reasons for treatment discontinuati	on	L	Т	FEC**
	Adverse event			□ → Complete "Adverse event" page
	otocol violation			
Subject decided to withdraw from product but is continuing to be follow	investigational ed per protocol			
Subject decided to withdraw	from the study			
Recurrence of disease or second prima (SPM) or contalateral breas	ary malignancy t cancer (CBC)			☐ → Complete "Recurrence of disease" or "SPM"-"CBC" page
	Death			□ → Complete "Death" page
Le	ost to follow-up			
Date of last study drug	administration:		I DD	MMM YYYY

<sup>\*&</sup>quot;No" should only be ticked for 'Did the patient complete [therapy] as per protocol?', if the study drug was permanently discontinued earlier than the protocol specified treatment duration.

<sup>\*\*</sup>L= Lapatinib; T=Trastuzumab; FEC

-1010C0111	uniber big i	-00 / EGF 100903	Auj	uvant Treatment completion
Cen	tre No.	Subject	No.	Page 144
Additional	comments a	nd Investigator's	signature	
				up to the treatment completion)
CRF page	Comments			
number				
A.II. I. (				
		e report form have be and complete.	een entered under	my authority and to the best of
Investigato	r's signature _			(Medically-qualified sub-investigator
				is allowed to sign the CRF, as long as he/she is listed on the form 1572)
Date	<u>I I I I</u> DD MMM	YYYY		as hershe is listed on the lottil 15/2)
		Y after request from a	data management	
	-		-	

## Guidelines for reporting of recurrence, second primary malignancy and contralateral breast cancer. Record the following:

- 1. the first event defining disease-free survival (local, regional or distant recurrence of invasive breast cancer, contralateral breast cancer, second non-breast malignancy, or death without prior cancer event),
- 2. the first distant breast cancer recurrence occurring at any time,
- 3. the first central nervous system (CNS) breast cancer recurrence occurring at any time,
- 4. the second primary malignancies occurring at any time and complete the adverse event form.

NOTE: Ductal carcinoma in situ (DCIS), lobular carcinoma in situ of the breast (LCIS) and myelodisplastic syndrome (MDS) are not considered recurrence events.

Recurrence of disease Page 145 Protocol number BIG 1-06 / EGF106903

Subject No.	
Centre No.	Recurrence of disease

Type of recurrence	Recurrence date (dd/mmm/yyyy)	Method of evaluation* C R	Biopsy No Yes	Biopsy date	Histology type
Local recurrence					
Breast surgical scar					
Ipsilateral breast					
Ipsilateral anterior chest wall					
Skin or soft tissue within the local area					
Regional recurrence					
Ipsilateral axillary					
Infraclavicular					
Internal mammary					
Skin or soft tissue within the regional area	ea				

<sup>\*</sup>Method: C=clinical; R=radiological (please report the radiological test in appropriate "Radiological examination" page, either the applicable visit page or the "Unscheduled radiological exams" page)

## Guidelines for reporting of recurrence, second primary malignancy and contralateral breast cancer. Record the following:

- 1. the first event defining disease-free survival (local, regional or distant recurrence of invasive breast cancer, contralateral breast cancer, second non-breast malignancy, or death without prior cancer event),
- 2. the first distant breast cancer recurrence occurring at any time,
- 3. the first central nervous system (CNS) breast cancer recurrence occurring at any time,
- 4. the second primary malignancies occurring at any time and complete the adverse event form.

NOTE: Ductal carcinoma in situ (DCIS), lobular carcinoma in situ of the breast (LCIS) and myelodisplastic syndrome (MDS) are not considered recurrence events.

Recurrence of disease Page 146 Protocol number BIG 1-06 / EGF106903

Histology type

Recurrence of disease				
Type of recurrence	Recurrence date N (dd/mmm/yyyy) ev	Method of evaluation* C R	Biopsy Bi No Yes	Biopsy date
Distant recurrence (Report the first distant recurrence at any time)	(ant recurrence at any time)			
Skin or lymph nodes other than specified on local / regional recurrence page	no b			
Bone				-
Lung				-
Liver				-
Pleural effusion				
Other distant site, specify				-
Other distant site, specify				-

\*Method: C=clinical; R=radiological (please report the radiological test in appropriate "Radiological examination" page, either the applicable visit page or the "Unscheduled radiological exams" page)

Meningitis carcinomatosa

## Guidelines for reporting of recurrence, second primary malignancy and contralateral breast cancer. Record the following:

- 1. the first event defining disease-free survival (local, regional or distant recurrence of invasive breast cancer, contralateral breast cancer, second non-breast malignancy, or death without prior cancer event),
- 2. the first distant breast cancer recurrence occurring at any time,
- 3. the first central nervous system (CNS) breast cancer recurrence occurring at any time,
- 4. the second primary malignancies occurring at any time and complete the adverse event form.

NOTE: Ductal carcinoma in situ (DCIS), lobular carcinoma in situ of the breast (LCIS) and myelodisplastic syndrome (MDS) are not considered recurrence events.

Second primary malignancy and contralateral BC		Page 147
3 / EGF106903	Subject No.	
Protocol number BIG 1-06 / EGF106903	Centre No.	

Type of recurrence	Recurrence date	Method of	Biopsy	Biopsy date	Histology type
p)	dd/mmm/yyyy)	evaluation*	No Yes		3

¥				
ט		ntralateral breast at any time)		
	cancer	Second primary malignancy (with the exception of contralateral breast cancer which should always be reported above) (report at any time)		
	Contralateral breast cancer	Second primary malic cancer which should al		

\*Method: C=clinical; R=radiological (please report the radiological test in appropriate "Radiological examination" page, either the applicable visit page or the "Unscheduled radiological exams" page)

Protocol number BIG	1-06 / EG	Post-	Post-event treatments		
Centre No.			Page 148		
		Subject		]	
				J	
Additional therapy for	r breast ca	ncer recu	irrence oi	second primary or c	ontralateral BC
malignancy (Please rep should be reported at any		first line of	treatment,	except for additional targ	eted therapies that
snould be reported at arry	· unic.j				
Chemotherapy					
		emotherapy	y after recu	rrence of breast cancer of	or second primary
malignacy or contralater	rai BC? □ No	□ Yes ·	→ Specii	fv below	
Agent name	Total no. of cycles	Initial dose	Units	Date started (dd/mmm/yyyy)	Date stopped (dd/mmm/yyyy)
Doxorubicin	Oi Cycles	4030	mg/m²	(dd/iiiiii/yyyy)	(dd/iiiiiii/yyyy)
Epirubicin	1		mg/m²		
·	<u> </u>				
Paclitaxel			mg/m²		
Docetaxel			mg/m²		
Capecitabine			mg/m²		
	<del> </del>				
Targeted therapy (report	t at any time)				
		eted thera	py after red	currence of breast cancer	or second primary
malignancy or contralate	erai BC?	□Yes -	→ Specii	fy helow	
	ή				
Agent name	Total no. of cycles	Dose	Units	Date started (dd/mmm/yyyy)	Date stopped (dd/mmm/yyyy)
Lapatinib	NA		mg/24Hr	(, , , , , , , , , , , , , , , , ,	(,,,,,,,
Trastuzumab*	1		mg/kg		<u> </u>
	<u> </u>				
* Report maintenance do	se (2 mg/kg	or 6 mg/kg	<u>'</u>		

Centre No.						
		9	Subject N	No.		Page 149
			T			
Additional therapy fo	r hreas	st cand	cer relap:	se or sec	ond primary maligna	nev (cont.)
			-			
					one therapy after recurr alateral BC?	ence of breast cancer
		□No	_	→ Spe		
Agent name			Dose	Units	Date started	Date stopped
			ļ		(dd/mmm/yyyy)	(dd/mmm/yyyy)
Tamoxifen				mg		
Anastrozole				mg		
Letrozole				mg		
Exemestane				mg		
Goserelin				mg		
Other LH-RH analogue:				mg		NA
		tomy	NA	NA		NA
Bilateral ovariectomy/oo	pherec	torriy				
Bilateral ovariectomy/oo	Did th	ne patie	nt receive imary mali	ignancy or	radiotherapy after recurr	ence of breast cancer
· · · · · · · · · · · · · · · · · · ·	Did the or see	ne patie	nt receive imary mali	ignancy or  → Spe  Units	contralateral BC?	rence of breast cancer  Radiation Therapy End Date
Radiotherapy	Did the or see	ne patie cond pr □ No	nt receive imary mali □ Yes	ignancy or  Spe  Units 1=Gy 2=cGy	contralateral BC? cify below  Radiation Therapy	Radiation Therapy
Radiotherapy	Did the or see	ne patie cond pr □ No iide	nt receive imary mali □ Yes	ignancy or  → Spe  Units 1=Gy	contralateral BC? cify below  Radiation Therapy Start Date	Radiation Therapy End Date
Radiotherapy	Did the or see	ne patie cond pr □ No	nt receive imary mali □ Yes	ignancy or  Spe  Units 1=Gy 2=cGy	contralateral BC? cify below  Radiation Therapy Start Date	Radiation Therapy End Date
Radiotherapy	Did the or see	ne patie cond pr □ No iide	nt receive imary mali □ Yes	ignancy or  Spe  Units 1=Gy 2=cGy	contralateral BC? cify below  Radiation Therapy Start Date	Radiation Therapy End Date
Radiotherapy	Did the or see	ne patie cond pr No iide right	nt receive imary mali □ Yes	ignancy or  Spe  Units 1=Gy 2=cGy	contralateral BC? cify below  Radiation Therapy Start Date	Radiation Therapy End Date

Protocol nu	ımber BIG 1-06 /	EGF106903	Additional comments
Cent	re No.	Subject No.	Page 150
Additional (Please add I		ou might have regarding the d	ata reported after treatment completion)
CRF page number	Comments		

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 151
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant r a new primary malignancy, please update the "Second primary malignancy and contralater."	e "Recurrence of disease" or the
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death	e. pe the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature  Date DD MMM YYYY  (Please sign and date only after request from data management)	(A medically qualified sub- investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)
- · · · · · · · · · · · · · · · · · · ·	

Protocol number	BIG 1-06 / EGF106903	Survival follow-up
Centre No.	Subject No.	Page 152
Patient status		
To be completed on	a yearly basis, <u>starting one year afte</u>	r the first recurrence of disease.
☐ Alive	or a new primary malignancy s	e <u>first</u> distant recurrence, a CNS recurrence ince the last "Survival follow-up" page was 'Recurrence of disease" or the "Second primary C" page.
☐ Death	→ Please complete "Death" page	
☐ Lost to	Follow-up	
☐ Subject	decided to withdraw study consent.	
Date of last	contact or death DD MMM	YYYY
should also The last da	be the last date the patient was kno	could either be the same as the previous
	nis case report form have been enter ccurate and complete.	ed under my authority and to the best of
Investigator's signatu	ure	(A medically qualified sub-
Date	MMM YYYY	investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)
(Please sign and dat	te only after request from data mana	gement)

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 153
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant r or a new primary malignancy since the last "completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study cons should also be the last date the patient was known to be alive The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e. pe the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature  Date DD MMM YYYY  (Please sign and date only after request from data management)	(A medically qualified sub- investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)
(. 1929 Sight and date only after request from data management)	

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 154
Patient status	
To be completed on a yearly basis, starting one year after the first recu	urrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant r or a new primary malignancy since the last " completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
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All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature	(A medically qualified sub-
Date DD MMM YYYY	investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)
(Please sign and date only after request from data management)	

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 155
Patient status	
To be completed on a yearly basis, starting one year after the first recu	urrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant r or a new primary malignancy since the last " completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study cons should also be the last date the patient was known to be alive The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e. oe the same as the previous
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Investigator's signature  Date DD MMM YYYY  (Please sign and date only after request from data management)	(A medically qualified sub- investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)
the state of the s	

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 156
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant r or a new primary malignancy since the last "completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study cons should also be the last date the patient was known to be alive The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e. pe the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature  Date DD MMM YYYY  (Please sign and date only after request from data management)	(A medically qualified sub- investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 157
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant re or a new primary malignancy since the last "S completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study consessions should also be the last date the patient was known to be alive. The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	uthority and to the best of
Investigator's signature	(A medically qualified sub- investigator is allowed to sign
Date DD MMM YYYY	the CRF if he/she is listed on the form FDA 1572)
(Please sign and date only after request from data management)	

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 158
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant r or a new primary malignancy since the last "s completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study cons should also be the last date the patient was known to be alive The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e. he the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature	(A medically qualified sub-
Date DD MMM YYYY	investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)
(Please sign and date only after request from data management)	

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 159
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant re or a new primary malignancy since the last "S completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	ப
(For patients "Lost to Follow-up" or that "withdrew study consessions should also be the last date the patient was known to be alive. The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e. e the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature	(A medically qualified sub-
Date DD MMM YYYY	investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)
(Please sign and date only after request from data management)	

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 160
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant r or a new primary malignancy since the last "s completed, please update the "Recurrence o malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study cons should also be the last date the patient was known to be alive The last date the patient was known to be alive could either b reported visit date or any date between the previous visit and	e. he the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature  Date	(A medically qualified sub- investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 161
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant r or a new primary malignancy since the last "completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study cons should also be the last date the patient was known to be alive The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e. pe the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature  Date DD MMM YYYY	(A medically qualified sub- investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)
(Please sign and date only after request from data management)	

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 162
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant r or a new primary malignancy since the last "completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study cons should also be the last date the patient was known to be alive The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e. he the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature	(A medically qualified sub-
Date DD MMM YYYY	investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)
(Please sign and date only after request from data management)	

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 163
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant not or a new primary malignancy since the last "Standard completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study consisted should also be the last date the patient was known to be alive. The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e. e the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature  Date DD MMM YYYY  (Please sign and date only after request from data management)	(A medically qualified sub- investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 164
Patient status	
To be completed on a yearly basis, starting one year after the first recu	urrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant or a new primary malignancy since the last "completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study cons should also be the last date the patient was known to be alive. The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e. be the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	authority and to the best of
Investigator's signature  Date DD MMM YYYY  (Please sign and date only after request from data management)	(A medically qualified sub- investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)
i ibaso sigil and date only alter request from data management)	

Protocol number BIG 1-06 / EGF106903	Survival follow-up
Centre No. Subject No.	Page 165
Patient status	
To be completed on a yearly basis, starting one year after the first recu	rrence of disease.
☐ Alive → If the patient has developed the <u>first</u> distant not or a new primary malignancy since the last "Standard completed, please update the "Recurrence of malignancy and contralateral BC" page.	Survival follow-up" page was
☐ Death → Please complete "Death" page.	
☐ Lost to Follow-up	
☐ Subject decided to withdraw study consent.	
Date of last contact or death DD MMM YYYY	
(For patients "Lost to Follow-up" or that "withdrew study consisted should also be the last date the patient was known to be alive. The last date the patient was known to be alive could either be reported visit date or any date between the previous visit and	e. e the same as the previous
All data entered in this case report form have been entered under my a my knowledge are accurate and complete.	outhority and to the best of
Investigator's signature  Date DD MMM YYYY  (Please sign and date only after request from data management)	(A medically qualified sub- investigator is allowed to sign the CRF if he/she is listed on the form FDA 1572)

Protocol number BIG 1-0	06 / EGF106903	Dea	Death
Centre No.	Subject No.	Page 1	166
Death			
Date of death DD	MMM YYYY	Every effort should be made to exercise diligence in reporting the complete date of death. Overall survival is an important study endpoint.	
Primary cause of death (che	eck one)		
Adver Adver Maligr	t cancer progression se event during study se event during treatment on the control of the contr	east cancer	
' ' '	☐ Unknown ☐ No ☐ Yes <del>→</del> Please sui	mmarize findings:	

# Additional signature page

Protocol number BIG 1-06 / EG	F1069	903						signature page				age		
Centre No.	Subj	ect	No.									F	Page 1	167
Additional signature page Please complete this page only when	instruc	eted	by da	ta m	anag	eme	nt							
All data entered in the case report form and to the best of my knowledge are a						bee	en ent	ered	unde	r my	autho	rity		
Visit up to and including: Week		or	Мо	onth		_	or		Year					
			comple				plica	ble)						
Non-visit forms	Pages	<u> </u>	ck all ι	ısea	page	es) ——								
Hormonotherapy	110													
Radiotherapy	111													
Concomitant treatments	112		113		114					,				
Administration of study drug: Paclitaxel	115		116											
Administration of FEC adjuvant treatment	117		118											
Administration of study drug: Lapatinib	119													
Investigational product compliance	120													
Administration of study drug: Trastuzumab	121		122		123		124		125					
Adverse event	126		127		128		129		130		131		132	
Unscheduled EKG	133		134											
Unscheduled LVEF	135		136		137									
Unscheduled radiological exams	138		139		140		141		142					
Adjuvant treatment completion	143													
Adjuvant treatment completion	144													
Recurrence of disease: local/regional	145													
Recurrence of disease: distant	146													
Second primary malignancy and CBC	147													
Post event treatments	148		149											
Additional comments	150													
Death	166													
Liver function tests	170		171		172		173		174		175		176	
Liver function tests	177		178		179		180		181		182		183	
Liver function tests	184		185		186		187		188		189		190	
Liver function tests	191		192		193		194		195		196		197	
Liver function tests	198				1									
Unscheduled liver function tests	199		200		201		202		203		204			
Additional pages, if any:														
Investigator's signature  (A medically qualified sub-investigator is all he/she is listed on the form FDA 1572)	lowed i	to si	gn the	CF	PF if	_ Da	ate	L	L L	<u>I</u> MM	<u>.                                    </u>		 YYYY	— — I

### Additional signature page

Protocol number BIG 1-06 / EG	Protocol number BIG 1-06 / EGF106903								3	igiic	ıtuı	e po	<sub>1</sub> ye
Centre No.	Subje	ct No.									F	Page 1	168
			$\top$										
			Щ										
Additional signature page													
Please complete this page only when	instructe	ed by da	ata n	nanad	eme	nt							
											.,		
All data entered in the case report forr and to the best of my knowledge are a					e bee	en ent	erea	unde	r my	autno	rity		
Visit up to and including: Week	(	or M	lonth			or		Year					
	(Please					oplica	ble)						
Non-visit forms	Pages (		usea	page	es)								
Hormonotherapy	110												
Radiotherapy	111												
Concomitant treatments	112			114									
Administration of study drug: Paclitaxel	115												
Administration of FEC adjuvant treatment	117												
Administration of study drug: Lapatinib	119												
Investigational product compliance	120	]											
Administration of study drug: Trastuzumab	121	] 122		123		124		125					
Adverse event	126	] 127		128		129		130		131		132	
Unscheduled EKG	133 □	] 134											
Unscheduled LVEF	135 🗆	] 136		137									
Unscheduled radiological exams	138	] 139		140		141		142					
Adjuvant treatment completion	143	]											
Adjuvant treatment completion	144	]											
Recurrence of disease: local/regional	145 □	]											
Recurrence of disease: distant	146 □	]		1									
Second primary malignancy and CBC	147	]											
Post event treatments	148 L	149											
Additional comments	150 □	]											
Death	166 □	]											
Liver function tests	170	] 171		172		173		174		175		176	
Liver function tests	177	] 178		179		180		181		182		183	
Liver function tests	184 🗆	] 185		186		187		188		189		190	
Liver function tests	191	] 192		193		194		195		196		197	
Liver function tests	198 □	]											
Unscheduled liver function tests	199 🗆	200		201		202		203		204			
Additional pages, if any:		'											
					-								
Investigator's signature					_ D	ate	بِــا	டி	1			1	Ш
(A medically qualified sub-investigator is all he/she is listed on the form FDA 1572)	owed to	sign th	e CF	<⊢ if			D	ט	MM	IIVI		YYYY	ı

## Additional signature page

Protocol number BIG 1-06 / EGI	Protocol number BIG 1-06 / EGF106903							5	igna	llui	e po	age
Centre No.	Subject	: No.								F	Page 1	169
Additional signature page	: 4 4				_							
Please complete this page only when i	ınstructea	by data m	ianag	emen	τ							
All data entered in the case report forn and to the best of my knowledge are a				beer	n ente	ered	undei	<sup>-</sup> my	autho	rity		
Visit up to and including: Week	or	Month		_	or		Year	_				
		complete o			olicab	ole)						
Non-visit forms		ck all used	page	s) 								
Hormonotherapy	110 🗆											
Radiotherapy	111 🗆											
Concomitant treatments	112 🔲	113 🔲	114									
Administration of study drug: Paclitaxel	115 🗆	116										
Administration of FEC adjuvant treatment	117 🗆	118										
Administration of study drug: Lapatinib	119 🔲											
Investigational product compliance	120 🗆											
Administration of study drug: Trastuzumab	121 🔲	122 🗆	123		124		125					
Adverse event	126 🗆	127 🔲	128		129		130		131		132	
Unscheduled EKG	133 🗆	134 🛚										
Unscheduled LVEF	135 🔲	136 🔲	137									
Unscheduled radiological exams	138 🔲	139 🔲	140		141		142					
Adjuvant treatment completion	143 🔲											
Adjuvant treatment completion	144 🗆											
Recurrence of disease: local/regional	145 🗆											
Recurrence of disease: distant	146 🗆											
Second primary malignancy and CBC	147 🗆											
Post event treatments	148 🗆	149 🗆										
Additional comments	150 🗆											
Death	166 🗆											
Liver function tests	170 🗆	171 🔲	172		173		174		175		176	
Liver function tests	177 🔲	178 🔲	179		180		181		182		183	
Liver function tests	184 🔲	185 🗆	186		187		188		189		190	
Liver function tests	191 🔲	192 🔲	193		194		195		196		197	
Liver function tests	198 🗆											
Unscheduled liver function tests	199 🔲	200 🗆	201		202		203		204			
Additional pages, if any:	,											
Investigator's signature	owed to s	ign the CF	RF if	_ Dat	te	DI	<u> </u>	I MM	ı l M		YYYY	— 니 I

Protocol number B	IG 1-06 / EGF106	8903		Live	er functi	ion tests
Centre No.	Sub	oject No.				Page 170
Screening	Sample collection da	te L	I I I I DD MMM	YYYY	J	
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (ASAT	)	U/I				
SGPT (ALAT)		U/I				
Alk. phosphat	ase L	U/I				

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

mg/dl

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Please check the blood tests and report any <u>clinically significant</u> abnormality on the "**Previous or current** diseases other than primary breast cancer and cardiovascular diseases" page 13.

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol numb	per BIG 1	-06 / EGF106	6903		Liv	er functi	ion tests
Centre	No.	Sub	ject No	).			Page 171
Week 4	Samp	ole collection da	te L	I I I I	l , , , , , , , , , , , , , , , , , , ,	J	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (	(ASAT)		U/I				
SGPT (	ALAT)		U/I				
Alk. pho	osphatase		U/I				

mg/dl

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol numbe	r BIG 1	-06 / EGF106	6903		Liv	er functi	ion tests
Centre No	). 	Sub	oject No	).			Page 172
Week 6	Samp	le collection da	te L	J J J J DD MMM	YYYY	J	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (AS	SAT)		U/I				
SGPT (AL	AT)		U/I				
Alk. phosp	hatase		U/I				

mg/dl

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number BIG Centre No.		6903 oject No	). 	Live	er funct	ion tests Page 173
Week 10 San	nple collection da	te L	DD MMM	YYYY		
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (ASAT)		U/I				
SGPT (ALAT)		U/I				
Alk. phosphatase	<u> </u>	U/I				

mg/dl

### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number E	BIG 1-06 / EG	F106903		Liv	er function te	sts
Centre No.		Subject N	0.		Page 1	174
Week 13	Sample collecti	ion date	ı l ı ı DD MMM	YYYY	J	
	Resu (use dot ". decimal sepa	" as	Unit if other unit used	<b>Norma</b> l Min	range* Max	
SGOT (ASA		U/I				
SGPT (ALAT	г)	U/I				

U/I

mg/dl

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Alk. phosphatase

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number	· BIG 1-	-06 / EGF106	6903		Liv	er functi	on tests
Centre No. Subject No.			).			Page 175	
Week 16	Samp	le collection da	te L	I I I I	YYYY	J	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (AS	SAT)		U/I				
SGPT (AL	AT)		U/I				
Alk. phosp	hatase		U/I				

mg/dl

### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number BIG 1-06 / EGF106903					Liver function tests		
	Centre No		S	ubject	No.		Page 176

#### **Pre-surgery visit**



	Result	Unit	Unit if other	Normal	Normal range*	
	(use dot "." as decimal separator)		unit used	Min	Max	
SGOT (ASAT)		U/I				
SGPT (ALAT)		U/I				
Alk. phosphatase		U/I				
Bilirubin total		mg/dl				

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number BIG	1-06 / EGF106	903		Liv	er funct	ion tests
Centre No.	Sub	ject No	).			Page 177
Week 1 FEC Sam	ple collection da	te L	I I I I	l , , , , , , , , , , , , , , , , , , ,	J	
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	l <b>range*</b> Max	
SGOT (ASAT)		U/I				
SGPT (ALAT)		U/I				
Alk. phosphatase		U/I				

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number BIG 1	I-06 / EGF106	8903		Liv	er funct	ion tests
Centre No.	Sub	oject No	).			Page 178
Week 4 FEC Sam	ple collection da	te L	DD MMM	l <sub>YYYY</sub>	Т	
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Norma</b> l Min	l range* Max	
SGOT (ASAT)		U/I				
SGPT (ALAT)		U/I				
Alk. phosphatase		U/I				

## NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number BIG Centre No.	)	Liv	er functi	on tests		
		ject No				3
Week 7 FEC Sar	nple collection dat	e L	DD MMM	YYYY	J	
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (ASAT)		U/I				
SGPT (ALAT)		U/I				
Alk phoenhatae	,	1.1/1				

Bilirubin total

mg/dl

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

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Centre No.	Subject No.	Page 180

## Week 10 (Week 1 targeted therapy)



	Result	Unit Unit if other		Normal range*	
	(use dot "." as decimal separator)		unit used	Min	Max
SGOT (ASAT)		U/I			
SGPT (ALAT)		U/I			
Alk. phosphatase		U/I			
Bilirubin total		mg/dl			

## NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

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Centre No.	Subject No.	Page 181

## Week 16 (Week 7 targeted therapy)



	Result	Unit	Unit if other	Normal	range*
	(use dot "." as decimal separator)		unit used	Min	Max
SGOT (ASAT)		U/I			
SGPT (ALAT)		U/I			
Alk. phosphatase		U/I			
Bilirubin total		mg/dl			

## NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Pro	rotocol number BIG 1-06 / EGF106903										Liv	er fu	nctio	on te	ests			
	C	enti	re N	0.				Sı	ubje	ct N	lo.						Page	182

#### Week 22 (Week 13 targeted therapy)



	Result	Unit	Unit if other	Normal	range*
	(use dot "." as decimal separator)		unit used	Min	Max
SGOT (ASAT)		U/I			
SGPT (ALAT)		U/I			
Alk. phosphatase		U/I			
Bilirubin total		mg/dl			

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Please check the blood tests and report any <u>clinically significant</u> abnormality on the "**Adverse event**" page.

tests

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Prot	Protocol number BIG 1-06 / EGF106903								Liver function tes	its
Centre No. Subject No.							Page 18	3		

## Week 28 (Week 19 targeted therapy)



	Result	Unit	Unit if other	Normal range*		
	(use dot "." as decimal separator)		unit used	Min	Max	
SGOT (ASAT)		U/I				
SGPT (ALAT)		U/I				
Alk. phosphatase		U/I				
Bilirubin total		mg/dl				

## NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Please check the blood tests and report any <u>clinically significant</u> abnormality on the "**Adverse event**" page.

Study: Neo-ALTTO v. 6.0 (19Mar09)

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Prot	Protocol number BIG 1-06 / EGF106903									Liver function tests	
Centre No. Subject No.								Page 184			

## Week 34 (Week 25 targeted therapy)



	Result	Unit	Unit if other	Normal	range*
	(use dot "." as decimal separator)		unit used	Min	Max
SGOT (ASAT)		U/I			
SGPT (ALAT)		U/I			
Alk. phosphatase		U/I			
Bilirubin total		mg/dl			

## NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Proto	Protocol number BIG 1-06 / EGF106903								Liver function tests	
Centre No. Subject No.							Page 185			

## Week 40 (Week 31 targeted therapy)



	Result	Unit	Unit if other	Normal	range*
	(use dot "." as decimal separator)		unit used	Min	Max
SGOT (ASAT)		U/I			
SGPT (ALAT)		U/I			
Alk. phosphatase		U/I			
Bilirubin total		mg/dl			

## NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Prot	Protocol number BIG 1-06 / EGF106903										Liver function tes	ts
Centre No. Subject No.									Page 18	6		

## Week 43 (Week 34 targeted therapy)



	Result	Unit	Unit if other	Normal	range*
	(use dot "." as decimal separator)		unit used	Min	Max
SGOT (ASAT)		U/I			
SGPT (ALAT)		U/I			
Alk. phosphatase		U/I			
Bilirubin total		mg/dl			

# NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol numbe	r BIG 1	-06 / EGF106	5903		Liv	er funct	ion tests
Centre No	).	Sub	oject No	).			Page 187
Month 12	Samp	ole collection da	te L	J J J DD MMM	YYYY	J	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (AS	SAT)		U/I				
SGPT (AL	AT)		U/I				
Alk. phosp	hatase		U/I				

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol numbe	r BIG 1	-06 / EGF106	6903		Liv	er functi	on tests
Centre No	). 	Sub	ject No	).			Page 188
Month 15	Samp	le collection da	te L	I I I I DD MMM	l ryyy	J	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (AS	SAT)		U/I				
SGPT (AL	.AT)		U/I				
Alk. phosp	ohatase		U/I				

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number BIG	1-06 / EGF106	6903		Liv	er funct	ion tests
Centre No.	Sub	oject No	).			Page 189
Month 18 Sam	nple collection da	te L	DD MMM	L , , , , , , , , , , , , , , , , , , ,	Т	
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Norma</b> l Min	l <b>range*</b> Max	
SGOT (ASAT)		U/I				
SGPT (ALAT)		U/I				
Alk. phosphatase		U/I				

Bilirubin total

mg/dl

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number	BIG 1	-06 / EGF106	5903		Liv	er funct	ion tests
Centre No.		Sub	oject No	).			Page 190
Month 24	Samp	le collection da	te L	DD MMM	l yyyy	J	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (ASA	AT)		U/I				
SGPT (ALA	AT)		U/I				
Alk. phosph	atase		U/I				

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number	BIG 1-0	06 / EGF106	903		Liv	er functi	on tests
Centre No.		Sub	ject No				Page 191
Month 36	Sample	collection dat	te L	I I I I	YYYY	J	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (ASA	AT)		U/I				
SGPT (ALA	T)		U/I				
Alk nhosnh	atase		LJ/I				

Bilirubin total

mg/dl

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number BI				Liv	er funct	ion tests
Centre No.	Sub	oject No	).			Page 192
Month 48 S	ample collection da	te L	DD MMM	YYYY	J	
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (ASAT)		U/I				
SGPT (ALAT)		U/I				
Alk. phosphata	se L	U/I				

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number B	BIG 1-06 / EGF10	6903		Live	er functi	on tests
Centre No.	Sul	bject No.				Page 193
Month 60	Sample collection da	ate L	L L MMM	l ı ı ı ı		
	Result (use dot "." as decimal separator)		Init if other unit used	<b>Normal</b> ı Min	range* Max	
SGOT (ASAT	г)	U/I				
SGPT (ALAT	.)	U/I				
Alk, phospha	itase L	U/I				

Bilirubin total

mg/dl

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol num	ber BIG 1	-06 / EGF106	5903		Liv	er funct	ion tests
Centre	No.	Sub	oject No	).			Page 194
Year 6	Samp	ole collection da	te L	I I I I	l , , , , , , , , , , , , , , , , , , ,	J	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT	(ASAT)		U/I				
SGPT	(ALAT)		U/I				
Alk. ph	osphatase		U/I				

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol n	umber BIG 1	-06 / EGF106	8903		Live	er functi	ion tests
Cen	tre No.	Sub	ject No	).			Page 195
Year 7	Samp	ole collection da	te L	ı l ı ı DD MMM	YYYY	I	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SG	OT (ASAT)		U/I				
SG	PT (ALAT)		U/I				
Alk	. phosphatase		U/I				

mg/dl

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Please check the blood tests and report any <u>clinically significant</u> abnormality on the "**Adverse event**" page.

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number	BIG 1	-06 / EGF106	5903		Liv	er functi	ion tests
Centre No		Sub	oject No	).			Page 196
Year 8	Samp	le collection da	te L	I I I I	l I I I	J	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (AS	AT)		U/I				
SGPT (ALA	AT)		U/I				
Alk. phospl	natase		U/I				

mg/dl

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Please check the blood tests and report any <u>clinically significant</u> abnormality on the "**Adverse event**" page.

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol number	BIG 1	-06 / EGF106	5903		Liv	er functi	ion tests
Centre No		Sub	oject No	).			Page 197
Year 9	Samp	ole collection da	te L	J J I I	l I I I	J	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SGOT (AS	AT)		U/I				
SGPT (ALA	AT)		U/I				,
Alk. phosp	hatase		U/I				

mg/dl

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Please check the blood tests and report any <u>clinically significant</u> abnormality on the "**Adverse event**" page.

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Protocol r	number BIG 1	I-06 / EGF106	6903		Live	er functi	ion tests
Cei	ntre No.	Sub	ject No	).			Page 198
Year 10	<b>)</b> Sam	ple collection da	te L	I I I I DD MMM	YYYY	l	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal</b> Min	range* Max	
SC	GOT (ASAT)		U/I				
SC	GPT (ALAT)		U/I				
All	k. phosphatase		U/I				

mg/dl

#### NCI CTCAE v. 3: haematology and biochemistry toxicity scale

Bilirubin total

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Please check the blood tests and report any <u>clinically significant</u> abnormality on the "**Adverse event**" page.

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

>rc	otocol number BIG 1-	06 / EGF106	6903		liver fur	ction tests
	Centre No.	Sub	oject No	ı		Page 199
	Sample collection date	DD	I I MMM	YYYY		
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal range*</b> Min Ma	
	SGOT (ASAT)		U/I			
	SGPT (ALAT)		U/I			
	Alk. phosphatase		U/I			
	Bilirubin total		mg/dl			
	Sample collection date	DD	I I MMM	YYYY	Named manage	
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal range*</b> Min Ma	
	SGOT (ASAT)		U/I			
	SGPT (ALAT)		U/I			
	Alk. phosphatase		U/I			
	Bilirubin total		mg/dl			
	Sample collection date	L L DD	I I MMM	YYYY		
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal range*</b> Min Ma	
	SGOT (ASAT)		U/I			
	SGPT (ALAT)		U/I			
	Alk. phosphatase		U/I			
	Bilirubin total		mg/dl			

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Pro	otocol number BIG 1-	liver fu	nction tests			
	Centre No.	Sul	oject No			Page 200
	Sample collection date	L L DD	I I MMM	YYYY		
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal range</b> <sup>3</sup> Min N	łax
	SGOT (ASAT)		U/I			
	SGPT (ALAT)		U/I			
	Alk. phosphatase		U/I			
	Bilirubin total		mg/dl			
	Sample collection date	DD DD	I I MMM	YYYY		
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal range</b> <sup>3</sup> Min N	lax
	SGOT (ASAT)		U/I			
	SGPT (ALAT)		U/I			
	Alk. phosphatase		U/I			
	Bilirubin total		mg/dl			
	Sample collection date	L L DD	I I MMM	L YYYY		
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal range</b> <sup>3</sup> Min N	łax
	SGOT (ASAT)		U/I			
	SGPT (ALAT)		U/I			
	Alk. phosphatase		U/I			
	Bilirubin total		mg/dl			

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

>rc	otocol number BIG 1-	06 / EGF106	6903		liver funct	ion test
	Centre No.	Sub	oject No			Page 201
	Sample collection date	L I DD	I I MMM	YYYY		
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	Normal range* Min Max	
	SGOT (ASAT)		U/I			-
	SGPT (ALAT)		U/I			_
	Alk. phosphatase		U/I			_
	Bilirubin total		mg/dl			-
	Sample collection date	Result (use dot "." as decimal separator)	MMM Unit	YYYY  Unit if other unit used	<b>Normal range*</b> Min Max	
	SGOT (ASAT)		U/I			_
	SGPT (ALAT)		U/I			-
	Alk. phosphatase		U/I			-
	Bilirubin total		mg/dl			-
	Sample collection date	DD  Result (use dot "." as decimal separator)	MMM Unit	YYYYY  Unit if other unit used	<b>Normal range*</b> Min Max	
	SGOT (ASAT)		U/I			_
	SGPT (ALAT)		U/I			_
	Alk. phosphatase		U/I			-
	Bilirubin total		mg/dl			_

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Protocol number BIG 1-	liver f	unction test			
Centre No.	Sul	oject No			Page 202
Sample collection date	L L DD	I I MMM	L YYYY		
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal rang</b> Min	<b>ye*</b> Max
SGOT (ASAT)		U/I			
SGPT (ALAT)		U/I			
Alk. phosphatase		U/I			
Bilirubin total		mg/dl			
Sample collection date	DD  Result (use dot "." as	MMM Unit	YYYYY  Unit if other unit used	<b>Normal ranç</b> Min	g <b>e*</b> Max
SGOT (ASAT)	decimal separator)	U/I	diffe doca	IVIIII	IVIAX
SGPT (ALAT)		U/I			
Alk. phosphatase		U/I			
Bilirubin total		mg/dl			
Sample collection date	L L DD	I I MMM	YYYY		
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal rang</b> Min	g <b>e</b> * Max
SGOT (ASAT)		U/I			
SGPT (ALAT)		U/I			
Alk. phosphatase		U/I			
Bilirubin total		mg/dl			

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Pr	otocol number BIG 1-	liver	function test			
	Centre No.	Sul	oject No			Page 203
	Sample collection date					
		Result (use dot "." as decimal separator)	MMM <b>Unit</b>	YYYY Unit if other unit used	<b>Normal ran</b> Min	ge* Max
	SGOT (ASAT)		U/I			
	SGPT (ALAT)		U/I			
	Alk. phosphatase		U/I			
	Bilirubin total		mg/dl			
	Sample collection date	L L DD	I I MMM	YYYY		
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal ran</b> Min	<b>ge*</b> Max
	SGOT (ASAT)		U/I			
	SGPT (ALAT)		U/I			
	Alk. phosphatase		U/I			
	Bilirubin total		mg/dl			
	Sample collection date	L L DD	I I	L L L L		
		Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Normal ran</b> Min	<b>ge*</b> Max
	SGOT (ASAT)		U/I			
	SGPT (ALAT)		U/I			
	Alk. phosphatase		U/I			
	Bilirubin total		mg/dl			

<sup>\*</sup> Please report the normal range as listed on the laboratory results

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SGOT (ALAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
SGPT (ASAT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Alkaline Phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	
Bilirubin total	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	

Protocol number BIG 1-	liv	ver tunct	ion tests			
Centre No.	Sub	oject No				Page 204
Sample collection date	L L DD	I I MMM	YYYY			
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Norma</b> Min	al range* Max	
SGOT (ASAT)		U/I				-
SGPT (ALAT)		U/I				-
Alk. phosphatase		U/I				-
Bilirubin total		mg/dl				-
Sample collection date	L L DD	I I	YYYY			
	Result (use dot "." as decimal separator)	Unit	Unit if other unit used	<b>Norma</b> Min	al range* Max	
SGOT (ASAT)		U/I				-
SGPT (ALAT)		U/I				-
Alk. phosphatase		U/I				-
Bilirubin total		mg/dl				_

<sup>\*</sup> Please report the normal range as listed on the laboratory results