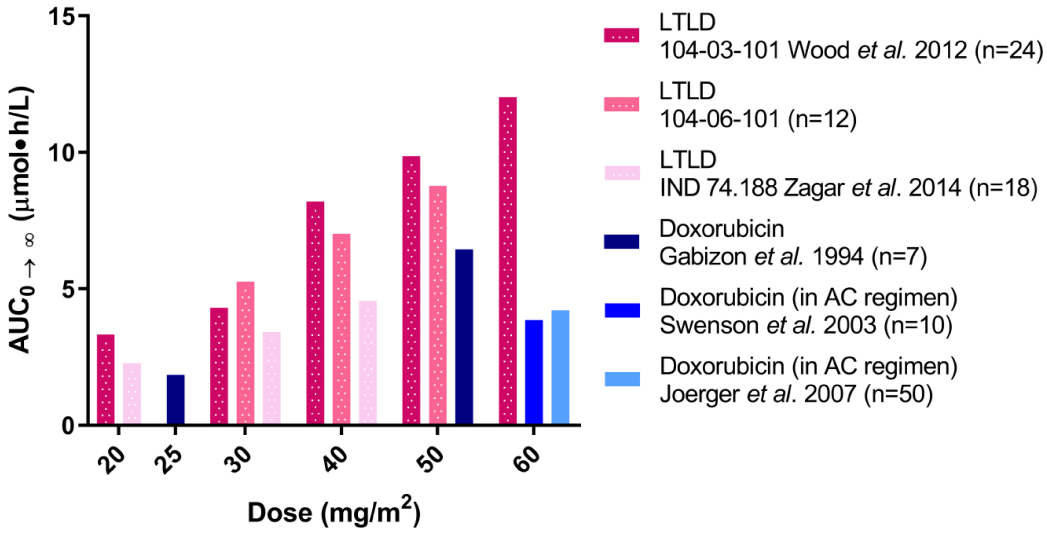
Supplementary materials:

de Maar JS, *et al. BMJ Open* 2021; 10:e040162. doi: 10.1136/bmjopen-2020-040162

Supplement 1 Comparison of AUC0-∞ of free doxorubicin for LTLD and conventional doxorubicin.

In order to obtain a systemic dose of free doxorubicin (due to leakage of LTLD at 37 °C) that is as similar to conventional doxorubicin at 60 mg/m^2 (which is the standard of care treatment for the patients that will be enrolled in this study) as possible (to avoid undertreatment) we will start at the dose of 50 mg/m^2 LTLD, and we will apply dose adjustments when necessary. To compare the systemic dose of free doxorubicin after LTLD plus hyperthermia to the systemic dose of conventional doxorubicin, we summarized the pharmacokinetic data of the three studies with LTLD in which total plasma doxorubicin and the metabolite doxorubicinol were measured with a validated assay (studies 104-03-101 [1], 104-06-101 [2], and IND #174,188 [3]). In these studies the Area Under the Curve from t=0 to infinity (AUC0-∞) of the metabolite doxorubicinol was measured. Note that in these studies LTLD was administered with hyperthermia or RFA treatment. Pharmacokinetic data on LTLD without heating are not available. The mean values were converted to the AUC0-∞ of 'free doxorubicin' based on the mean ratios between doxorubicinol and doxorubicin found in three studies (0.3826, 0.47 and 0.514 respectively, with a mean of 0.456) [4-6]. We compared these AUC0-∞ values of 'free doxorubicin' from the LTLD studies with the AUC0-∞ values of doxorubicin in pharmacokinetic studies of conventional doxorubicin [7-9]. Figure S2 displays the AUC0-∞ of three studies with conventional doxorubicin (actual doxorubicin values are portrayed) and the AUC0-∞ of three studies with LTLD (calculated 'free doxorubicin' values are portrayed). The figure shows that the calculated 'free doxorubicin' after LTLD 50 mg/m^2 is at least equal to that of conventional doxorubicin at 60 mg/m^2.

Figure S2: Comparison of the AUC0-∞ of "free" plasma doxorubicin for LTLD + heat (calculated based on doxorubicinol concentration) and conventional doxorubicin.



Supplementary References

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Supplement 2 Dose adjustments in the i-GO study.

Individual dose adjustments and/or delays may be made based on the emergence of specific adverse events.

Adverse events consist of:

- Systemic toxicity
- Locoregional toxicity

S2.1 Systemic toxicity

Myelosuppression

Dose adjustments in case of myelosuppression are summarized in figure S2-1.

If ANC <1.5 x 10^9/L, then the LTLD and cyclophosphamide doses will be held and re-evaluated for treatment in one week. Any second occurrence of ANC <1.5 x10^9/L will require a decrease in LTLD dose to 40 mg/m^2. The cyclophosphamide will remain unchanged. LTLD and cyclophosphamide will be administered at day 14 (two weeks after the scheduled dose) if the ANC ≥ 1.5 x 10^9/L. In case of recurrence of ANC <1.5 x10^9/L with the decreased LTLD dose, study participation will end and the patient will continue treatment with the standard of care AC regimen.

If platelets are < 100 x 10^9/L, then the LTLD and cyclophosphamide doses will be held and re-evaluated for treatment in one week. Any second occurrence of platelets < 100 x 10^9/L will require a decrease in LTLD dose to 40 mg/m^2. The cyclophosphamide will remain unchanged. These doses will be administered at day 14 (two weeks after the scheduled dose) if the platelets are ≥ 100 x10^9/L. In case of recurrence of platelets < 100 x 10^9/L with the decreased LTLD dose, study participation will end and the patient will continue treatment with the standard of care AC regimen.
If a patient requires drug-withholding for more than 14 days, then the patient will be withdrawn from the study.

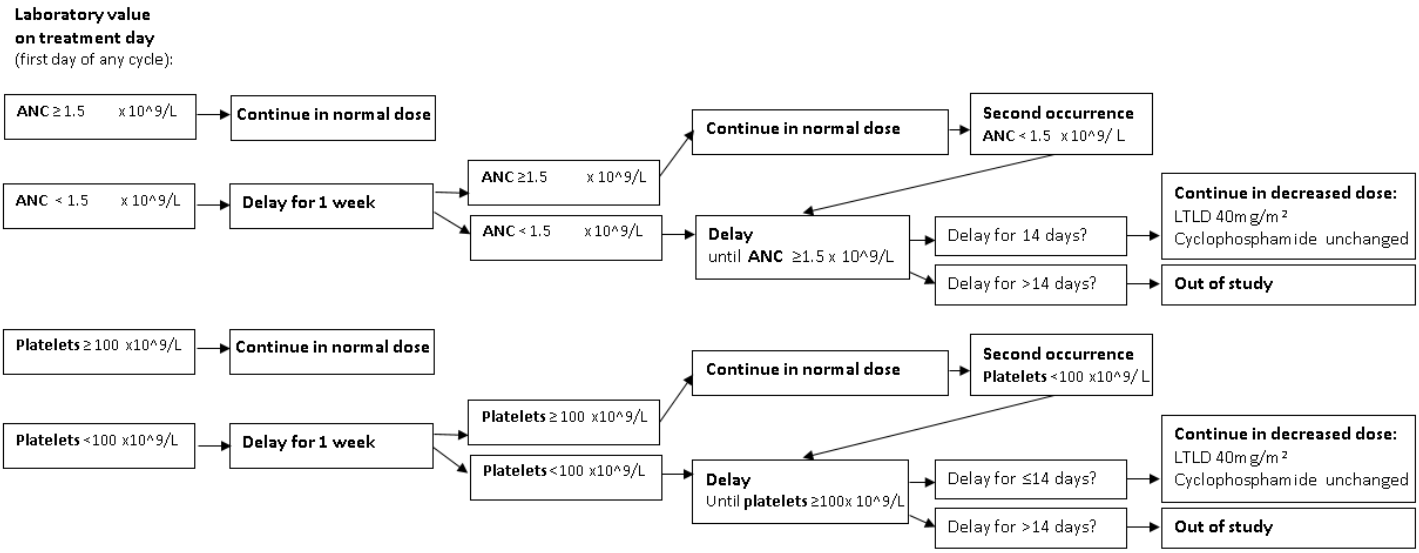

Figure S2.1: Flow chart of dose adjustments for myelosuppression

Hypersensitivity reactions

No dose reductions will be made for hypersensitivity reactions.

Table S2: Suggested Management for Hypersensitivity Reactions

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, mild flushing, mild rash (Grades 0-1)	Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient Complete study drug infusion at the initial planned rate
Moderate to Severe symptoms: any symptom that is not mild (see list above) such as generalized pruritus, generalized flushing, generalized rash, dyspnea, hypotension with systolic BP < 80 mm Hg, bronchospasm, angioedema and generalized angioedema. (Grades 2-4)	WITHDRAW FROM STUDY
Anaphylaxis (Grade 4)	WITHDRAW FROM STUDY

Abnormal Liver Tests

If a patient develops abnormal liver tests, they will be evaluated for causal factors such as bile duct obstruction or liver pathology, with an abdominal ultrasound. If a cause is found, this must be resolved before continuing the treatment. If no other cause than the study treatment is found (or the cause cannot be resolved), patients will have the following dose reductions (summarized in figure S2-2).

If bilirubin ≥25 µmol/L, then the LTLD and cyclophosphamide doses will be held and re-evaluated for treatment in one week. Any second occurrence of bilirubin ≥25 µmol/L will require a dose adjustment to 40mg/m^2 LTLD. If the bilirubin is still 25-50 µmol/L after one week, the patient will be treated with a decrease in LTLD dose to 25 mg/m^2 (50% of the original dose) and unchanged cyclophosphamide dose. If the bilirubin has normalized < 25 µmol/L after one week, the patient will be treated with a decrease in LTLD dose to 40 mg/m^2, the cyclophosphamide dose will remain unchanged. In case bilirubin ≥25 µmol/L recurs after previous LTLD dose reduction, study participation will end and the patient will continue treatment with the standard of care AC regimen.
If the bilirubin ≥ 50 µmol/L, treatment will be delayed until < 50 µmol/L. If a patient requires drug-withholding for more than 14 days, then she will be withdrawn from the study.

If bilirubin <25µmol/L and AF ≤ 600 U/L, but ASAT and ALAT are mildly elevated (1.6-3.5xULN), the patient will be treated with a decrease in LTLD dose to 40 mg/m^2 and unchanged cyclophosphamide dose,without delay. In case mildly elevated ASAT or ALAT recur after previous LTLD dose reduction, study participation will end and the patient will continue treatment with the standard of care AC regimen.
If AF > 5xULN (>600U/L) or ASAT > 3,5xULN (>105U/L) or ALAT > 3,5xULN (>123 U/L), treatment will be delayed until liver tests have recovered (bili<25 µmol/L, AF ≤5xULN and ASAT/ALAT≤3.5xULN). Then the patient will be treated with a decrease in LTLD dose to 40 mg/m^2 and unchanged cyclophosphamide dose. In case the elevated AF (> 5xULN), ASAT (> 3,5xULN) or ALAT (> 3,5xULN) recur after the LTLD dose reduction, study participation will end and the patient will continue treatment with the standard of care AC regimen.
If a patient requires drug-withholding for more than 14 days, then she will be withdrawn from the study.

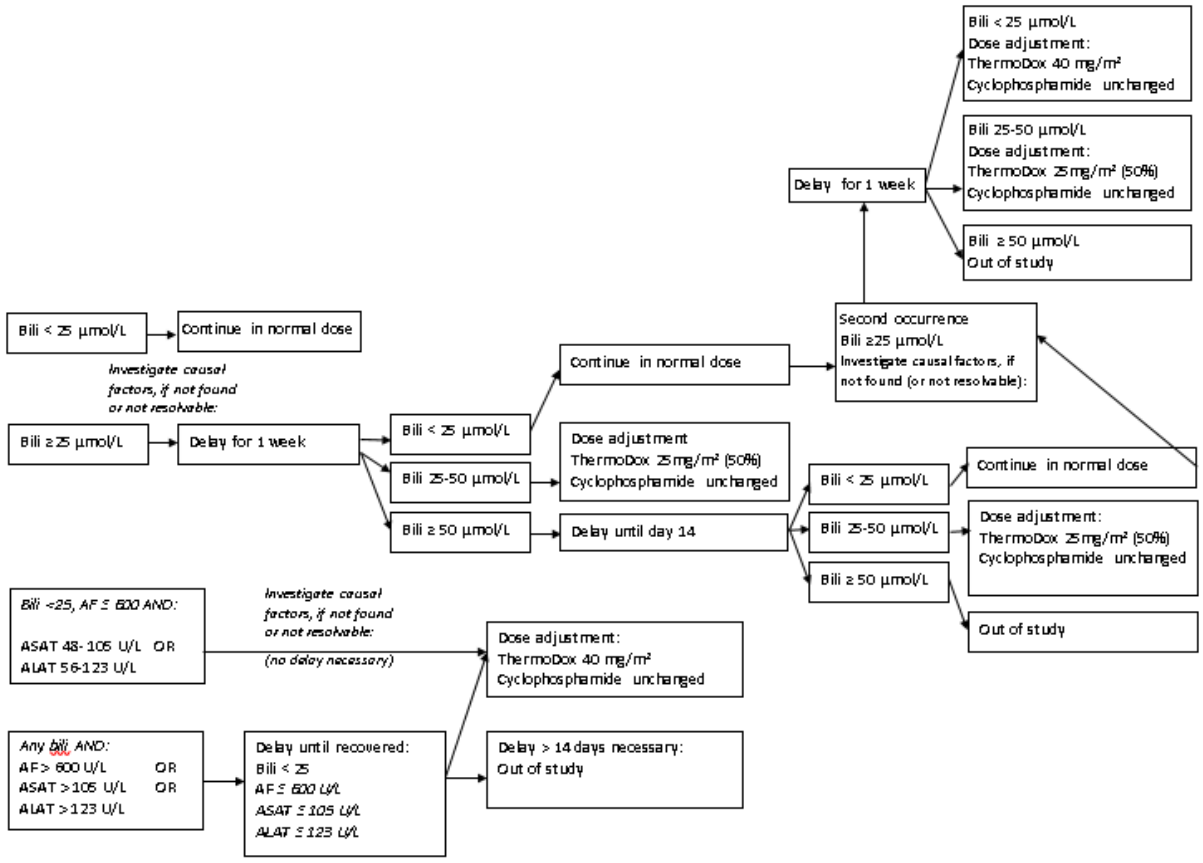

Figure S2.2: Flow chart of dose adjustments for abnormal liver tests

Mucositis

If mucositis is present on any treatment day, then treatment should be held until mucositis has resolved. If mucositis of Grade ≥ 3 occurs, then reduce the dose of LTLD to 40 mg/m^2, while the cyclophosphamide dose remains unchanged for subsequent cycles. In case mucositis of grade ≥3 recurs after the LTLD dose reduction, study participation will end and the patient will continue treatment with the standard of care AC regimen. If a patient requires drug-withholding for more than 14 days, then the patient will be withdrawn from the study.

Ventricular Function

Patients who are receiving protocol therapy will be removed from study treatment under the following conditions:
Signs (tachycardia, S3, elevated jugular venous pressure) AND symptoms of congestive heart failure (edema, dyspnea, paroxysmal nocturnal dyspnea, orthopnea) OR
a decline in LVEF of > 15% while the LVEF remains > 40% OR
a decline to an LVEF of ≤ 40%.

Patients in this category should be followed with an ejection fraction assessment every three months until stable.

Other adverse events

For other non-hematologic toxicity ≥ grade 3, no dose modification is required. Instead, such subjects will not be re-treated until the severity of the non-hematologic toxicity drops to ≤ grade 1. If a patient requires drug-withholding for more than 14 days, then the patient will be removed from the trial.

S2.2 Locoregional toxicity

Post-procedural pain

If a patient experiences post-procedural pain in the treated breast with:

- a Numeric Rate Scale (NRS) of 7 or higher (severe pain) for more than 60 minutes within 24u hours without pain medication, OR
- a NRS of 5 or higher (moderate to severe pain) for more than 60 minutes within 24u hours that does not respond to adequate pain medication,
- Any pain that the patients finds unacceptable or unbearable

then in the next cycle the hyperthermia time will be reduced by 25%: 45 minutes of MR-HIFU treatment. This level of pain is also considered a dose limiting loco-regional toxicity (loco-regional DLT).

If the patient experiences the above specified level of pain again after the hyperthermia time reduction, de time will be reduced further to 30 minutes of MR-HIFU treatment.

If the above specified level of pain still persists/recurs the patient will be withdrawn from the trial.

Skin effects

If a grade 1 (CTCAE) skin burn is occurs on the treated breast on any treatment day, then treatment should be held until the skin burn has resolved.

If a patient requires treatment withholding for more than 14 days, then the patient will be removed from the trial.

If the skin burn is resolved in ≤ 14 days the hyperthermia time in the next cycle will be reduced by 25%: 45 minutes of MR-HIFU treatment. If a grade 1 skin burn recurs after dose reduction the hyperthermia time will be further reduced to 30 minutes of MR-HIFU treatment. If the burn recurs after that, the patient will be withdrawn from the study.

If a grade 2 burn occurs on the treated breast the patient will immediately be withdrawn from the study.

For other adverse effects of the skin of the treated breast, that are suspected to be related to the study treatment, treatment will be delayed until the severity of the skin toxicity drops to ≤ grade 1. The hyperthermia time will be reduced by 25% in the next cycle. If a patient requires treatment withholding for more than 14 days, then the patient will be removed from the trial. Skin burns and other adverse effects of the skin of the treated breast of grade 1 or higher are considered dose limiting loco-regional toxicities (loco-regional DLTs).

S2.3 Dose adjustments, dose delay or withdrawal from study, based on technical difficulties

In the study design we specified that we aim to perform 60 minutes of hyperthermia to the primary tumor at a temperature of 40ºC-42ºC, however, the ability to achieve this is also a feasibility parameter. It is possible that in certain patients, the aim will not be achieved, which will lead to an individual (unintended) adjustment of hyperthermia dose in that case. Furthermore, if MR-thermometry is insufficiently accurate to provide a safe MR-HIFU treatment, that treatment is stopped for safety reasons and the patient will receive the standard treatment of doxorubicin and cyclophosphamide.
If we experience technical difficulties during the MR-HIFU treatment (such as dysfunction of the MR-HIFU method, loss of power, mechanical difficulties) and we cannot guarantee the safety and feasibility of an individual patient's MR-HIFU treatment, the patient will receive the standard treatment of doxorubicin and cyclophosphamide.

After the technical difficulties have been resolved, the patient can still receive MR-HIFU and LTLD in the next treatment cycle or cycles.
If for one patient, hyperthermia treatment was for any reason insufficient (i.e. the target temperature 40-42°C was not reached or was only maintained for less than 30 minutes), in two separate treatment cycles, the patient will be excluded from the study, because the treatment is not considered feasible for that patient.

If the target temperature of 40-42°C is not reached, LTLD will not be administered (paragraph 8.3.15). Instead, conventional doxorubicin will be administered. However, if the temperature is initially reached, LTLD infusion is started and shortly afterwards the temperature becomes and remains insufficient, LTLD infusion will be continued as planned. In this case it is no longer possible to replace LTLD with conventional doxorubicin, as this would lead to an unreliable dose. If this scenario occurs twice the patient will be excluded from the study, as described above.

Supplement 3 Restrictions to concomitant medications and products

Concurrent use of any of the following medications is strictly prohibited: protease inhibitors, cyclosporine, carbamazepine, phenytoin, valproic acid, paclitaxel, trastuzumab and other liposomal drugs (AbelectTM, Ambisome™, NyotranTM, etc.) or lipid-complexed drugs

Doxorubicin is a substrate of CYP3A4, CYP2D6 and P-glycoprotein (P-gp). As detailed in in table S3-1, inducers and inhibitors of these enzymes, as well as medication that acts with doxorubicin via other pathways could result in drug interactions. Caution will be exercised with regard to all the medications mentioned in table S3-1, for interactions are theoretically possible. If deemed necessary, clinically safe and feasible, these medications will be withheld or substituted before participation in the study.

Pre-specified exceptions were made for cyclophosphamide, dexamethasone, propofol, aprepitant and clemastine. These medications will be used as explained in appendix C.

Liposomal drugs (AbelectTM, Ambisome™, NyotranTM, etc.), or lipid-complexed drugs, or intravenous fat emulsions could change the pharmacokinetic profile of LTLD and should not be administered to study subjects while on the trial.

Subjects may take any medication that is not restricted by the protocol and would not be expected to interfere with the intent and conduct of the study. Chronic medications should be dosed on a stable regimen, if possible. In case of medications restricted by the protocol, adequate washout times must be observed. All medications at the time of screening and within 30 days prior to study treatment and other treatments taken by the subject during the study, including those treatments initiated prior to enrollment (ICF signing), must be recorded.

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Table S3.1 Concomitant medications and products with possible interactions

Sources: (1-6)	Increased risk of toxicity	CYP3A4	CYP2D6	P-gp	Wash-out
Antineoplastic therapy					
bortezomib		inhibitor			
cyclophosphamide[1]	Cardiotoxicity / hemorrhagic cystitis	inhibitor			
cytarabine	Miscellaneous[2]				
dasatinib		inhibitor			
docetaxel		inhibitor			
etoposide		inhibitor			
5-fluorouracil	Cardiotoxicity				
ifosfamide		inhibitor			
imatinib		inhibitor			
lapatinib				inhibitor	
lomustine		inhibitor			
6-mercaptopurin: 6-MP / purinethol	Hepatotoxicity				
methotrexate	Hepatotoxicity				
methoxsalen		inhibitor			
mitoxantrone		inhibitor			
nafcillin		inducer			
paclitaxel	Cardiotoxicity				
plicamycin***	Hematologic				
rifamycin agents (all)		inducer			14 days
rifabutin		inducer**			14 days
rifampicin		inducer**		inducer**	14 days
rifapentine		inducer			14 days

[1] Pre-specified exceptions are described below

[2] Necrotizing colitis manifested by typhlitis (caecal inflammation), bloody stools, and severe and sometimes fatal infections have been associated with a combination of doxorubicin given by intravenous push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days. Source: Pfizer 2010.

* Mentioned as powerful inhibitor/inducer in the KNMP Kennisbank.
Note: Relevance of an interaction also depends on properties of the substrate, such as therapeutical width, biological availability or another route of metabolism.
https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/G1126.html

** Mentioned as inhibitor/inducer in the KNMP Kennisbank
https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/G1126.html

*** Prohibited medication in the Phase I trial at Duke (IND#74,188)

Table S3.1 Concomitant medications and products with possible interactions (continued)

	Increased risk of toxicity	CYP3A4	CYP2D6	P-gp	Wash-out
sorafenib[3]	Possible dose modification				
streptozocin***	Hematologic				
teniposide		inhibitor			
trastuzumab	Cardiotoxicity				24 weeks
vinblastine		inhibitor			
vincristine		inhibitor			
vinorelbine		inhibitor			
(anti-) Hormonal medication					
abirateron			inhibitor		
anastrozole		inhibitor			
danazol		inhibitor			
drospirenone		inhibitor			
ethinyl estradiol		inhibitor			
mestranol		inhibitor			
mifepristone		inhibitor			
progesterone[4]	Hematologic	inhibitor			
tamoxifen		inhibitor			
testosterone		inhibitor			
Calcium channel blockers					
amlodipine		inhibitor			
diltiazem	Cardiotoxicity	inhibitor			7 days
felodipine		inhibitor			
nicardipine (cardene)		inhibitor			
nifedipine		inhibitor			
nisoldipine		inhibitor			
verapamil	Cardiotoxicity	inhibitor		inhibitor**	7 days
	Hospital pharmacist's advice: in case of this interaction, no action is needed				
Bètablockers					
propranolol	Cardiotoxicity				
carvedilol				inhibitor	
Angiotensin receptor blockers					
irbesartan		inhibitor			
losartan		inhibitor			

[3] In clinical studies, both an increase of 21% and 47%, and no change in the AUC of doxorubicin were observed with concomitant treatment with sorafenib 400 mg twice daily. The clinical significance of these findings is unknown. Source: Pfizer 2010.

[4] In a published study, progesterone was given intravenously to patients with advanced malignancies (ECOG PS< 2) at high doses (up to 10 g over 24 hours) 12 concomitantly with a fixed doxorubicin dose (60 mg/m^2) via bolus injection. Enhanced doxorubicin-induced neutropenia and thrombocytopenia were observed. Source: Pfizer 2010.

* Mentioned as powerful inhibitor/inducer in the KNMP Kennisbank.
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Table S3.1 Concomitant medications and products with possible interactions (continued)

Anti-arrhythmic agents					
	Increased risk of toxicity	**CYP3A4**	**CYP2D6**	**P-gp**	**Wash-out**
amiodarone		inhibitor	inhibitor	inhibitor**	6 months
dronedarone				inhibitor	
propafenon			inhibitor	inhibitor	
quinidine (kinidine)		inhibitor	powerful* inhibitor	inhibitor**	
Statins					
atorvastatin		inhibitor			
fluvastatin		inhibitor			
lovastatin		inhibitor			
pravastatin		inhibitor			
Anticonvulsants *Hospital pharmacist's advice: the concentration of phenytoin and other antiepileptics can be affected by oncolytics, decreasing the antiepileptic effect. Dose adjustment is needed.*					
barbiturate agents		inducer			
	Hospital pharmacist's advice: interaction is only theoretical, no action is needed				
carbamazepine[5]		inducer**		inducer**	
fosphenytoin[5]		inducer			
pentobarbital		inducer			
phenobarbital ***		inducer**		inducer**	
phenytoin[5]***		inducer**		inducer**	
primidone		inducer**		inducer**	
oxcarbazepine		inducer			
valproic acid (depakine)[5]		inhibitor			
Antidepressants					
bupropion			powerful* inhibitor		
desipramine		inhibitor			
duloxetine			inhibitor		
fluoxetine		powerful* inhibitor			
fluvoxamine		inhibitor			7 days
mirtazapine		inhibitor			
nefazodone		inhibitor			7 days
norfluoxetine		?	inhibitor		
paroxetine		inhibitor	powerful* inhibitor		
selegiline		inhibitor			
sertraline		inhibitor	inhibitor		
tranylcypromine		inhibitor			
trazodone		inhibitor			
venlafaxine		inhibitor			

[5] The levels of carbamazepine, phenytoin and valproic acid can temporarily be affected by doxorubicin, with the risk of sub effective anti-epileptic dosage.

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Note: Relevance of an interaction also depends on properties of the substrate, such as therapeutical width, biological availability or another route of metabolism.
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Table S3.1 Concomitant medications and products with possible interactions (continued)

	Increased risk of toxicity	CYP3A4	CYP2D6	P-gp	Wash-out
Antipsychotics					
clozapine	Hematologic	inhibitor			
haloperidol		inhibitor			
olanzapine		inhibitor			
pimozide		inhibitor			
	Increased risk of toxicity	**CYP3A4**	**CYP2D6**	**P-gp**	**Wash-out**
risperidone		inhibitor			
ziprasidone		inhibitor			
Thyreostatics ***					
thionamids: e.g.	Hematologic				
carbimazole	Hematologic				
propylthiouracil	Hematologic				
thiamazol / methimazole	Hematologic	inhibitor			
Immune suppressive agents					
azathioprine***	Hematologic / Immune suppressive				
cyclosporine/cyclosporine ***	Immune suppressive	inhibitor		inhibitor**	
	Hospital pharmacist's advice: The combination of anthracyclines and ciclosporin should be avoided				
interferon	Hematologic				
sirolimus		inhibitor			
tacrolimus		inhibitor			
Antibiotics					
azithromycin		inhibitor			
chloramphenicol***	Hematologic	inhibitor			
clarithromycin		powerful* inhibitor		inhibitor	7 days
ciprofloxacin		inhibitor			
doxycycline		inhibitor			
erythromycin		powerful* inhibitor		inhibitor **	7 days
norfloxacin		inhibitor			
quinupristin		inhibitor			
telithromycin		inhibitor			
tetracycline		inhibitor			
troleandomycin		inhibitor			7 days
Antimycotics					
amphotericin B***	Nephrotoxicity				
clotrimoxazole		inhibitor			
fluconazole		inhibitor			7 days
flucytosine***	Hematologic				
itraconazole		powerful* inhibitor		inhibitor	7 days
ketoconazole		powerful* inhibitor		inhibitor**	7 days

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Note: Relevance of an interaction also depends on properties of the substrate, such as therapeutical width, biological availability or another route of metabolism.
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Table S3.1 Concomitant medications and products with possible interactions (continued)

	Increased risk of toxicity	CYP3A4	CYP2D6	P-gp	Wash-out
metronidazole		inhibitor			
miconazole		inhibitor			
posaconazol		inhibitor			
sulconazole		inhibitor			
terbinafine			inhibitor		
voriconazole		powerful* inhibitor			7 days
Anti (retro-) viral agents *Hospital pharmacist's advice: In case of HIV-protease inhibitors, the interaction will always be discussed with the local pharmacist, doxorubicin is discouraged in this group.*					
atazanavir		Inhibitor			
amprenavir		Inhibitor			7 days
boceprevir		Inhibitor			
cobicistat		powerful* inhibitor		inhibitor**	
delavirdine		Inhibitor			7 days
efavirenz		inducer			
fosamprenavir		Inhibitor			
ganciclovir***	Hematologic				
indinavir		Inhibitor			7 days
interferon***	Hematologic				
lopinavir		Inhibitor		inhibitor**	7 days
nelfinavir		Inhibitor			7 days
nevirapine		Inducer			
ritonavir		powerful* Inhibitor	powerful* inhibitor	inhibitor**	7 days
saquinavir		Inhibitor		inhibitor	7 days
simeprevir				inhibitor**	
telaprevir				inhibitor	
tipranavir				inhibitor	
zidovudine***	Hematologic				
Miscellaneous anti-infectious agents					
clofazimine		Inhibitor			
isoniazid		Inhibitor			
mefloquine		Inhibitor			
pentamidine		Inhibitor			
primaquine		Inhibitor			
quinine (kinine)		Inhibitor	inhibitor		
Glucocorticoids[6]					
betamethasone		inducer			
cortisone (> 50 mg)		inducer			14 days
dexamethasone (> 1.5 mg)		inducer		inducer	14 days

* Mentioned as powerful inhibitor/inducer in the KNMP Kennisbank.
Note: Relevance of an interaction also depends on properties of the substrate, such as therapeutical width, biological availability or another route of metabolism.
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Table S3.1 Concomitant medications and products with possible interactions (continued)

	Increased risk of toxicity	CYP3A4	CYP2D6	P-gp	Wash-out
hydrocortisone (> 40 mg		inducer			14 days
methylprednisolone (>8mg[8]),		inducer			14 days
prednisolone		inducer			
prednisone (> 10 mg)		inducer			14 days
Sedatives					
dexmedetomidine		inhibitor			
diazepam		inhibitor			
midazolam		inhibitor			
propofol[9]		inhibitor			
Pain medication					
colchicine***	Hematologic				
diclofenac		inhibitor			
dihydroergotamine		inhibitor			
ergotamine		inhibitor			
Fentanyl		inhibitor			
lidocaine		inhibitor			
paracetamol		inhibitor			
	Hospital pharmacists advice: This interaction is not clinically relevant, no action is needed				
Antacids					
Hospital pharmacists advice: This interaction is not clinically relevant, no action is needed					
rennies	Modify gastric acidity				1 hour before and after
mylanta / maalox (aluminum hydroxide, magnesium hydroxide simethicone)	Modify gastric acidity				1 hour before and after
tums	Modify gastric acidity				1 hour before and after
Other GI agents					
aprepitant [10]		inhibitor			7 days

[8] Methylprednisolone at a single high dose (32mg) did not affect CYP3A4 activity and treatment with 8mg methylprednisolone daily for 9 days did not result in clinically significant induction of CYP3A3. (Villikka et al 2001)

* Mentioned as powerful inhibitor/inducer in the KNMP Kennisbank.
Note: Relevance of an interaction also depends on properties of the substrate, such as therapeutical width, biological availability or another route of metabolism.
https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/G1126.html
** Mentioned as inhibitor/inducer in the KNMP Kennisbank
https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/G1126.html
*** Prohibited medication in the Phase I trial at Duke (IND#74,188)

Table S3.1 Concomitant medications and products with possible interactions (continued)

	Increased risk of toxicity	CYP3A4	CYP2D6	P-gp	Wash-out
cimetidine		inhibitor	inhibitor		7 days
lansoprazole		inhibitor		inhibitor	
nizatidine		inhibitor			
omeprazole		inhibitor		inhibitor	
	Hospital pharmacists advice: This interaction is not clinically relevant, no action is needed				
pantoprazole				inhibitor	
rabeprazole		inhibitor			
Histamine antagonists					
azelastine		inhibitor			
cimetidine		inhibitor			
clemastine[11]		inhibitor			
diphenhydramine			inhibitor		
Herbal or dietary ingredients or supplements					
caffeine		inhibitor			
	Hospital pharmacists advice: This interaction is not clinically relevant, no action is needed				
cannabis oil				inhibitor (10)	
citrus fruits (other than grapefruit: sour orange/bitter orange, pomelo, sweetie/oroblanco)		inhibitor			7 days
echinacea		inducer (11)			14 days
evening primrose oil		inducer (12)	inhibitor (12)		14 days
ginkgo biloba		inducer (12)			14 days
ginseng	not conclusive(11, 13)				14 days
golden seal (yellow root, Hydrastis Canadensis)		inhibitor (14)	inhibitor (14)		
grape fruit (or juice)		inhibitor			7days
grape seed		inhibitor (13)			14 days
kava (piper methysticum)	not conclusive (13)				14 days
St. John's Wort (hypericum)		inducer**		inducer**	14 days
turmeric (curcuma longa)		inhibitor (15)		inhibitor (16)	
valerian	not conclusive (14)				14 days
Other					
acetazolamide (Diamox)		inhibitor			
aminoglutethimide		inducer			

[11] Pre-specified exceptions are described below

* Mentioned as powerful inhibitor/inducer in the KNMP Kennisbank.
Note: Relevance of an interaction also depends on properties of the substrate, such as therapeutical width, biological availability or another route of metabolism.
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*** Prohibited medication in the Phase I trial at Duke (IND#74,188)

Table S3.1 Concomitant medications and products with possible interactions (continued)

	Increased risk of toxicity	CYP3A4	CYP2D6	P-gp	Wash-out
bromocriptine		inhibitor			
bosentan		inducer**			
chlorzoxazone		inhibitor			
cinacalcet			inhibitor		
conivaptan		inhibitor			
coumarins (vitamin K antagonists)	Possible fluctuation of coagulation times. Increased susceptibility to bleeding when thrombocytopenia occurs.				
	Hospital pharmacist's advice: Change to another anticoagulant is advised (e.g. LMWH)				
disulfiram		inhibitor			
entacapone		inhibitor			
glibenclamide/glyburide		inhibitor			
hydralazine		inhibitor			
live viruse vaccines	miscellaneous[12]				
methadone		inhibitor			
mirabegron			inhibitor**		
modafinil		inducer			
orphenadrine		inhibitor			
oxybutynin		inhibitor			
pergolide		inhibitor			
pilocarpine		inhibitor			
ranolazine		inhibitor		inhibitor	
sildenafil		inhibitor			
ticlopidine		inhibitor			
zalfirlukast		inhibitor			
Caution with (not strictly prohibited, consider monitoring)					
digoxin	Doxorubicin can lower it's serum concentration				
uric acid lowering agents	Doxorubicin can increase serum uric acid concentration (such as sulfinpyrazone*** and probenecid ***)				
sorafenib	It might increase the doxorubicin dose				
dexrazoxane[13]	It might result in lower response rates to doxorubicin				

[12] Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving doxorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. Source: Pfizer 2010

[13] In a clinical study of women with metastatic breast cancer, the concurrent use of the cardioprotectant, dexrazoxane, with the initiation of a regimen of fluorouracil, doxorubicin, and cyclophosphamide (FAC) was associated with a lower tumor response rate. Source: Pfizer 2010.

* Mentioned as powerful inhibitor/inducer in the KNMP Kennisbank.
Note: Relevance of an interaction also depends on properties of the substrate, such as therapeutical width, biological availability or another route of metabolism.
https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/G1126.html
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https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/G1126.html
*** Prohibited medication in the Phase I trial at Duke (IND#74,188)

S3.2 Pre-specified exceptions (possible interactions accepted)

1. Cyclophosphamide

"The addition of cyclophosphamide to doxorubicin treatment does not affect exposure to doxorubicin, but may result in an increase in exposure to doxorubicinol, a metabolite. Doxorubicinol only has 5% of the cytotoxic activity of doxorubicin. Concurrent treatment with doxorubicin has been reported to exacerbate cyclophosphamide-induced hemorrhagic cystitis."(2) Concurrent cyclophosphamide treatment sensitizes the heart to the cardiotoxic effects of doxorubicin(17). However, since the AC regimen is frequently studied and used in daily practice, we anticipate a similar incidence of adverse events due to this interaction.

6. Glucocorticoids (dexamethasone)

Dexamethasone in the doses administered as premedication in this study induces CYP3A4 (7, 18), which could lower the doxorubicin concentration. However in the previous phase I and II dose finding studies (19), similar dosages of dexamethasone were administered (24 hours prior to treatment "dexamethasone 8 to 10 mg or an equivalent dose of a similar steroid consistent with local practice, every 12 hours x 3 doses" and 30 minutes prior to administration "IV Dexamethasone 20 mg"), therefore this interaction is accounted for in the maximum tolerable dose.

We will to administer dexamethasone in the premedication regimen as specified in the protocol, according to our local practice for the prevention of allergic reactions.

Additional dosages of glucocorticoids (above the specified dosages) are prohibited.

9. Propofol

A dosage-dependent inhibitory effect of propofol on cytochrome P450 3A4 has been described(20), indicating that a minimum clinical dosage could induce a significant inhibition of CYP 3A4 activity.

There is only one in vivo study were propofol decreased the clearance of midazolam, possibly via competitive inhibition of hepatic CYP3A4(21). Since no adverse events due to administration of propofol in combination with CYP3A4 substrates have been reported, we anticipate no severe interaction and administrate propofol as specified in the protocol.

10. Aprepitant

As described by Dushenkov et al. "coadministration of aprepitant with antineoplastics may result in SS pharmacokinetic alterations in serum levels of cytotoxics, with the best documentation for cyclophosphamide, ifosfamide and erlotinib. (…) To date, there are no data convincingly linking adverse outcomes due to coadministration of aprepitant and antineoplastics"(22).

Since the use of aprepitant as antiemetic in the dosages specified in the protocol is part of our hospital's standard practice for the AC chemotherapy regimen, and there is no convincing evidence against it, we will administer aprepitant as specified in the protocol. Additional dosages of aprepitant will be prohibited.

11. Clemastine

Clemastine may inhibit CYP3A4 activity and therefore alter doxorubicin metabolism. However clemastine is an essential part of the premedication regimen in our hospital for the prevention of allergic reactions. Since there are no reports in literature of clinically significant interactions with clemastine, and H1- antihistamine agents were also used in the dose finding study(19), we anticipate no severe interactions in our study and will administer clemastine as specified in the protocol.

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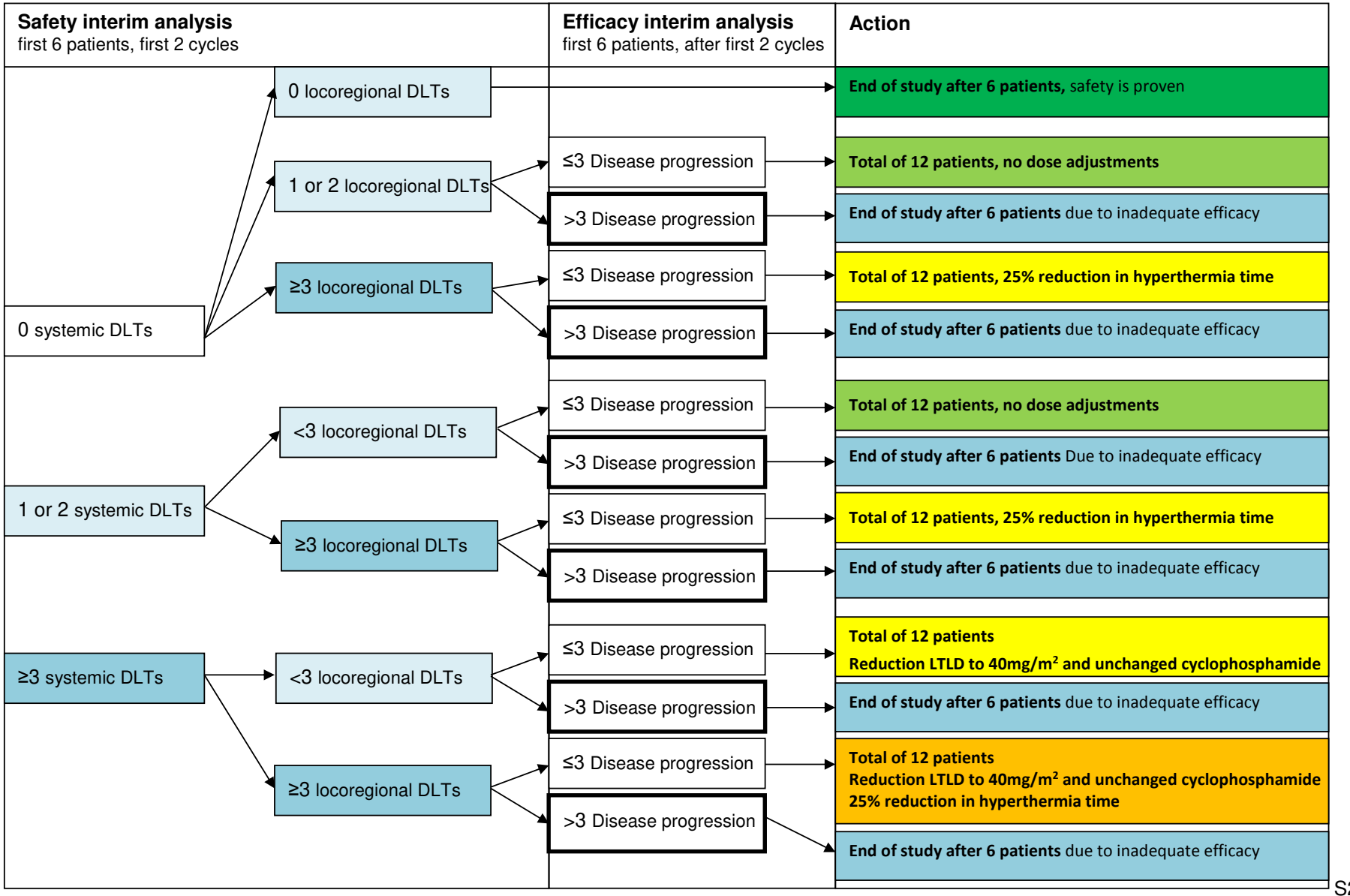
Supplement 4 Flow-chart interim analysis



Supplement 5 Data Safety Monitoring Board Charter

DMC (DSMB) charter for the i-GO study

Version 3, 14-01-2019

CONTENT	
1. INTRODUCTION	
Name (and sponsor's ID) of trial plus ISRCTN and/or EUDRACT number	• Trial name: Image-guided targeted doxorubicin delivery with hyperthermia to optimize loco-regional control in breast cancer; the i-GO feasibility study. Phase I Feasibility Study of High-Intensity Focused Ultrasound-Induced Hyperthermia (HIFU), Lyso-Thermosensitive Liposomal Doxorubicin (LTLD), and Cyclophosphamide for Metastatic Breast Cancer • Trial sponsor: Imaging division and Cancer Center, University Medical Center (UMC) UTRECHT • Type of trial: Investigational drug trial and investigational medical device trial • Number of patients to be included: 6-12 • Number of sites: single center (UMC Utrecht) • Estimated trial duration: 3 years • EUDRACT number: 2015-005582-23 • METC protocol number: NL67422.041.18 • ClinicalTrials.gov Identifier: to be determined • Principal investigator: B.B.M. Suelmann • Coordinating investigator: J. S. de Maar
Objectives of trial, including interventions being investigated	Primary objective: To determine safety, tolerability and feasibility of the administration of LTLD + HIFU inducing local hyperthermia, combined with cyclophosphamide in metastatic breast cancer patients. Secondary objective: Efficacy; to assess pathologic and clinically objective response from study treatment A flow chart of the trial design is included (Figure 1).
Outline of scope of charter	*The purpose of this document is to describe the roles and responsibilities of the independent DMC for the i-GO trial, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees.*
2. ROLES AND RESPONSIBILITIES	
A broad statement of the aims of the committee	*"To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial."*
Terms of reference	*The DMC should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Principal Investigator.* *The DMC should inform the Principal Investigator and Head of Department of Medical Oncology if, in their view:* *the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that the study treatment is clearly contraindicated or unsafe, and there was a reasonable expectation that this new evidence would materially influence patient management.*

Specific roles of DMC	Interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. A selection of specific aspects could be compiled from the following list: • assess data quality, including completeness (and by so doing encourage collection of high quality data) • monitor recruitment figures and losses to follow-up • monitor evidence for treatment harm (eg toxicity data, SAEs, deaths) • Monitor the interim safety and efficacy analysis as specified in the study protocol in section 10.4 • decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some participant subgroups • suggest additional data analyses • advise on protocol modifications suggested by investigators or sponsors (eg to inclusion criteria, trial endpoints, or sample size) • monitor compliance with previous DMC recommendations • considering the ethical implications of any recommendations made by the DMC • assess the impact and relevance of external evidence
3. BEFORE OR EARLY IN THE TRIAL	
Whether the DMC will have input into the protocol	All potential DMC members should have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins the trial will have undergone review a research ethics committee. Therefore, if a potential DMC member has major reservations about the trial (eg the protocol or the logistics) they should report these to the PI and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Whether the DMC will meet before the start of the trial	It is recommended that, if possible, the DMC meets before the trial starts or early in the course of the trial, to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators. The DMC should meet within one year of recruitment commencing.
Any issues specific to the disease under study	Issues specific to the disease under study: • The population consists of patients with metastatic breast cancer (stage IV disease), who have not received previous chemotherapy or surgery (previous antihormonal therapy is permitted) • It concerns a non-curable disease. Median survival is approximately 2 years, however there is a great heterogeneity in survival, ranging from a few months to many years, with 10-15 % of patients surviving ten years and more. • Most patients included in this trial will have the possibility to receive more treatment lines after this trial. • Goal of the treatment in this stage of disease is to maintain or improve the quality of life and to improve survival. • The natural course of the disease and the comorbidity are not always easy to distinguish from toxicity caused by the experimental treatment

Any specific regulatory issues	The DMC should be aware of any regulatory implications of their recommendations.
Any other issues specific to the treatment under study	• The investigational drug (ThermoDox) and the co-intervention cyclophosphamide are chemotherapeutics • As with the majority of chemotherapy regimens, toxicities can be expected including bone-marrow toxicity, nausea, fatigue, stomatitis, alopecia, constipation, and musculoskeletal chest pain. These adverse events are expected in standard treatment as well. • All chemotherapy agents are potentially teratogenic and mutagenic. • Specific regulations apply for the administration and handling of chemotherapy (UMC Utrecht protocols will be followed) • The study treatment consists of an investigational drug as well as an investigational device.
Whether members of the DMC will have a contract	• Membership of the DMC (in agreement with the contents of this charter) will be accepted by the individual members and confirmed in writing and after submission of a signed and dated curriculum vitae (CV). The signed CV will be kept in the study file at the clinical trial bureau Medical Oncology. • DMC members will sign a non-conflict of interest statement (Annex 1) in regard to this study which will be in the study file at the clinical trial bureau Medical Oncology.
4. COMPOSITION	
Membership and size of the DMC	The members will be independent of the trial (eg will not be involved with the trial in any other way or have some competing interest that could impact on the trial). Any competing interests, both real and potential, will be declared. The members of the DMC for this trial are: (1) *Hanneke van Laarhoven* *Medical oncologist at the Academic Medical Center (AMC) Amsterdam* *Clinician, experienced in the field of (medical) oncology and experienced in performing clinical trials* (2) *Harm van Tinteren* *Head of scientific administration/biometrics department at the Antoni van Leeuwenhoek (AVL) hospital. Biostatistical reviewer.* (3) *Geertjan van Tienhoven* *Radiation oncologist at the Academic Medical Center (AMC) Amsterdam* *Clinician, experienced in the field of (radiation) oncology and experienced in performing clinical trials*
The Chair, how they are chosen and the Chair's role. (Likewise, if relevant, the vice-Chairman)	Hanneke van Laarhoven will be the chair of the DMC. The Chair has previous experience of serving on DMCs and experience of chairing meetings, and is able to facilitate and summarize discussions. The Chair was chosen by the investigators.
The responsibilities of the DMC statistician	The DMC membership will include a statistician to provide independent statistical expertise.
The responsibilities of the trial statistician	The project team will not have a trial statistician, this is not considered necessary based on the trial design. *The coordinating investigator* will produce the report to the DMC.
The responsibilities of the PI	The PI, may be asked, and should be available, to attend open sessions of the DMC meeting.

5. RELATIONSHIPS	
Clarification of whether the DMC are advisory (make recommendations) or executive (make decisions)	The DMC makes recommendations to the investigators.
Payments to DMC members	Members will be reimbursed for travel expenses and for the costs of teleconferencing (if applicable).
The need for DMC members to disclose information about any competing interests	Competing interests should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. (See Annex 1) DMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
6. ORGANISATION OF DMC MEETINGS	
Expected frequency of DMC meetings	The DMC will meet approximately five times, during the trial. The exact frequency of meetings will depend upon trial events. The DMC will meet at least yearly.
Whether meetings will be face-to-face or by teleconference	The first meeting should ideally be face-to-face to facilitate full discussion and allow members to get to know each other. It is recommended that all subsequent meetings should be face-to-face if possible, with teleconference as a second option.
How DMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	The format of the meetings will be: 1. Open session: **Introductory meeting** Before start of the trial. 2. Closed session: **first data evaluation** Once the first three patients completed two treatment cycles (if necessary extra open session for clarification of specific concerns) 3. Closed session: **safety and efficacy interim analysis** Once the first six patients completed two treatment cycles. (if necessary extra open session for clarification of specific concerns) 4. (If applicable) Closed session: **further safety and efficacy analysis** Once the first twelve patients completed two treatment cycles. (if necessary extra open session for clarification of specific concerns) 5. Closed session: **follow up data evaluation**, **final evaluation** The closed session will be restricted to the DMC members. The minutes of the closed session will be recorded by one of the members of the DMC. Minutes from the closed session will be recorded separately from the minutes of the open session and stored securely by the Chair. Closed session minutes, finalized by signature of the Chair, will be maintained in confidence and retained until discarded in accordance with applicable statutory regulation. The open session will be attended by representatives of the study investigators (in general the coordinating investigator). Data presented in the open session may include enrolment data, individual AE data, baseline characteristics, overall data accuracy and compliance data or issues, and other administrative data. Minutes of the open session will be recorded by one of the members of the DMC. Minutes will be finalized upon signature of the Chair and maintained in the study file at the clinical trial bureau Medical Oncology in accordance with applicable statutory regulation.

7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION	
Intended content of material to be available in open sessions	*Open sessions: Accumulating information relating to recruitment and data quality (eg data return rates, treatment compliance) will be presented. Toxicity details based on pooled data will be presented and total numbers of events for the primary outcome measure (safety, tolerability and feasibility) and other outcome measures may be presented, at the discretion of the DMC.*
Intended content of material to be available in closed sessions	*The same material will be available in the closed and open sessions.*
Will the DMC be blinded to the treatment allocation	Not applicable.
Who will see the accumulating data and interim analysis	The DMC members perform the interim analysis (safety and efficacy), based on the data provided by the coordinating investigator, and report their recommendations to the principal investigator. DMC members do **not** have the right to share confidential information with anyone outside the DMC, including the PI.
Who will be responsible for identifying and circulating external evidence (eg from other trials/ systematic reviews)	Identification and circulation of external evidence (eg from other trials/ systematic reviews) is not the responsibility of the DMC members. The PI or the trials office team will collate any such information.
To whom the DMC will communicate the decisions/ recommendations that are reached	The DMC will report its recommendations in writing to the PI.
Whether reports to the DMC be available before the meeting or only at/during the meeting	The DMC will receive the report from the coordinating investigator at least 2 weeks before any meetings.
What will happen to the confidential papers after the meeting	*The DMC members should destroy their reports after each meetings. Fresh copies of previous reports will be circulated with the newest report before each meeting.*
8. DECISION MAKING	
What decisions/recommendations will be open to the DMC	Possible recommendations could include: • No action needed, trial continues as planned • Early stopping due, for example, to clear harm of a treatment, futility, or external evidence • Stopping recruitment within a subgroup • Extending recruitment or extending follow-up • Sanctioning and/or proposing protocol changes
The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules	The planned statistical analyses are described in chapter 10 of the study protocol. Specifically, an interim safety evaluation and an interim efficacy evaluation will be performed (section 10.4 of the study protocol) : In summary, at the interim evaluations:

	The trial will continue to accrue until a total of 12 subjects have been treated if both the following occur: • a maximum of three of the first six subjects show disease progression after cycle 2; **AND:** • either one or two systemic DLTs (dose limiting toxicities) were seen among the first two cycles of the first six subjects **OR** •(if no systemic DLTs were seen) any locoregional DLT was seen among the first two cycles of the first six subjects Specific criteria for dose adjustments for the entire study population are also specified in section 10.4 of the study protocol.
How decisions or recommendations will be reached within the DMC	Every effort should be made for the DMC to reach an unanimous decision. However, if this is not possible, the majority vote will decide. It is important that the implications (eg ethical, statisticial, practical, financial) for the trial be considered before any recommendation is made. The Chair will summarise discussions and encourage consensus; it may be best for the Chair to give their own opinion last.
When the DMC is quorate for decision-making	*Effort should be made for all members to attend. The coordinating investigator will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if at least one statistician and one clinician, including the Chair will be present. If the DMC is considering recommending major action after such a meeting the DMC Chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMC.*
Can DMC members who cannot attend the meeting input	If the report is circulated before the meeting, DMC members who will not be able to attend the meeting may pass comments to the DMC Chair for consideration during the discussions.
What happens to members who do not attend meetings	*If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DMC. If a member does not attend a third meeting, they should be replaced.*
Whether different weight will be given to different endpoints (eg safety/efficacy)	Safety and efficacy interim analyses are equally important and both determine whether the trial will be continued, as specified in section 10.4 of the study protocol.
Any specific issues relating to the trial design that might influence the proceedings, eg cluster trials, equivalence trials, multi-arm trials	The safety interim analysis and efficacy interim analysis will both be performed once the first six patients completed two treatment cycles. It is possible (and expected) that when the sixth patient completes her second treatment cycle, the first patient will already have completed all treatment cycles.

9. REPORTING	
To whom will the DMC report their recommendations/decisions, and in what form	The DMC will report their recommendations/decisions in the form of a letter to the PI and coordinating investigator, within 2 weeks. A copy of the letter will be kept in the study file at the Clinical trial bureau Medical Oncology.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	As described in chapter 6 of this charter minutes of the meetings will be taken by one of the DMC members and will be kept at the clinical trial bureau.
What will be done if there is disagreement between the DMC and the body to which it reports	*"If the DMC has serious problems or concerns with the PI's decision a meeting should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting should be chaired by a senior member of the trials office staff or an external expert who is not directly involved with the trial."*
10. AFTER THE TRIAL	
Publication of results	At the end of the trial there may be a meeting to allow the DMC to discuss the final data with principal trial investigators and give advice about data interpretation. The trial results will be published in a correct and timely manner.
The information about the DMC that will be included in published trial reports	DMC members should be named and their affiliations listed in the main report. A brief summary of the timings and conclusions of DMC meetings should be included in the body of this paper.
Any constraints on DMC members divulging information about their deliberations after the trial has been published	The DMC may discuss issues from their involvement in the trial when permission is agreed with the PI.

I hereby declare that I have read the charter and that I agree with its contents.

Name: _____

Signed: _____ **Date:** _____

UMC Utrecht

Supplement 6.1 Patient informed consent form in English

The i-GO study: treatment of breast cancer using chemotherapy encapsulated in temperature sensitive nanoparticles, in combination with local warming of the tumour.

- I have read the information letter. I was able to ask questions. My questions have been sufficiently answered. I had sufficient time to decide whether or not I will participate.
- I know that participation is voluntary. I also know that at any moment, I can decide not to participate after all or to quit the study. I don't have to provide a reason for that.
- I give consent to inform my general practitioner, treating medical specialist(s) and pharmacy that I participate in this study.
- I give consent to request information (medical data, laboratory results and previously made scans) from my general practitioner and treating medical specialist(s) from other hospitals.
- I give consent to notify my general practitioner and/or treating medical specialist(s) about unexpected findings that are or could be of importance to my health.
- I know that I cannot become pregnant during the study.
- I consent to collect and use my data and blood samples in the way and for the causes that are described in the information letter.
- I know that, in order to monitor the study, certain persons will have access to all my data. These persons are stated in the information letter. I give consent for access by these persons.
- I give consent to keep my data at the UMC Utrecht for 15 years after this study.
- I □ **do**
  □ **do not**
  give consent to use my personal data for future research on the topic of breast cancer, during the 15 year that the data have to be kept.
- I □ **do**
  □ **do not**
  give consent to approach me after this study for a follow-up study or other research on the topic of breast cancer.
- I know that, in case I have side effects of the treatment, coded data on the side effects will be provided to Profound Medical and Celsion. These data cannot be traced back to me personally.
- I □ **do**
  □ **do not**
  give consent to provide coded data (other than side effects) to Profound Medical and Celsion. These data cannot be traced back to me personally.

- I want to participate in this study.

Name study subject:

Signature: Date : __ / __ / __

UMC Utrecht

I declare that I have fully informed this subject on the mentioned study.
If, during the duration of the study, information will become available that could affect the subject's consent, then I will timely inform her about that.

Name investigator (or representative):

Signature: Date: __ / __ / __

UMC Utrecht

Supplement 6.2 Patient informed consent form for Biobank research in English

Biobank research of the i-GO study

(This is a separate part of the i-GO study, for which you can give consent separately)

- I □ **do**
  □ **do not** give consent to draw **extra blood** which will be coded and kept indefinitely in the Central Biobank of the UMC Utrecht, for future research on the topic of breast cancer.
- I □ **do**
  □ **do not**
  give consent to use my body material that has been obtained during breast biopsies, breast surgery or biopsies of metastases (to confirm my diagnosis or after the end of this study), to use this body material for further research and to keep it, as is explained in the patient information letter.
- I □ **do**
  □ **do not**
  give consent to keep my data at the UMC Utrecht for longer than 15 years and to use it for future research on the topic of breast cancer.
- I know that I can withdraw my consent to the Biobank research at any moment. I don't have to provide a reason for that.

Name study subject:

Signature: Date : __ / __ / __

I declare that I have fully informed this subject on the mentioned study.
If, during the duration of the study, information will become available that could affect the subject's consent, then I will timely inform her about that.

Name investigator (or representative):

Signature: Date: __ / __ / __