



Development of sample and data access committees and procedures for all users:

Explanatory note:

After many discussions within the consortium, the ethical committee (EC) and legal department of UZ/KU Leuven, it was decided to work through a central procedure being one central EC (UZ/KU Leuven) and one central legal department (UZ/KU Leuven) in order to facilitate and accelerate the implementation of samples and data collection from ILC patients within the consortium. In addition to the set-up of a prospective metastatic samples and data collection, a retrospective collection of primary ILC data was also developed in parallel.

Multi-centric retrospective data collection:

The protocol aiming to collect multi-centric retrospective primary ILC pathological and clinical data has been written and was approved by the central EC of UZ/KU Leuven on the 17/08/2020 (S64063). Waiver has been asked and was granted for informed consent. The legal department of UZ/KU Leuven has drafted data transfer agreement (DTA) which has been sent to the different participating centers of the consortium which are (in addition to UZ/KU Leuven) 1) GZA Hospital Saint-Augustinus, Antwerp, Belgium; 2) Institut Jules Bordet, Brussels, Belgium; 3) Institut Curie, Paris, France; 4) Charité Universitätsmedizin, Berlin, Germany 5) Guy's center, London, UK. DTA has been discussed, approved and signed by all the members except for Guy's center who recently joined the initiative and for who the procedure is ongoing. Importantly, participating centers from Lobsterpot who want to join later can always do so. Locally diagnosed primary ILC pathological and clinical data have been centrally collected by UZ/KU Leuven for 2856 female patients diagnosed between January 2000 and December 2020 with non-metastatic pure (i.e. not mixed with other histological types) ILC. Data have been centrally analyzed by UZ/ KU Leuven and were presented at the San Antonio Breast Cancer Symposium (SABCS) end of last year (2022). A first manuscript was drafted and is currently being reviewed by the members of the consortium. In addition, new members have showed interest in joining this initiative (Luxemburg and Italy) and discussions are being conducted in order to define the collaboration. Finally, after discussion within the consortium, it was decided to use this large data set to set-up new sub studies being: The evaluation of the distribution of HER2-



low breast cancer in ILC; To evaluate and compare the prognostic performance of prediction tools like PREDICT and Adjuvatorium; To investigate large structural variation in the genome of ILC patients with a special focus on pleiomorphic ILC cases. For this last sub-study, a new collaboration has been set-up with the University of Pittsburgh Medical Center (UPMC) located in US which includes, on the top of pathological and clinical data, a retrospective collection of primary frozen tissue blocks collected at surgery for some ILC patients in order to apply some genomics assays. Protocol (S64063) has been amended to reflect the new sub-studies and was approved by the central EC of UZ/KU Leuven on the 02/12/2022. A material transfer agreement (MTA) has been drafted by UZ/KU Leuven, shared with UPMC and signed recently. All these new-sub studies are currently ongoing.

Multi-centric prospective data and samples collection:

Enhancing access to samples in late-stage ILC is crucial to advance research and ultimately patient care. One way of doing so is through research autopsies, a procedure in which samples are collected after death for the purpose of translational research. Advantages of this approach are the possibility of sampling to completion, multiregional sampling (to reflect spatial heterogeneity within each lesion), and high-volume sampling to allow different techniques to be performed. UZ/KU Leuven has developed in the last 2 years, an institutional post-mortem tissue donation program which is called UPTIDER (S64410), and which was ethically approved on the 30/11/2020. A general paper on UPTIDER summarizing general set-up, sample and data collection and logistical details is being drafted. Currently, 9 ILC patients have signed the informed consent form of UPTIDER and 8 autopsies have been performed. A total of 1925 body fluids samples and 1825 tissue samples were collected up to now. In addition to UZ/KU Leuven, UPMC has also recently joined this initiative. They have set-up a similar tissue donation program (including similar data and samples collection) in which 3 ILC patients were included and were autopsied so far (regulatory matters are being dealt at UPMC). An MTA has been drafted by UZ/KU Leuven and signed by UPMC in order to exchange material and data for ILC patients between the 2 programs. Currently some experiments (including pathological and genomics-based assays) are ongoing on the entire UZ-KU Leuven ILC cohort. Material is about to be exchanged between UZ/KU Leuven and UPMC.

Multi-centric retrospective data collection:

As mentioned above, UZ/KU Leuven is acting as the central coordinator and has dealt with ethically and legal requirements. In order to exchange patient's data, DTA has been



drafted and a common Excel based database (DB) has been designed (Table 1). Transfer of data has been done through secure e-mails exchange. The common DB includes patient specific factors, primary tumor pre-treatment, neoadjuvant therapy, surgery, pathology resection specimen, adjuvant therapy, local recurrence, metastatic disease, first line treatment metastases, second line treatment metastases, all lines of treatment ever administered for metastatic disease, death and follow-up data. The DB was also including detailed explanation on the meta data to be collected and was including some rules and validation steps. Users have been provided with guidelines, were asked not to deviate from the DB and its content and have been given some timelines. In addition, if users want to get access to this DB for future research, a new collaboration is being set-up (see above for examples), protocol is being amended and new DTA (or MTA if needed) are being drafted. There is no general guidelines for retrospective samples collection (when needed) due to the “retrospective” nature per se. The data access committees (DAC) is being defined as the members of the consortium participating to the collection of retrospective data (and samples). They discuss general goals and new sub-studies on ad-hoc meetings. Ad-hoc meetings being held with the specific users.

Multi-centric prospective data and samples collection

Now, UZ/KU Leuven and UPMC are working together on this specific task. They have dealt with regulatory matters, and they have developed similar procedures to collect data and samples. MTA has been drafted in order to exchange samples and data. The specific procedures at UZ/KU Leuven are the following. For capturing relevant patient and tumour characteristics, an electronic case report form (eCRF) was designed in REDCap®. Data collected at UPTIDER inclusion encompasses medical and familial history, cancer characteristics at diagnosis, location and timing of the metastases, anticancer treatments and their responses on a patient-level as well as on an individual lesion-level, histopathological characteristics of the primary and -where available- of the metastases, relevant laboratory results (tumour markers, sequencing results), and imaging reports. Dynamic structured query language (SQL) was implemented to allow for the registration of treatment responses on an individual lesion-level given the important heterogeneity described above. For the registration and management of patient samples a LabCollector®-based lab management system was set up. Samples that are planned to be collected during the autopsy based on latest imaging and on research interests for each patient, are first registered on a coded sheet (“tissue donation plan”). The donation plan includes expected sample type, sample location using ICD-O-3 codes, and sample



processing strategy. Standardly included samples are liquid biopsies from all body fluids and healthy samples of the brain, breast, lung, heart, liver, kidney, and adipose tissue. For all patients known tumor lesions are added to the donation plan, along with adjacent normal tissue samples, where possible. Previously locally treated lesions are also registered, including irradiated breast/thoracic wall tissue and tissue from irradiated metastatic sites. Within this tissue donation plan, for each sampling site different processing methods are encoded. Standard processing for tissue samples results in three mirrored samples: one formalin-fixed paraffin-embedded (FFPE), one fresh frozen (FF) and one fresh frozen in optimal cutting temperature compound (FF_OCT). Depending on the size of the lesion and scientific interest, additional fresh samples (FRESH) to develop in vivo and ex vivo models (WG5), samples frozen in carboxymethylcellulose (FF_CMC) and samples frozen slowly in freezing medium (FF_DMSO) are encoded. For very large lesions multiregional sampling can be planned. This donation plan is then imported into our lab management system, resulting in preregistration of the samples, while the addition of samples is still possible during the autopsy. All get a unique QR code and a sample specific ID allowing a robust tracking. In addition, upon signature of the ICF, inclusion sampling of easy-access liquid biopsies (blood, urine, saliva) is performed. In case the patient undergoes diagnostic or therapeutic sampling of other body fluids after inclusion (such as ascites, pleural fluid, cerebrospinal fluid), wherever possible the fluids are collected. Premortem archived tissue samples, if available, are requested from the pathology biobank of the hospital where they are stored. Historical DNA extracted from tissue or plasma, if available, is requested from the department of human genetics of UZ Leuven. Historical blood samples (plasma/extracted genomic DNA) collected prospectively for translational research by the Multidisciplinary Breast Centre of UZ Leuven (S63773), are also requested. All these samples are registered in the LabCollector® and will, where possible, undergo the same downstream analyses as the samples collected at autopsy and allow for longitudinal evaluation of disease features. For guidelines about prospective collection of body fluids and tissue samples at UZ/KU Leuven, please see deliverable 3.2.

At both institutions, data (either clinical or related to samples) can be downloaded from the different web-based management systems into Excel based files which can be exchanged via secure e-mails. Access to sample and data to future users will be done through protocol amendment, MTA or DTA set-up.



Table 1: retrospective meta data collection



Entry field	Explanation	Type of entry
Patient specific factors		
patient_id	pseudonymized ID	open field
participating_site	site of inclusion	drop down list
date_of_diagnosis	date in dd/mm/yyyy of first malignant biopsy if unknown date of first contact regarding invasive lobular cancer	open field
date_of_birth	date in dd/mm/yyyy of birth	open field
age_at_diagnosis (y)	age of patient in years at the time of primary diagnosis	open field
age_category	category of age at the time of primary diagnosis	drop down list
gender	M= male, F= female	drop down list
height (m)	in meters, at time of diagnosis primary	open field
weight (kg)	in kg, at time of diagnosis primary	open field
BMI	calculated, at diagnosis primary (weight (kg)/height (m) ²)	calculated automatically
BMI category	category of calculated BMI	drop down list
body_surface_area	calculated at diagnosis primary (0.20247 x height (m) ^{0.725} x weight (kg) ^{0.435})	calculated automatically
smoking	is the patient a present smoker, past smoker or did he/she never smoke	drop down list
alcohol_abuse	is there a history of alcohol abuse reported	drop down list
hypertension	is there a personal history of arterial hypertension, if present is it well treated	drop down list
hyperlipidemia	is there a personal history of hyperlipidemia, if present is it well treated	drop down list
diabetes	is there a personal history of diabetes + type, if present is it well treated	drop down list
comorbidities	are there any known comorbidities other than hypertension, hyperlipidemia and diabetes: auto-immune diseases, other cancer types, cardiac disease... Please list all known comorbidities	open field
age_menarche (y)	age of first menstruation, if unknown	open field
oral_anticonceptive_use	has the patient ever used oral contraceptives?	drop down list
oral_anticonceptive_duration (y)	how many years has the patient taken OAC, if applicable and if known	open field
age_first_pregnancy (y)	age at first child birth, if applicable	open field
pregnancy_A	number of abortions, if applicable	open field
pregnancy_B	number of patius/child births, if applicable	open field
pregnancy_G	number of gravidus/pregnancies, if applicable	open field
menopausal_status	pre or post-menopausal at timing of diagnosis, if in transition, to be considered as premenopausal	drop down list
age_menopause (y)	age of patient when menopause occurred, if premenopausal insert NA, if not known in case of postmenopausal insert unknown	drop down list
hormone_replacement	has the patient ever used hormone replacement therapy in case of postmenopausal	drop down list
familial_history_breast_ovary	is there a history of breast or ovarian cancer in the family?	drop down list
familial_history_breast_ovary_line	are the affected relatives first or second degree relatives? If no history, select NA	drop down list
germline_mutation_status	is the patient known with a germline mutation in one of the genes from the list? Select unknown in case not known and negative in case a test was done but no mutation was found. In case of a mutation that is not in the list, please provide it in the following field.	drop down list
germline_mutation_status_other	provide the mutation that was not in the drop down list, if applicable	open field
primary_date_of_histological_diagnosis	date in dd/mm/yyyy	open field
primary_laterality	left or right or bilateral	drop down list
TNM_T_at_diagnosis	clinical T classification according to TNM classification of malignant tumors	drop down list
TNM_CN_at_diagnosis	clinical N classification according to TNM classification of malignant tumors	drop down list
TNM_CM_at_diagnosis	clinical M classification according to TNM classification of malignant tumors	drop down list
diameter_radiology_at_diagnosis (mm)	of largest focus, in mm	open field
breast_density_score_mammogram	breast type on mammogram using the birads classification 4th edition published in 2003: type A < 25% glandular, type B approximately 25-50% glandular, type C approximately 51-75% glandular, type D >75% glandular, or NA if not available	drop down list
tumor_grade_biopsy	histological grade (biopsy) reported on biopsy, if multifocal, then dominant focus is considered	drop down list
ER_Allred_biopsy	ER-status performed on biopsy if performed using modified Allred score, if multifocal, then dominant focus is considered	drop down list
ER_H_score_biopsy	ER-status performed on biopsy if performed using H-score (0-300), if multifocal, then dominant focus is considered	open field
PR_Allred_biopsy	PR-status performed on biopsy if performed using modified Allred score, if multifocal, then dominant focus is considered	drop down list
PR_H_score_biopsy	PR-status performed on biopsy if performed using H-score (0-300), if multifocal, then dominant focus is considered	open field
HER2_IHC_score_biopsy	HER2-immunohistochemical status, if performed on biopsy, if multifocal, then dominant focus is considered	drop down list
HER2_FISH_biopsy	HER2-FISH status on biopsy, if applicable	drop down list
HER2_ratio_biopsy	HER2-FISH ratio on biopsy, if applicable	open field
Ki67_biopsy (%)	value of Ki67 of biopsy if available in pathology report	open field
number_of_suspected_foci	how many foci are suspected on core, or MRI not available on mammogram or ultrasound	open field
neo_adjuvant_therapy	did the patient receive any kind of therapy (endocrine, immunotherapy, chemotherapy) prior to surgery	drop down list
neo_adjuvant_therapy_start_date	date in dd/mm/yyyy of the first day of the first cycle of neoadjuvant therapy	open field
neo_adjuvant_chemotherapy_scheme	scheme of chemotherapy, drop down list	drop down list
neo_adjuvant_chemotherapy_BSA_used	was the dose calculated according to BSA of the patient? Yes or no	drop down list
neo_adjuvant_chemotherapy_BSA_capping	if BSA was used, was the dose capped at 2m ² ? Yes or no	drop down list
neo_adjuvant_chemotherapy_completion	was the chemotherapy completed, defined as completion of 85% of the proposed dose	drop down list
neo_adjuvant_HER2_therapy_scheme	scheme of HER2-therapy, drop down list	drop down list
neo_adjuvant_endocrine_therapy_scheme	scheme of endocrine therapy, drop down list	drop down list
neo_adjuvant_endocrine_therapy_duration (m)	how many months was the endocrine therapy given prior to surgery	open field
neo_adjuvant_other	open field if patient received any other type of therapy (e.g. window of opportunity trial)	open field
neo_adjuvant_therapy_end_date	date in dd/mm/yyyy of the last day of neoadjuvant therapy	open field
Surgery		
surgery_date	date in dd/mm/yyyy of the surgery (first surgery)	open field
surgery_type_breast	mastectomy vs lumpectomy (= breast conserving surgery)	drop down list
surgery_type_axilla	sentinel (SN) vs axillary clearance (ALN) or SN followed by ALN in same or subsequent surgery	drop down list
TNM_TT_resection_specimen	T-classification according to TNM classification of malignant tumors	drop down list
TNM_CN_resection_specimen	N-classification according to TNM classification of malignant tumors	drop down list
diameter_pathology_resection_specimen (mm)	of largest focus, in mm	open field
residual_tumorbed (mm)	in case of neoadjuvant therapy, zone of original tumor defined by signs of therapy response if explicitly mentioned in mm	open field
number_of_foci_resection_specimen	number of invasive foci	open field
lobular_subtype	histological subtype if specified in pathology report of resection specimen or biopsy	drop down list
tumor_grade_resection_specimen	histological grade (bloom-score) reported on resection specimen, if multifocal, then dominant focus is considered	drop down list
resection_margin_resection_specimen	was the tumor completely resected?	drop down list
ER_Allred_resection_specimen	ER-status performed on resection specimen if performed using modified Allred score, if multifocal, then dominant focus is considered, if not repeated on resection state, please repeat score of biopsy	drop down list
ER_H_score_resection_specimen	ER-status performed on resection specimen if performed using H-score (0-300), if multifocal, then dominant focus is considered, if not repeated on resection state, please repeat score of biopsy	open field
PR_Allred_resection_specimen	PR-status performed on resection specimen if performed using modified Allred score, if multifocal, then dominant focus is considered, if not repeated on resection state, please repeat score of biopsy	drop down list
PR_H_score_resection_specimen	PR-status performed on resection specimen if performed using H-score (0-300), if multifocal, then dominant focus is considered, if not repeated on resection state, please repeat score of biopsy	open field
HER2_IHC_score_resection_specimen	HER2-immunohistochemical status, if performed on resection specimen, if multifocal, then dominant focus is considered, if not repeated on resection state, please repeat score of biopsy	drop down list
HER2_FISH_resection_specimen	HER2-FISH status on resection specimen, if applicable, if not repeated on resection state, please repeat score of biopsy	drop down list
HER2_ratio_resection_specimen	HER2-FISH ratio on resection specimen, if applicable, if not repeated on resection state, please repeat score of biopsy	open field
Ki67_resection_specimen (%)	value of Ki67 if available in pathology report	open field
E-cadherin	is the tumor positive or negative for E-cadherin, results of biopsy if not available on resection specimen	drop down list
Antibody_E_cadherin	which antibody was used in the form of E-cadherin (if not available in report), please ask pathology department which antibody was used in the period 2000-2012 and fill out for all results	open field
B-catenin	is the tumor positive or negative for B-catenin, results of biopsy if not available on resection specimen	drop down list
p120_catenin	is the tumor positive or negative for p120 catenin, results of biopsy if not available on resection specimen	drop down list
lymphatic_invasion_resection_specimen	was there lymphatic invasion in the resection specimen	drop down list
presence_DCIS_resection_specimen	is DCIS present in the resection specimen	drop down list
presence_LCIS_resection_specimen	is LCIS present in the resection specimen	drop down list
total_ALN_removed	total amount of lymph nodes prelevated (sentinel included)	open field
positive_ALN	total amount of positive lymph nodes (sentinel included)	open field
ALN_maxdiameter (mm)	maximal diameter in mm of metastasis to lymph node if applicable	open field
Adjuvant therapy		
radiotherapy	radiotherapy performed at site of surgery?	drop down list
GEP_type	was there a gene expression profiling (GEP) performed for this patient, which type?	drop down list
GEP_outcome	in case of GEP, was the patient genomic low, intermediate or high risk, if not performed NA	drop down list
adjuvant_chemotherapy	was chemotherapy given in adjuvant setting	drop down list
adjuvant_chemotherapy_scheme	scheme of first line chemotherapy, if list not applicable, please fill in the agent in 'adjuvant_other'	drop down list
adjuvant_HER2	was HER2-therapy given in adjuvant setting	drop down list
adjuvant_HER2_scheme	scheme of first line HER2-therapy, if list not applicable, please fill in the agent in 'adjuvant_other'	drop down list
adjuvant_endocrine_therapy	did the patient get post-surgery endocrine therapy?	drop down list
adjuvant_endocrine_therapy_scheme1	if the patient got endocrine therapy, which first line agent/scheme did the patient get? if list not applicable, please fill in the agent in 'adjuvant_other'	drop down list
adjuvant_endocrine_therapy_scheme1_duration (m)	number of months scheme1 of endocrine therapy was taken	open field
adjuvant_endocrine_therapy_scheme2	if the patient got endocrine therapy, which second line agent/scheme did the patient get (in case of switch of therapy)? if list not applicable, please fill in the agent in 'adjuvant_other'	drop down list
adjuvant_endocrine_therapy_scheme2_duration (m)	number of months scheme2 of endocrine therapy was taken	open field
adjuvant_other	agents that were not listed in chemo, endocrine or her2 fields	open field
Local recurrence		
locoregional_recurrence	did patient present with locoregional recurrence (i.e. ipsilateral breast and/or axilla)? yes or no	drop down list
date_locoregional_recurrence	dd/mm/yyyy if applicable	open field
recurrence_contralateral_breast	did patient present with contralateral recurrence (i.e. contralateral breast and/or axilla)? yes or no	drop down list
date_recurrence_contralateral_breast	dd/mm/yyyy if applicable	open field
Metastatic disease		
recurrence_metastatic_breast	occurrence of metastasis after surgery for primary (cM0 at diagnosis), Yes or no?	drop down list
date_recurrence_metastatic_breast	dd/mm/yyyy if applicable	open field
meta_brain_first_metastases	occurrence of brain metastases at first diagnosis of metastatic setting	drop down list
meta_bones_first_metastases	occurrence of bone metastases at first diagnosis of metastatic setting	drop down list
meta_skin_first_metastases	occurrence of skin metastases at first diagnosis of metastatic setting	drop down list
meta_lungs_first_metastases	occurrence of lung metastases at first diagnosis of metastatic setting	drop down list
meta_liver_first_metastases	occurrence of liver metastases at first diagnosis of metastatic setting	drop down list
meta_abdomen_extrahepatic_first_metastases	occurrence of abdominal (extrahepatic) metastases at first diagnosis of metastatic setting	drop down list
meta_reproductiveorgans_first_metastases	occurrence of metastases in reproductive organs at first diagnosis of metastatic setting	drop down list
meta_lymph_nodes_first_metastases	occurrence of lymph node metastases at first diagnosis of metastatic setting	drop down list
meta_other_first_metastases	occurrence of other metastases at first diagnosis of metastatic setting, please state which site	open field
First line treatment metastases		
surgery_1st_line_metastatic	first line resection surgery of metastatic locations? Yes or no	drop down list
radiotherapy_1st_line_metastatic	first line radiotherapy on metastatic locations? Yes or no	drop down list
chemotherapy_1st_line_metastatic	first line chemotherapy scheme in case chemotherapy was administered	drop down list
HER2_1st_line_metastatic	first line HER2-therapy in case HER2-therapy was administered	drop down list
endocrine_therapy_1st_line_metastatic	first line endocrine therapy in case endocrine therapy was administered	drop down list
treatment_1st_line_other_metastatic	open field if patient received any other type of therapy (e.g. in clinical trials)	open field
treatment_reduction_1st_line_metastatic	was there a reduction of dosage or cycles of the treatment due to adverse events?	drop down list
clinical_response_1st_line_metastatic	clinical response to therapy (complete remission CR, partial remission PR, stable disease SD, progressive disease PD or not applicable NA)	drop down list
first_progression_distant_disease_metastatic	progression of metastasis, Yes or no?	drop down list
date_first_progression_metastatic	dd/mm/yyyy if applicable	open field
radiotherapy_2nd_line_metastatic	second line radiotherapy on metastatic locations? Yes or no	drop down list
chemotherapy_2nd_line_metastatic	second line chemotherapy scheme in case chemotherapy was administered	drop down list
HER2_2nd_line_metastatic	second line HER2-therapy in case HER2-therapy was administered	drop down list
endocrine_therapy_2nd_line_metastatic	second line endocrine therapy in case endocrine therapy was administered	drop down list
treatment_2nd_line_other_metastatic	open field if patient received any other type of therapy (e.g. in clinical trials)	open field
treatment_reduction_2nd_line_metastatic	was there a reduction of dosage or cycles of the treatment due to adverse events?	drop down list
clinical_response_2nd_line_metastatic	clinical response to therapy (complete remission CR, partial remission PR, stable disease SD, progressive disease PD or not applicable NA)	drop down list
date_second_progression_distant_disease_metastatic	progression of metastasis, Yes or no?	drop down list
date_second_progression_metastatic	dd/mm/yyyy if applicable	open field
All lines of treatment ever administered for metastatic disease		
number_of_lines_metastatic	number of total lines given to patient in metastatic setting	open field
radiotherapy_all_metastatic	was radiotherapy ever performed during treatment in metastatic setting	drop down list
chemotherapy_number_lines_all_metastatic	how many lines of chemotherapy did the patient receive in metastatic setting	open field
HER2_number_lines_all_metastatic	how many lines of HER2-therapy did the patient receive in metastatic setting	open field
endocrine_therapy_number_lines_all_metastatic	how many lines of endocrine therapy did the patient receive in metastatic setting	open field
treatment_other_all_metastatic	which other types of treatment not belonging to the above mentioned categories did the patient receive in metastatic setting	open field
Death		
death	is the patient deceased? Yes or no	drop down list
date_of_death	date in dd/mm/yyyy of death if applicable otherwise NA	open field
cause_of_death	is the death related to breast cancer or not?	drop down list
Follow-up		
date_last_FU	date in dd/mm/yyyy of last follow up (in own center, with other physician or in other center with clear communication to your center)	open field
Comments	any relevant information that was not filled out in the other fields or that specifies answers of other fields	open field