Omission of surgery and sentinel lymph node dissection in clinically low-risk HER2positive breast cancer with high HER2 addiction and a complete response following standard anti- HER2-based neoadjuvant therapy (ELPIS trial)

STATISTICAL ANALYSIS REPORT

Protocol code:	HCB-ONC001 ELPIS (ML41519)
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Study Principal Investigators:	Aleix Prat and Tomás Pascual

CLÍNIC BARCELONA Hospital Universitari

IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

FUNDACIÓ CLÍNIC BARCELONA

This statistical analysis report has been prepared, reviewed and approved by:

Report generated by:	Samyukta Chillara
	Data Analyst
	SOLTI
Date	24/02/2024
Reviewed and approved by:	Guillermo Villacampa
	Data Science Manager
	SOLTI
Date:	27/02/2025

Guillermo Villacampa
Firmado digitalmente por Guillermo Villacampa
Fecha: 2025.02.27 14:55:06 +01'00'

Reviewed and approved by:	Tomas Pascual
	Study Principal Investigator
	SOLTI
Date:	27/02/2025

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1. Introduction

1.1 Scope of the report

Content:

This report contains the analysis of the ELPIS trial: Omission of surgery and sentinel lymph node dissection in clinically low-risk HER2positive breast cancer with high HER2 addiction and a complete response following standard anti- HER2-based neoadjuvant therapy.

Author:
The data science unit of SOLTI performed these analyses and prepared this report.

Purpose:
The purpose of this report is to provide the statistical analysis, results, tables and listings of the study.

Data status:
The data base used for the analysis was closed on 07/01/2025.

This analysis report is based on the version 2.0 of the ELPIS trial protocol.

1.2 Trial Summary

Study title	Omission of surgery and sentinel lymph node dissection in clinically low-risk HER2-positive breast cancer with high HER2 addiction and a complete response following standard anti-HER2-based neoadjuvant therapy - ELPIS
Trial Phase	*II*
Clinical Indication	HER2-positive HER2-enriched and ERBB2-high early breast cancer
Trial Type	Single arm
Type of control	-
Route of administration	Intravenous and subcutaneous
Trial Blinding	No
Treatment Groups	-Tumor size ≤ 2 cm: Paclitaxel/trastuzumab/pertuzumab (TDM-1 if residual disease) -Tumor size > 2 cm and ≤ 4cm: Antracycline based chemotherapy followed by Paclitaxel/trastuzumab/pertuzumab (TDM-1 if residual

	disease)

Trial Design

This is a prospective, single arm, open-label, unicenter, exploratory study in women with primary operable HER2-positive, HER2-enriched(HER2-E)/ERBB2-high breast cancer according to PAM50 intrinsic subtype and a ERBB2 pre-defined cutoff (high vs low ERBB2 expression), to evaluate the omission of surgery and sentinel lymph node dissection in patients with HER2-E and ERBB2 high breast cancer who achieving a complete response following standard anti-HER2-based neoadjuvant therapy with paclitaxel/trastuzumab/pertuzumab (and anthracycline based chemotherapy in case of tumor size >2cm and ≤ 4 cm).

The primary trial objective is to estimate the loco-regional invasive disease-free survival (LR- IDFS) at 3-year of patients who achieve a complete response based on imaging (i.e. Magnetic resonance imaging [MRI]) and a stereotactic-guided vacuum-assisted breast biopsy (VAB), and omit loco-regional surgery.

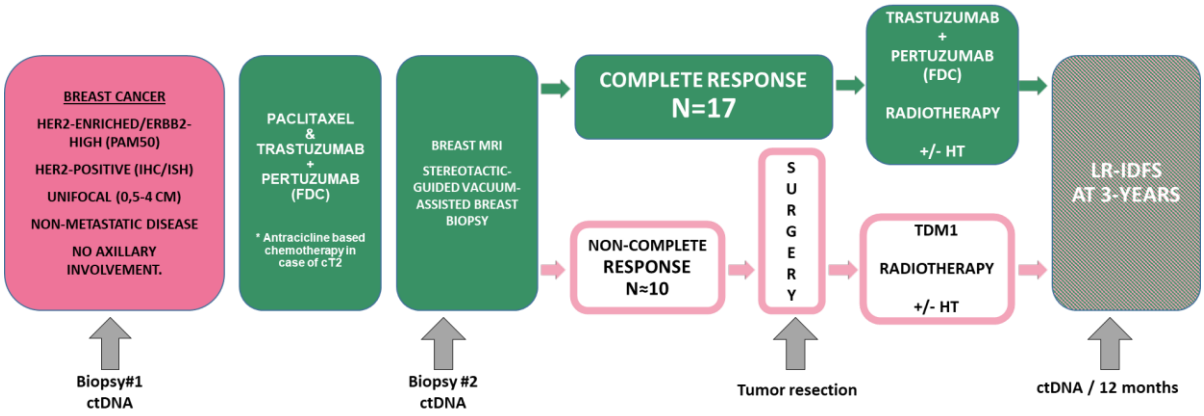

Figure 1Trial design

Screening and allocation

All patients must have known estrogen receptor (ER), progesterone receptor (PgR) and HER2 status locally assessed by immunohistochemistry (IHC) and/or in situ hybridization (ISH), according to ASCO/CAP guidelines(1, 2). An Archived Formalin-Fixed Paraffin-Embedded (FFPE) specimen with adequate quantity and quality of tumor tissue must be provided. If not available, the patient must agree to re-biopsy. Breast MRI and breast and axillar ultrasound (US), performed shortly prior to Day 1 of treatment as per standard of care (≤42 days), should be available for confirmation of baseline tumor ≤ 4 cm and a negative ipsilateral axilla.

PAM50 test and ERBB2 levels to be determined in a central laboratory. Patients with a subtype other than HER2-E and/or low ERBB2 levels will not be allocated (screening failures). Remaining tissue will be kept for additional translational studies for those patients randomized in the study.

Neoadjuvant period

HER2-enriched/ERBB2-high patients will be eligible for the trial. After confirmation of all eligibility criteria, eligible patients will receive:

- Patients with clinical size tumors ≤2cm: paclitaxel IV 80mg/m^2 every week for 12 weeks with trastuzumab and pertuzumab Subcutaneous Fixed-Dose Combination (FDC) (a loading dose of 1200 mg pertuzumab and 600 mg trastuzumab followed by a maintenance dose of 600 mg pertuzumab and 600 mg trastuzumab once every 3 weeks) for 5 cycles. In total, neoadjuvant therapy will last for 13 weeks.

- Patients with clinical size tumors >2cm and ≤4 cm: AC (doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 IV) or EC (epirubicin 90 mg/m2 and cyclophosphamide 600 mg/m2 IV) accordance to local guidelines every 3 weeks for 4 cycles (Cycles 1-4), followed by paclitaxel IV 80mg/m^2 every week for 12 weeks with trastuzumab and pertuzumab Subcutaneous Fixed-Dose Combination (FDC) (a loading dose of 1200 mg pertuzumab and 600 mg trastuzumab followed by a maintenance dose of 600 mg pertuzumab and 600 mg trastuzumab once every 3 weeks) for 5 cycles. In total, neoadjuvant therapy will last for 25 weeks.

After neoadjuvant treatment, a breast MRI will be performed. If a complete response is observed on breast MRI, patients will undergo a stereotactic-guided VAB of the marker area to obtain 12 cylinders of breast parenchyma, which is equivalent to 2 grams of tissue.

Omission of surgery

If no invasive tumor cells and no *in situ* disease are identified in the stereotactic-guided VAB, patients will be eligible to omit loco-regional surgery. Whole breast radiotherapy without nodal radiotherapy will then be performed. Trastuzumab and pertuzumab FDC will be continued to complete 1 year of treatment and adjuvant endocrine therapy will be indicated according to hormonal receptor status by IHC.

In those patients who have omitted the surgery, if clinical or radiological local recurrence of the breast tumor is suspected at any time during the follow up, an imaging assessment and biopsy must be obtained for confirmation. If local recurrence disease is confirmed, the patient would undergo surgery for a primary breast tumor and a selective sentinel lymph node biopsy, with axillary emptying according to the result of the same.

Surgery

If invasive tumor cells and/or *in situ* disease are identified, patients will undergo surgery. Breast and axillary surgery will be done according to local practice procedures. The type of surgery performed will be recorded. Surgery samples of the residual tumor tissue will be collected regardless of whether they completed full neoadjuvant treatment. All patients will continue with Trastuzumab-emtansine (TDM1) completing 1 year of treatment (14 cycles) and adjuvant endocrine therapy will be indicated according to hormonal receptor status by IHC. Patients who have undergone surgery will receive radiotherapy treatment according to standard clinical practice. Adjuvant TDM-1 will be administered concurrently with radiotherapy.

Treatment follow-up

The first safety follow-up visit for the study treatment will be scheduled for all patients 28 days (+/- 7 days) after the last dose of any Investigational Medicinal Product (IMP) and it will be called as end of treatment visit.

Afterwards, patients will be followed as scheduled in Section 6 of the protocol, up to end of study or the patient withdraws consent or until death, whichever occurs first. During these follow-up contacts survival status, post-study anticancer therapy evaluation, and clinical data will be collected as needed. Telephone contact is acceptable.

All ≥ grade 2 AEs will be followed up until improvement to baseline levels, grade 1 or complete recovery, the patient withdraws consent, patient's death or lost to follow-up. Patients who discontinue study drugs for any reason will be followed up to end of study (as defined in Section 6) or up to study termination, whichever occurs first. A summary of the study assessments is reported in Section 6: Schedule of assessments and study procedures.

End of study

The end of study will be 3 years from surgery of the last patient (if surgery is performed), up to 3 years from stereotactic-guided VAB of the last patient (if surgery is not performed), or the trial is terminated by the sponsor, whichever occurs first. The end of the trial is defined as the date of the last visit of last subject undergoing the trial. This data point will be considered LPLV (Last Patient Last Visit).

1.3 Study Objectives and Endpoints

Primary Endpoints

Objective	**Endpoint**
To evaluate the possibility of omission of surgery and sentinel lymph node dissection in clinically low-risk HER2-positive breast cancer with high HER2 addiction and a complete response following standard neoadjuvant chemotherapy and dual HER2 blockade.	To estimate the loco-regional invasive disease-free survival (LR-IDFS) at 3-year of patients who achieve a complete response based on imaging and a stereotactic-guided vacuum-assisted breast biopsy, and omit loco-regional surgery. 3-years LR-IDFS rate defined as time from the first date of no disease (i.e., date of stereotaxic guided biopsy) to loco-regional recurrence. Loco-regional recurrence is defined as recurrence of breast cancer in the same breast parenchyma as the original primary lesion, the axilla, regional lymph nodes, chest wall and/or skin of the ipsilateral breast.

Secondary Endpoints

Objectives	**Endpoints**
1. To assess measures of clinical benefit of both arms	1.1 To estimate the disease-free survival at 3years and 5-years of patients who achieve a complete response based on imaging (i.e. MRI) and a stereotaxic guided biopsy and omit loco-regional surgery following neoadjuvant chemotherapy and dual HER2 blockade. 1.2 To estimate the disease-free survival at 3years and 5-years of patients who do not achieve a complete response based on imaging (i.e. MRI) following neoadjuvant chemotherapy and dual HER2 blockade. 1.3 To compare the rate of pathological complete response (pCR) between the treatment groups by HR status.
2. Analyze the financial impact of the omission of breast cancer surgery.	2.1 To compare the cost in patients with and without breast cancer surgery, not only direct cost for hospitals/public health system, but also indirect cost for public system
3. To assess the effect of investigational treatment and standard treatment on patient reported outcomes (PROs).	3.1 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), version 3. 3.2 EORTC QLQ-BR23 (breast cancer-specific questionnaire).
4. To evaluate the safety and tolerability of investigational treatment and their corresponding standard treatment.	4.1 Incidence, duration and severity of Adverse Events (AEs) assessed by the NCI Common Terminology for Classification of Adverse Events (CTCAE) version 5, including dose reductions, delays and treatment discontinuations.

2. Study Population

2.1 Overall and analysis population

Overall, 20 patients were screened for the study. However, only 5 were finally selected for the study treatment after meeting all the inclusion criteria and signing the ICF.

Table 1 Screening population

	N = 20[1]
ER percent	
Median (Q1, Q3)	60 (0, 90)
Min, Max	0, 100
Mean (SD)	46 (42)
PR percent	
Median (Q1, Q3)	12 (0, 50)
Min, Max	0, 80
Mean (SD)	24 (29)
ki67 percent	
Median (Q1, Q3)	35 (20, 50)
Min, Max	18, 75
Mean (SD)	39 (19)
HER2IHC	
2+	7 (37%)
3+	12 (63%)
HER2 ISH	
Amplified	7 (100%)
[1]n (%)	
	N = 20[1]
Study Eligibility	7 (35%)
Eligibility_PAM50	
Her2-Enriched /ERBBB2-high	7 (100%)
Reason for non-eligibility	
Non-fulfillment of Selection Criteria (different than non-HER2E subtype)	2 (15%)
Other	3 (23%)
Patient with non Her2-Enriched /ERBBB2-high	8 (62%)
Other reasons for non-eligibility	
LIVER METASTASIS	1 (33%)
MULTICENTRIC TUMOR	2 (67%)
[1]n (%)	

As a summary, 2 out of the 5 patients were hormone receptor (HR) positive and all the patients showed HER2 enrichment.

Table 2 ITT population: HR, HER2, ki67

Subject	ER percent	PR percent	ki67 percent	HER2IHC	HER2 ISH
ELPIS-004	0	0	60	3+	
ELPIS-006	100	50	45	2+	Amplified
ELPIS-008	0	0	60	3+	
ELPIS-009	18	15	40	3+	
ELPIS-020	0	4	25	3+	

2.2 Treatment timelines

3. Demographic and baseline characteristics

Table 3 and Table 4 (patient listing) show the baseline characteristics of all the patients treated in this study. All the enrolled patients are female, “caucasian” with no previous cancer history. 80 % (4/5) of the patients are postmenopausal and 20 % (1/5) pre-menopausal. All the patients showed ECOG grades between 0-1.

Table 3 Patient demographics, baseline ECOG, Previous medical history

	N = 5[1]
Race	
Caucasian	5 (100%)
Menopausal Status	
Postmenopausal (at least 12 months without menses prior to neoadyuvance onset or bilateraloophorectomy total)	4 (80%)
Premenopausal	1 (20%)
Pregnancy test done	
2021-03-26	1 (100%)
Pregnancy test result	
Negative	1 (100%)
[1]n (%)	
	N = 5[1]
ECOG baseline	
Grade 0 - Fully active able to carry on all pre-disease performance without restriction	4 (80%)
Grade 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work	1 (20%)
[1]n (%)	
	N = 5[1]
Previous Cancer history	
No	5 (100%)
[1]n (%)	

Table 4 Patient demographics,, Previous medical history (patient listing)

Subject	Race	Menopausal Status	Pregnancy test result	Previous Cancer history
ELPIS-004	Caucasian	Premenopausal	Negative	No
ELPIS-006	Caucasian	Postmenopausal*		No
ELPIS-008	Caucasian	Postmenopausal*		No

ELPIS-009	Caucasian	Postmenopausal*		No
ELPIS-020	Caucasian	Postmenopausal*		No

*at least 12 months without menses prior to neoadyuvance onset or lateraloophorectomy total

Table 5 shows the baseline ECOG, vital signs, LVEF and ECG test results of the patients treated. All the patients showed elevated blood pressure. 4 out of 5 patients presented grade 0 ECOG and 1 patient with grade 1. Of the patients tested, heart functioning (5/5) and ECG (2/2) was normal

Table 5 Baseline ECOG, vital signs and LVEF (patient listings)

	ECOG	BP		**Heart rate**	LVEF		**Lead ECG**		
Subject		**systolic**	**diastolic**		**Test**	**%**	performed	Reason not performed	results
ELPIS-004	Grade 0	133	85	85	ECHO	56	Yes		Normal
ELPIS-006	Grade 0	126	80	74	ECHO	62	No	By mistake	
ELPIS-008	Grade 0	129	93	101		55	No		
ELPIS-009	Grade 1	107	88	85	MUGA	64	No	not applicable	
ELPIS-020	Grade 0	147	88	79	ECHO	60	Yes		Normal

*Grade 0- Fully active able to carry on all pre-disease performance without restriction
*Grade 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work
*ECHO – echocardiography
*MUGA - multiple-gated acquisition

Tumor Assessment

Baseline tumor assessments by physical examination, imaging, MRI, mammography and ultrasound are shown as patient level listings in tables 6,7,8.

Table 6 Baseline tumor assessment: physical exam

Subject	Physical exam	Breast cancer site	Breast tumor measurement	Other physical exam	height	weight
ELPIS-004	Yes	Left	17	Normal	169	56.8
ELPIS-006	Yes	Right	17	Normal	156	73.0
ELPIS-008	Yes	Left	14	Normal	156	71.0
ELPIS-009	Yes	Left	14	Normal	161	86.0
ELPIS-020	Yes	Right	19	Normal	155	57.0

Table 7 Baseline tumor assessment: histology, grade

Subject	Date of diagnosis	Primary tumor histologic type	Histologic grade	Clinical T stage
ELPIS-004	2021-03-03	Ductal	G3	T1c
ELPIS-006	2021-07-23	Ductal	G2	T1c
ELPIS-008	2021-09-30	Ductal	G3	T1c
ELPIS-009	2021-09-30	Ductal	G2	T1c
ELPIS-020	2023-04-27	Ductal	G2	T1c

Table 8 Baseline tumor assessment: MRI, mammography, ultrasound

Subject	MRI	Maximal diameter (MRI)	Mammography	Longest diameter/short axis (Mamo)	Ultrasound
ELPIS-004	Yes	16	Yes	17	Yes
ELPIS-006	Yes	18	Yes	17	Yes
ELPIS-008	Yes	14	Yes	12	Yes
ELPIS-009	Yes	14	Yes	22	Yes
ELPIS-020	Yes	19	Yes	18	Yes

Hematology and Chemistry

Tables 9, 10 report the hematology and chemistry test results of each treated patient (as ‘in range’ or ‘out of range’). None of the ‘out of range’ values were clinically relevant.

Table 9 Baseline: Hematology

Subject	Hematology done	Hemoglobin	Hematocrit	Red blood cell count	Platelet count	White blood cell count	Neutrophils	Bands cells	Lymphocytes	Monocytes	Eosinophils	Basophils
ELPIS-004	Yes	In range	In range	In range	In range	In range	Out of range	Not done	In range	In range	In range	In range
ELPIS-006	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-008	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-009	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-020	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range

Table 10 Baseline: Chemistry

Subject	Chemistry done	Sodium	Potassium	Calcium	Glucose	Creatinin	BilirubinDirect	Bilirubin	Protein	Alkaline phosphatase	AST	ALT
ELPIS-004	Yes	In range	In range	In range	In range	In range	In range	Out of range	In range	Out of range	In range	In range
ELPIS-006	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-008	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-009	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-020	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range

Adverse Events at Baseline

None of the patients showed any adverse events at baseline after signing the ICF.

Table 11 Baseline adverse events

	N = 5[1]
Has the patient experienced any adverse event after after signing the ICF	
No	5 (100%)

[1]n (%)

4. Study treatments

4.1 Neoadjuvant treatment

Cycle 1

Table 12 Cycle1 ECOG, vital signs (patient listings)

Subject	ECOG Cycle1	BP performed	reason for not performing	BP systolic	BP diastolic	Heart rate
ELPIS-004	Grade 0	No	It is the same as the screening			
ELPIS-006	Grade 0	No	It is the same as the screening			
ELPIS-008	Grade 0	No	it is the same at screening			
ELPIS-009	Grade 1	No	It´s the same at screening			
ELPIS-020	Grade 0	Yes		148	95	83

*Grade 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work
*Grade 0- Fully active able to carry on all pre-disease performance without restriction

Hematology and Chemistry was not reported as it was the same as screening.

Table 13 Cycle 1 treatment date and dosage

Subject	Treatment with Paclitaxel						Treatment with Trastuzumab/Pertuzumab	
	Day1		Day 8		Day 15		Treatment	Date
	Date	Dose	Date	Dose	Date	Dose		
ELPIS-004	2021-03-30	130	2021-04-06	130	2021-04-13	130	Yes	2021-03-30
ELPIS-006	2021-08-24	142	2021-08-31	142	2021-09-07	142	Yes	2021-08-24
ELPIS-008	2021-10-20	140	2021-10-27	140	2021-11-03	140	Yes	2021-10-20
ELPIS-009	2021-11-24	157	2021-12-02	157	2021-12-08	157	Yes	2021-11-24
ELPIS-020	2023-06-08	125	2023-06-15	125	2023-06-22	125	Yes	2023-06-08

Cycle 2

Table 14 Cycle2 ECOG, vital signs (patient listings)

Subject	ECOG Cycle2	BP performed	BP systolic	BP diastolic	Heart rate
ELPIS-004	Grade 0	Yes			73
ELPIS-006	Grade 0	Yes	119	84	78
ELPIS-008	Grade 1	Yes	153	95	104
ELPIS-009	Grade 1	Yes	107	88	85
ELPIS-020	Grade 0	Yes	144	90	81

*Grade 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work
*Grade 0- Fully active able to carry on all pre-disease performance without restriction

Table 15 Cycle 2 treatment date and dosage

Subject	Treatment with Paclitaxel						Treatment with Trastuzumab/Pertuzumab	
	Day1		Day 8		Day 15		Treatment	Date
	Date	Dose	Date	Dose	Date	Dose		
ELPIS-004	2021-04-20	130	2021-04-27	130	2021-05-04	130	Yes	2021-04-20
ELPIS-006	2021-09-15	142	2021-09-22	142	2021-09-29	142	Yes	2021-09-15
ELPIS-008	2021-11-17	140	2021-11-24	140	2021-12-01	140	Yes	2021-11-17
ELPIS-009	2021-12-16	157	2021-12-22	157	2021-12-29	157	Yes	2021-12-16
ELPIS-020	2023-06-28	125	2023-07-05	125	2023-07-12	125	Yes	2023-06-28

Table 16 Cycle2: Hematology

Subject	Hematology done	Hemoglobin	Hematocrit	Red blood cell count	Platelet count	White blood cell count	Neutrophils	Bands cells	Lymphocytes	Monocytes	Eosinophils	Basophils
ELPIS-004	Yes	In range	In range	In range		In range	In range	Not done	In range	In range	In range	In range
ELPIS-006	Yes	Out of range	In range	In range	In range	In range	Out of range	In range	In range	In range	In range	In range
ELPIS-008	Yes	In range	In range	In range	In range	In range	Out of range	In range	In range	Out of range	In range	In range
ELPIS-009	Yes	In range	In range	In range	In range	Out of range	In range	In range	In range	In range	In range	In range
ELPIS-020	Yes	In range	In range	In range	In range	Out of range	In range	In range	In range	In range	In range	In range

Table 17 Cycle 2: Chemistry

Subject	Chemistry done	Sodium	Potassium	Calcium	Glucose	Creatinin	BilirubinDirect	Bilirubin	Protein	Alkaline phosphatase	AST	ALT
ELPIS-004	Yes	In range	In range	In range	In range	In range	Out of range	Out of range	In range	Out of range	In range	In range
ELPIS-006	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-008	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-009	Yes											
ELPIS-020	Yes	In range	In range	In range	Out of range	In range	Not done	In range	In range	In range	In range	In range

Cycle 3

Table 18 Cycle3 ECOG, vital signs (patient listings)

Subject	ECOG Cycle1	BP performed	reason for not performing	BP systolic	BP diastolic	Heart rate
ELPIS-004	Grade 0	Yes		131	91	99
ELPIS-006	Grade 0	Yes		97	74	72
ELPIS-008	Grade 1	Yes		143	92	104
ELPIS-009	Grade 1	Yes		106	77	89
ELPIS-020	Grade 0	Yes		139	85	88

*Grade 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work
*Grade 0- Fully active able to carry on all pre-disease performance without restriction

Table 19 Cycle 3 treatment date and dosage

Subject	Treatment with Paclitaxel						Treatment with Trastuzumab/Pertuzumab	
	Day1		Day 8		Day 15		Treatment	Date
	Date	Dose	Date	Dose	Date	Dose		
ELPIS-004	2021-05-11	130	2021-05-18	130	2021-05-25	130	Yes	2021-05-11
ELPIS-006	2021-10-06	142	2021-10-14	142	2021-10-20	142	Yes	2021-10-06
ELPIS-008	2021-12-09	140	2021-12-15	140	2021-12-22	140	Yes	2021-12-09
ELPIS-009	2022-01-07	157	2022-01-13	157	2022-01-20	157	Yes	2022-01-07
ELPIS-020	2023-07-19	102	2023-07-26	102	2023-08-02	102	Yes	2023-07-19

Table 21 Cycle 3: Hematology

Subject	Hematology done	Hemoglobin	Hematocrit	Red blood cell count	Platelet count	White blood cell count	Neutrophils	Bands cells	Lymphocytes	Monocytes	Eosinophils	Basophils
ELPIS-004	Yes	In range	In range	In range	In range	In range	In range	Not done	In range	In range	In range	In range
ELPIS-006	Yes	Out of range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-008	Yes	In range	In range	In range	In range	In range	Out of range	In range	In range	Out of range	In range	In range
ELPIS-009	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-020	Yes	In range	In range	Out of range	In range	Out of range	In range	In range	In range	In range	In range	In range

Table 20 Cycle3: Chemistry

Subject	Chemistry done	Sodium	Potassium	Calcium	Glucose	Creatinin	BilirubinDirect	Bilirubin	Protein	Alkaline phosphatase	AST	ALT
ELPIS-004	Yes	In range	In range	In range	In range	In range	In range	Out of range	In range	In range	In range	In range
ELPIS-006	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-008	Yes	In range	In range	In range	Out of range	In range	In range	In range	In range	In range	In range	In range
ELPIS-009	Yes	In range	In range	In range	In range	Out of range	In range	In range	In range	In range	Out of range	Out of range
ELPIS-020	Yes	In range	In range	In range	In range	In range	Not done	In range	Out of range	In range	In range	In range

Cycle 4

Table 22 Cycle4 ECOG, vital signs (patient listings)

Subject	ECOG Cycle1	BP performed	reason for not performing	BP systolic	BP diastolic	Heart rate
ELPIS-004	Grade 0	Yes		122	88	80
ELPIS-006	Grade 0	Yes		100	75	79
ELPIS-008	Grade 1	Yes		138	80	100
ELPIS-009	Grade 1	Yes		125	81	91
ELPIS-020	Grade 0	Yes		121	62	96

*Grade 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work
*Grade 0- Fully active able to carry on all pre-disease performance without restriction

Table 23 cycle 4 treatment and dosage

Subject	Treatment with Paclitaxel				Treatment with Trastuzumab/Pertuzumab	
	Day1		Day 15		Treatment	Date
	Date	Dose	Date	Dose		
ELPIS-004	2021-06-01	130	2021-06-15	130	Yes	2021-06-01
ELPIS-006	2021-10-27	142	2021-11-10	142	Yes	2021-10-27
ELPIS-008	2021-12-29	140	2022-01-12	140	Yes	2021-12-29
ELPIS-009			2022-02-18	126	Yes	2022-01-27
ELPIS-020	2023-08-09	102			Yes	2023-08-09

Table 25 Cycle 4: Hematology

Subject	Hematology done	Hemoglobin	Hematocrit	Red blood cell count	Platelet count	White blood cell count	Neutrophils	Bands cells	Lymphocytes	Monocytes	Eosinophils	Basophils
ELPIS-004	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-006	Yes	Out of range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-008	Yes	Out of range	In range	Out of range	In range		In range	In range	In range	In range	In range	In range
ELPIS-009	Yes	Out of range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-020	Yes	Out of range	In range	Out of range	In range	In range	In range	In range	In range	In range	In range	In range

Table 24 Cycle4: Chemistry

Subject	Chemistry done	Sodium	Potassium	Calcium	Glucose	Creatinin	BilirubinDirect	Bilirubin	Protein	Alkaline phosphatase	AST	ALT
ELPIS-004	Yes	In range	In range	In range	In range	In range	In range	Out of range	Out of range	Out of range	In range	In range
ELPIS-006	Yes	In range	Out of range	Out of range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-008	Yes	In range	In range	In range	Out of range	In range	Not done	In range	In range	In range	In range	In range
ELPIS-009	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-020	Yes	In range	In range	In range	In range	In range	Not done	In range	Out of range	In range	In range	In range

Cycle 5

Table 26 Cycle5 ECOG, vital signs (patient listings)

Subject	ECOG Cycle1	BP performed	reason for not performing	BP systolic	BP diastolic	Heart rate
ELPIS-004	Grade 0	Yes		116	86	84
ELPIS-006	Grade 0	Yes		114	79	79
ELPIS-008	Grade 1	Yes		128	94	104
ELPIS-009	Grade 1	Yes		105	81	90
ELPIS-020	Grade 0	Yes		140	88	84

*Grade 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work
*Grade 0- Fully active able to carry on all pre-disease performance without restriction

Table 27 Cycle 5 treatment and dosage (patient listing)

Subject	Treatment with Paclitaxel						Treatment with Trastuzumab/Pertuzumab	
	Day1		Day 8		Day 15		Treatment	Date
	Date	Dose	Date	Dose	Date	Dose		
ELPIS-004	2021-06-22	130					Yes	2021-06-22
ELPIS-006							Yes	2021-11-17
ELPIS-008							Yes	2022-01-19
ELPIS-009							Yes	2022-02-25
ELPIS-020	2023-09-05	102					Yes	2023-09-05

4.2 Pre-surgery

Cycle 5 day 1

Table 28 Cycle 5, Day1: MRI and Ultrasound (patient listing)

Subject	MRI date	MRI residual	MRI maximal diameter	Ultrasound date	Ultrasound maximal diameter
ELPIS-004	2021-06-23	No		2021-06-29	0
ELPIS-006	2021-11-17	Yes	12	2021-11-18	0
ELPIS-008	2022-01-19	Yes	9	2022-01-21	3
ELPIS-009	2022-02-25	No		2022-02-25	1
ELPIS-020	2023-09-06	No		2023-09-07	0

Table 29 Pre-surgery: ECOG, LVEF (patient listing)

Subject	ECOG* pre surgery	LVEF date	LVEF* determinant	LVEF percentage
ELPIS-004	Grade 0			
ELPIS-006	Grade 0	2021-11-02	MUGA	64
ELPIS-008	Grade 1	2022-01-05	MUGA	57
ELPIS-009	Grade 1	2022-02-15	MUGA	67
ELPIS-020	Grade 0	2023-09-29	ECHO	59

*Grade 0- Fully active able to carry on all pre-disease performance without restriction
*Grade 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work
*ECHO – echocardiography
*MUGA - multiple-gated acquisition

VAB

Sterio-guided VAB was performed for 3 of the 5 patients who underwent nroadjuvant treatment. Table 30 shows the ER, PR, ki67, HER2 (IHC and ISH) measurements from the tumor collected during this procedure.

Table 30 VAB

Subject	Has VABB been performed	Has tumor obtened	ER status	PR status	ki67 percentage	HER2 IHC	HER2 ISH
ELPIS-004	No						
ELPIS-006	Yes	Yes	100	50	45	2+	Amplified
ELPIS-008	Yes	Yes	0	0	60	3+	
ELPIS-009	No						
ELPIS-020	Yes	Yes	0	0	1	3+	

4.3 Surgery

3 of the 5 treated patients underwent conservative surgery after the neo-adjuvant treatment. The pathological tumor characteristics for each patient is shown in table 32. Two of the patients who underwent surgery showed pathological complete response (pCR).

Table 31 Surgery: surgery type and dates

Subject	Has surgery been done	Pathologic surgery type	Surgery visit date
ELPIS-004	No		
ELPIS-006		Conservative surgery	2021-12-10
ELPIS-008		Conservative surgery	2022-02-09
ELPIS-009			
ELPIS-020		Conservative surgery	2023-09-26

Table 32 Surgery: tumor pathology

Subject	cellularity(%)	% of cancer that is insitu	Pathologic grade	Pathologic Tstage	Pathologic *Nstage	Pathologic RCB	Pathological tumor type	insitu	Pathologic pCR
ELPIS-004									
ELPIS-006	40	25	G2	T1c	pN0 (i-): pT0	RCB-I	Ductal NA	Yes DCIS	No
ELPIS-008	50	0	G3	T1b	pN0 (i-)	RCB-II	-Other CARCINOMA INFILTRANTE ESPECIAL,	Yes DCIS	Yes
ELPIS-009									
ELPIS-020	0	5	G2	T1c	pN0 (i-) pT0	RCB-I	Ductal NA	No NA	Yes

*pNo: no regional node metastases are present, IHC negative

Radiotherapy

3 patients underwent radiotherapy (2 after 1 month post surgery)

Table 33 Adjuvant treatment: Radiotherapy

Subject	Has radiotherapy been given	Radiotherapy initiation	Radiotherapy end date
ELPIS-004	Yes	2021-08-23	2021-09-17
ELPIS-006	Yes	2021-12-29	2022-03-02
ELPIS-020	Yes	2023-11-06	2023-11-24

4.1 Adjuvant treatment (complete response)

Three patients who showed complete response were given adjuvant treatment with Trastuzumab/Pertuzumab.

Table 34 Adjuvant treatment (complete response): physical exam

Subject	Physical exam results	Pregnancy test results
ELPIS-004	Normal	Negative
ELPIS-009	Normal	
ELPIS-020	Normal	

Table 35 Adjuvant treatment (complete response): ECOG, vitals

Subject	ECOG adjuvant	BP systolic	BP diastolic	Heart rate
ELPIS-004	Grade 0	112	83	81
ELPIS-009	Grade 0	107	77	95
ELPIS-020	Grade 0	165	79	76

*Grade 0- Fully active able to carry on all pre-disease performance without restriction
*Grade 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work

Table 36 Adjuvant treatment (complete response): treatment

Subject	Treatment with Trastuzumab/Pertuzumab	Treatment date
ELPIS-004	Yes	2021-07-22
ELPIS-009	Yes	2022-03-18
ELPIS-020	Yes	2023-10-18

Table 37 Adjuvant treatment (complete response): Hematology

Subject	Hematology done	Hemoglobin	Hematocrit	Red blood cell count	Platelet count	White blood cell count	Neutrophils	Bands cells	Lymphocytes	Monocytes	Eosinophils	Basophils
ELPIS-004	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-009	Yes	In range	In range	In range	In range	In range	In range	Not done	In range	In range	In range	In range
ELPIS-020	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range

Table 38 Adjuvant treatment (complete response): Chemistry

Subject	Chemistry done	Sodium	Potassium	Calcium	Glucose	Creatinin	BilirubinDirect	Bilirubin	Protein	Alkaline phosphatase	AST	ALT
ELPIS-004	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-009	Yes	In range	In range	In range	In range	In range	Not done	In range	In range	In range	In range	In range
ELPIS-020	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range

1.1 Adjuvant treatment (non-complete response)

Table 39 Adjuvant treatment (non-complete response): Physical exam

Subject	Physical exam results	Pregnancy test results
ELPIS-006	Normal	Negative
ELPIS-008	Normal	Negative
ELPIS-020	Normal	Negative

Table 40 Adjuvant treatment (non-complete response): ECOG, vitals

Subject	ECOG adjuvant	BP systolic	BP diastolic	Heart rate
ELPIS-006	Grade 1	111	81	76
ELPIS-008	Grade 1	140	90	98
ELPIS-020	Grade 0	165	79	76

*Grade 0- Fully active able to carry on all pre-disease performance without restriction
*Grade 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work

Three patients not showing complete response were treated with TDM1 in the adjuvant setting.

Table 41 Adjuvant (non-complete response) treatment

Subject	Treatment with TDM1	Treatment date	Treatment dosage (mg)
ELPIS-006	Yes	2021-12-30	263
ELPIS-008	Yes	2022-03-04	238
ELPIS-020	Yes	2023-10-18	194

Table 42 Adjuvant treatment (non complete response): Hematology

Subject	Hematology done	Hemoglobin	Hematocrit	Red blood cell count	Platelet count	White blood cell count	Neutrophils	Bands cells	Lymphocytes	Monocytes	Eosinophils	Basophils
ELPIS-006	Yes	Out of range	Out of range	Out of range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-008	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-020	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range

Table 43 Adjuvant treatment (non-complete response): Chemistry

Subject	Chemistry done	Sodium	Potassium	Calcium	Glucose	Creatinin	BilirubinDirect	Bilirubin	Protein	Alkaline phosphatase	AST	ALT
ELPIS-006	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	Out of range
ELPIS-008	Yes	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range
ELPIS-020	Yes	In range	In range	In range	In range	In range	Not done	In range	In range	In range	In range	In range

1.2 Follow up

Follow up assessment was conducted for 4 out of the 5 patients treated in this study.

Table 44 Follow up: ECOG and physical exam

Subject	ECOG follow up	Physical exam results	Physical exam date
ELPIS-004	Grade 0	Normal	2022-07-21
ELPIS-006	Grade 0	Normal	2023-02-08
ELPIS-008	Grade 0	Normal	2023-03-29
ELPIS-009	Grade 0	Normal	2023-03-24

Table 45 Follow up: tumor assessment

Subject	Mammography done	Mammography date	Mammography longest diameter/short axis	Ultrasound done	Ultrasound date	Ultrasound longest diameter/short axis	MRI done	MRI date	MRI longest diameter/short axis
ELPIS-004	Yes	2022-07-01	0	Yes	2022-07-01	0	No		
ELPIS-006	No			No			No		
ELPIS-008	Yes	2023-02-14	0	Yes	2023-02-14	0	No		
ELPIS-009	Yes	2023-01-04	0	Yes	2023-01-04	0	Yes	2023-03-06	0

5. Study Endpoint analysis

5.1 Primary Endpoint

To estimate the loco-regional invasive disease-free survival (LR-IDFS) at 3-year of patients who achieve a complete response based on imaging and a stereotactic-guided vacuum-assisted breast biopsy, and omit loco-regional surgery. However, there is not enough follow-up to estimate the LD-iDFS at 3-years. No data from the primary endpoint can be shown.

5.2 Secondary Endpoints

Clinical benefit

Pathological complete response (pCR) was observed in 2 of the 5 treated patients – both with negative HR status.

Table 46 pCR

				VABB				baseline			
Subject	**p T,N stage**	**RCB**	**pCR**	**ER**	**PR**	**ki67 %**	**HER2 IHC**	**ER**	**PR**	**Ki67**	**HER2 IHC**
ELPIS-008	pN0 (i-) pT0	RCB-II	Yes	0	0	60	0	0	0	60	3+
ELPIS-020	pN0 (i-) pT0	RCB-I	Yes	0	0	1	0	0	4	25	3+

Patient reported outcomes (PROs)

The following was observed from 4 (out of 5 patients treated) PROs completed during screening and after adjuvant treatment:

Physical and Role Functioning
All patients show good physical functioning (questions 1-5), with minimal physical limitations. However, there is slight reduction in prolonged physical activites and strenuous activities in all patients and role functioning (questions 6-7) in 2 patients reports after treatment.

Emotional and Social Well-being
One patient showed increase in irritability after treatment. For the other patients, emotional well being (questions 21-24) shows improvement post treatment. 2 patient reports suggested a decrease in social functioning (questions 26-27) after treatment while the other 2 showed an increase.

Cognitive Functioning
While one patient showed improved cognitive functioning (questions 20, 25), 2 patient reports showed a slight decrease after treatment.

The reports show an overall decrease in global health status from baseline to after treatment.

Table 47 Patient reported outcomes: Screening and after treatment

Subject	**ELPIS-004**		**ELPIS-006**	**ELPIS-008**		**ELPIS-009**		**ELPIS-020**	
	Screening	**After treatment**	**Screening**	**Screening**	**After treatment**	**Screening**	**After treatment**	**Screening**	**After treatment**
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	A little	A little	A little	Not at all	A little	A little	A little	Quite a bit	Quite a bit
2. Do you have any trouble taking a long walk?	Not at all	A little	A little	Not at all	Not at all	Not at all	A little	Not at all	A little
3. Do you have any trouble taking a short walk outside of the house?	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all
4. Do you need to stayin bed or a chair during the day?	A little	A little	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all
5. Do you need help with eating, dressing, washing yourself or using the toilet?	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all
6. During the past week Were you limited in doing either your work or other daily activities?	A little	A little	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	A little
7. During the past week Were you limited in pursuing your hobbies or other leisure time activities?	A little	Quite a bit	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	A little
8. During the past week Were you short of breath?	Not at all	Not at all	A little	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all
9. During the past week Have you had pain?	Not at all	Quite a bit	Not at all	Not at all	Quite a bit	Not at all	Not at all	A little	A little

10. During the past week Did you need to rest?	A little	Not at all	A little	Not at all	Quite a bit	Not at all	Not at all	A little	A little
11. During the past week Have you had trouble sleeping?	Not at all	A little	Not at all	Not at all	Quite a bit	Not at all	Not at all	Very much	Very much
12. During the past week Have you felt weak?	A little	A little	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	A little
13. During the past week Have you lacked appetite?	Not at all	Not at all	Not at all	Not at all	A little	Not at all	Not at all	A little	A little
14. During the past week Have you felt nauseated?	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all
15. During the past week Have you vomited?	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all
16. During the past week Have you been constipated?	Not at all	A little	Not at all	Not at all	Not at all	Not at all	Not at all	A little	Quite a bit
17. During the past week Have you had diarrhea?	A little	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all
18. During the past week Were you tired?	Quite a bit	Quite a bit	A little	Not at all	A little	Not at all	A little	A little	A little
19. During the past week Did pain interfere with your dailyactivities?	A little	A little	Not at all	Not at all	A little	Not at all	Not at all	Not at all	A little
20. During the past week Have you had difficulty in concentrating on things,like reading a newspaper or watching television?	Not at all	A little	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all
21. During the past week Did you feel tense?	Quite a bit	Quite a bit	Not at all	Very much	Quite a bit	Not at all	Not at all	Quite a bit	A little
22. During the past week Did you worry?	Quite a bit	Quite a bit	Not at all	Very much	Quite a bit	Not at all	Not at all	Quite a bit	A little
23. During the past week Did you feel irritable?	Not at all	Quite a bit	Not at all	Not at all	Quite a bit	A little	Not at all	A little	A little

24. During the past week Did you feel depressed?	Not at all	A little	Not at all	Very much	Quite a bit	A little	Not at all	A little	A little
25. During the past week Have you had difficulty remembering things?	Not at all	Not at all	Not at all	Not at all	A little	Not at all	Not at all	A little	Not at all
26. During the past week Has your physical condition or medical treatment interfered with your family life?	Not at all	Not at all	Not at all	Not at all	A little	A little	Not at all	Very much	Quite a bit
27. During the past week Has your physical condition or medical treatment interfered with your social activities?	Not at all	A little	Not at all	Not at all	A little	A little	A little	Very much	Very much
28. During the past week Has your physical condition or medical treatment caused you financial difficulties?	Not at all	Very much	Not at all	Not at all	Not at all	Not at all	Not at all	Not at all	A little
29. How would you rate your overall health during the past week?	4	4	5	6	4	6	6	5	3
30. How would you rate your overall quality of life during the past week?	5	4	5	6	5	6	6	5	4
Global health status*	4.5	4	5	6	4.5	6	6	5	3.5

*Global health status = (score.Q 29 + score.Q 30) / 2

Safety and tolerability

Refer to Section 6: Safety analysis for tables and patient listings of all the adverse events, treatment related adverse events,

6. Safety Analysis

6.1 Adverse Events

All adverse events

Table 48 shows all adverse events reported in this study. The number of events shown in this table include grade changes as a separate event. Alopecia and diarrhea were the most frequent AE (4 out of 5 patients) followed by asthenia, ALT increase, AST increase and dysgeusia among others.

Table 48 All adverse events

AE term	Number of patients	Number of events
alopecia	4	7
asthenia	3	6
diarrhea	4	4
hiporexia	1	4
alat increase	2	3
asat increase	2	2
covid19	2	2
dysgeusia	2	2
plaquetopenia	1	2
anemia	1	1
anxiety	1	1
arthralgia	1	1
artromyalgia	1	1
cefalea	1	1
cough	1	1
decrease hemoglobine	1	1
discomfort upper back region	1	1
epigastralgia	1	1
epigastric pain	1	1

AE term	Number of patients	Number of events
epitelitis	1	1
epithelitis	1	1
epithelitis with moist desquamation in the submammary fold	1	1
eritema face and hands	1	1
erythema on arma and hands	1	1
erythema on arms and hands	1	1
erythema on hands	1	1
erythematous reaction	1	1
feet erythema	1	1
fosfatase alcaline increase	1	1
hands neurotoxicity	1	1
headache	1	1
hiporexya	1	1
increase alat	1	1
increase of fosfatase alcaline	1	1
increase of sodium	1	1
increase of total bilirubine	1	1
mucositis	1	1
muscle pain	1	1
neurotoxicity in foot	1	1
occasional epistaxis	1	1
onychodystrophy	1	1
onycholysis	1	1
parotiditis	1	1
plantar erythema	1	1
radiodermitis	1	1
rheums	1	1
sporadic pinprick in radiotherapy area	1	1

AE term	Number of patients	Number of events
upper respiratory tract infection	1	1

Treatment related adverse event

Paclitaxel

Table 49 shows the adverse events related to Paclitaxel treatment. The number of events shown in this table include grade changes as a separate event. Alopecia was the most frequent AE (4 out of 5 patients).

Table 49 TRAEs: Paclitaxel

AE term	Number of patients	Number of events
alopecia	4	7
asthenia	2	2
dysgeusia	2	2
anemia	1	1
arthralgia	1	1
cefalea	1	1
diarrhea	1	1
eritema face and hands	1	1
erythema on arma and hands	1	1
erythema on arms and hands	1	1
erythema on hands	1	1
feet erythema	1	1
hands neurotoxicity	1	1
headache	1	1
hiporexya	1	1
mucositis	1	1
neurotoxicity in foot	1	1
occasional epistaxis	1	1
onychodystrophy	1	1
onycholysis	1	1

AE term	Number of patients	Number of events
plantar erythema	1	1

Trastuzumab

Table 50 shows the adverse events related to Trastuzumab treatment. The number of events shown in this table include grade changes as a separate event. Diarrhea was the most frequent AE (4 out of 5 patients).

Table 50 TRAEs: Trastuzumab

AE term	Number of patients	Number of events
diarrhea	4	4
asthenia	1	1
cough	1	1
dysgeusia	1	1
erythematous reaction	1	1
hiporexya	1	1
muscle pain	1	1

Pertuzumab

Table 51 shows the adverse events related to Pertuzumab treatment. The number of events shown in this table include grade changes as a separate event. Diarrhea was the most frequent AE (4 out of 5 patients).

Table 51 TRAEs: Pertuzumab

AE term	Number of patients	Number of events
diarrhea	4	4
asthenia	1	1
cough	1	1
dysgeusia	1	1
erythematous reaction	1	1
hiporexya	1	1
muscle pain	1	1

TDM-1

Table 52 shows the adverse events related to TDM-1 treatment. The number of events shown in this table include grade changes as a separate event. ALT and AST increase were most frequent AEs (2 out of 3 patients).

Table 52 TRAEs: TDM-1

AE term	Number of patients	Number of events
hiporexia	1	4
alat increase	2	3
asthenia	1	3
asat increase	2	2
plaquetopenia	1	2
anemia	1	1
decrease hemoglobine	1	1
epigastralgia	1	1
epigastric pain	1	1
fosfatase alcaline increase	1	1
increase alat	1	1
increase of fosfatase alcaline	1	1
increase of total bilirubine	1	1

Serious adverse events

No serious adverse events were reported in this study

AE patient listings

ELPIS-004

No action was taken for any of the adverse events reported for this patient.

Table 53 AE patient listings 1

AE term	grade	Treatment given	Paclitaxel		Trastuzumab		Pertuzumab		TDM1	
			relation	action taken	relation	action taken	relation	action taken	relation	action taken
alopecia	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
epithelitis	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
arthralgia	Grade 1	No	Possibly related	None	Unrelated	None	Unrelated	None	Unrelated	None
onycholysis	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
covid19	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None

ELPIS-006

No action was taken for any of the adverse events reported for this patient.

Table 54 AE patient listing 2

AE term	grade	Treatment given	Paclitaxel		Trastuzumab		Pertuzumab		TDM1	
			Relation	Action taken	Relation	Action taken	Relation	Action taken	Relation	Action taken
diarrhea	Grade 1	Yes	Unrelated	None	Probably related	None	Probably related	None	Unrelated	None
alopecia	Grade 2	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
anemia	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Probably related	None

AE term	grade	Treatment given	Paclitaxel		Trastuzumab		Pertuzumab		TDM1	
			Relation	Action taken	Relation	Action taken	Relation	Action taken	Relation	Action taken
alat increase	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Possibly related	None
asat increase	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
plaquetopenia	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
plaquetopenia	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
increase of fosfatase alcaline	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None

ELPIS-008

For this patient, study medication was interrupted due to upper respiratory tract infection (grade 1). This AE was not related to any of the treatments

Table 55 AE patient listing 3

AE term	grade	Treatment given	Paclitaxel		Trastuzumab		Pertuzumab		TDM1	
			Relation	Action taken	Relation	Action taken	Relation	Action taken	Relation	Action taken
upper respiratory tract infection	Grade 1	Yes	Unrelated	study medication interrupted	Unrelated	Study medication interrupted	Unrelated	Study medication interrupted	Unrelated	None
diarrhea	Grade 1	No	Unrelated	None	Probably related	None	Probably related	None	Unrelated	None
alopecia	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
anxiety	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
erythema on hands	Grade 1	Yes	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
occasional epistaxis	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
eritema face and hands	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None

AE term	grade	Treatment given	Paclitaxel		Trastuzumab		Pertuzumab		TDM1	
			Relation	Action taken	Relation	Action taken	Relation	Action taken	Relation	Action taken
epigastric pain	Grade 3	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
alopecia	Grade 2	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
onychodystrophy	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
increase alat	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
epigastralgia	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
radiodermitis	Grade 2	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
epitelitis	Grade 2	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
alat increase	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
fosfatase alcaline increase	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
alopecia	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
alat increase	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
discomfort upper back region	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
increase of total bilirubine	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
decrease hemoglobine	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
hiporexia	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
hiporexia	Grade 2	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
hiporexia	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
asthenia	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
asat increase	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None

AE term	grade	Treatment given	Paclitaxel		Trastuzumab		Pertuzumab		TDM1	
			Relation	Action taken	Relation	Action taken	Relation	Action taken	Relation	Action taken
asthenia	Grade 2	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
hiporexia	Grade 2	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None
asthenia	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Probably related	None

ELPIS-009

This patient presented erythema on arms and hands and feet due to which study medication was modified. This AE was probably related to Paclitaxel treatment.

Table 56 AE patient listing 4

AE term	grade	Treatment given	Paclitaxel		Trastuzumab		Pertuzumab		TDM1	
			Relation	Action taken	Relation	Action taken	Relation	Action taken	Relation	Action taken
muscle pain	Grade 1	No	Unrelated	None	Possibly related	None	Possibly related	None	Unrelated	None
diarrhea	Grade 1	No	Unrelated	None	Possibly related	None	Probably related	None	Unrelated	None
cough	Grade 1	No	Unrelated	None	Possibly related	None	Possibly related	None	Unrelated	None
asthenia	Grade 1	No	Possibly related	None	Unrelated	None	Unrelated	None	Unrelated	None
dysgeusia	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
headache	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
plantar erythema	Grade 3	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
erythema on arms and hands	Grade 2	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
mucositis	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None

AE term	grade	Treatment given	Paclitaxel		Trastuzumab		Pertuzumab		TDM1	
			Relation	Action taken	Relation	Action taken	Relation	Action taken	Relation	Action taken
cefalea	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
feet erythema	Grade 1	No	Probably related	Study medication modified	Unrelated	None	Unrelated	None	Unrelated	None
erythema on arms and hands	Grade 1	No	Probably related	Study medication modified	Unrelated	None	Unrelated	None	Unrelated	None
hands neurotoxicity	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
rheums	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
increase of sodium	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
epithelitis with moist desquamation in the submammary fold	Grade 2	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
erythematous reaction	Grade 1	No	Unrelated	None	Probably related	None	Probably related	None	Unrelated	None
asthenia	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
sporadic pinprick in radiotherapy area	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
parotiditis	Grade 2	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None
artromyalgia	Grade 1	No	Unrelated	None	Unrelated	None	Unrelated	None	Unrelated	None

ELPIS-020

For this patient, study medication was interrupted due to COVID-19. This AE was not related to any of the treatments

Table 57 AE patient listing 5

AE term	grade	Treatment given	Paclitaxel		Trastuzumab		Pertuzumab		TDM1	
			Relation	Action taken	Relation	Action taken	Relation	Action taken	Relation	Action taken
alopecia	Grade 1	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
alopecia	Grade 2	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
diarrhea	Grade 1	No	Probably related	None	Probably related	None	Probably related	None	Unrelated	None
dysgeusia	Grade 1	No	Probably related	None	Probably related	None	Probably related	None	Unrelated	None
hiporexya	Grade 1	No	Probably related	None	Probably related	None	Probably related	None	Unrelated	None
asthenia	Grade 1	No	Probably related	None	Probably related	None	Probably related	None	Unrelated	
neurotoxicity in foot	Grade 2	No	Probably related	None	Unrelated	None	Unrelated	None	Unrelated	None
covid19	Grade 2	No	Unrelated	study medication interrupted	Unrelated	Study medication interrupted	Unrelated	Study medication interrupted	Unrelated	None