1. SYNOPSIS/ABSTRACT

Title

Prospective, non-interventional study assessing the diagnostic, therapeutic proceedings and safety of anti-HER2 treatment in elderly patients (≥70 years old) with HER2 positive breast cancer in routine clinical practice in Poland - multicenter, observational study (HEROLD)

Keywords

HER2 positive breast cancer, elderly patients, Perjeta, Herceptin

Rationale and Background

Breast cancer is the most common malignant tumor in women, with a global prevalence of more than 1 million patients. The annual mortality rate is approximately 450,000 deaths (American Cancer Society). Due to the growing average life expectancy of women in Poland, population of elderly females is increasing significantly. According to the Central Statistical Office (CSO) forecast, the number of women over the age of 65 years will increase from 3.65 million in 2015 to 4.94 million in 2030. Currently there is a relative lack of data from studies specifically designed for elderly population, which would be able to address the question of safety, tolerance and efficiency of therapeutic choices of HER family agents. Additionally, patients are often reluctant to enroll in clinical trials because of misconceptions and inadequate efforts in explaining the benefits of such participation by geriatricians. For these reasons, there is a need for comprehensive assessment of the course of anti-HER2 targeted therapies (Herceptin SC or Herceptin IV with or without Perjeta IV) in the population of older women that focuses on safety and tolerance of the treatment. The most vital aspect of such study is broadening of knowledge about adverse events affecting this population as well as frequency of discontinuations of anti-HER2 treatment caused by adverse events. At the same time there is a need for appraisal of what part of the population of patients with HER2 positive breast cancer at the age of 70 years or above is not qualified for chemotherapy and targeted therapies and what are reasons of disqualification from anti-HER2 therapy.
For information on the condition under observation and on Herceptin SC or Herceptin IVwith or without Perjeta IV please refer to the most recent version of the SPC.

Research Question and Objectives

Due to the extending length of the average life expectancy for women in Poland, population of elderly female is increasing significantly. According to the Central Statistical Office (CSO) forecast the number of women over the age of 65 years will increase from 3.65 million in 2015 to 4.94 million in 2030. The risk of developing and dying from breast cancer increases with age. According to the National Cancer Registry in Poland in 2013 women aged 65+ accounted for 37.4% of the whole group, whereas deaths in this age group accounted for 55.9% of all deaths caused by breast cancer. This group of women is particularly challenging to treat because of the associated comorbidities and general health. Age alone is often considered as a factor in the decision process of the type of adjuvant treatment or even disqualifying from chemotherapy and / or molecular targeted therapy. Population of elderly patients has not been taken into consideration in many

clinical trials. Furthermore, the number of enrolled patients did not match the number of elderly patients in the actual population. Example could be HERA, a prospective Phase III study assessing the efficacy of adjuvant treatment with Herceptin, where only 16.2% of randomized patients were over 60 years old. For this reason, there is a need for comprehensive assessment of the course of anti-HER2 targeted therapies (Herceptin SC or Herceptin IV with or without Perjeta IV) in the population of older women. At the same time there is a need to try to answer the question of what part of the population of patients with HER2 positive breast cancer at the age of 70 years or above is not qualified for chemotherapy and targeted therapies and identifying the reason of disqualification for anti-HER2 therapy. Data concerning secondary study objectives will be analyzed among all included patients while primary safety objectives focus on the population subgroup defined as those patients who qualify for anti-HER2 therapy and are prescribed anti-HER treatment (Herceptin SC or Herceptin IV with or without Perjeta IV).

Objectives

Primary Objectives – Safety

The safety objectives of this study pertain to a subgroup consisting of patients treated with anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) and are as follows:

•To assess frequency of discontinuation of anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) caused by adverse events

•To evaluate safety of anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) and summarize frequency of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESIs)

•To evaluate frequency of anti-HER2 treatment interruptions, discontinuations and reintroductions

•To assess the completion of the assumed treatment plan (Herceptin SC or Herceptin IV with or without Perjeta IV). Treatment plan will be assumed as completed when patient completes 18 cycles or one year of treatment (for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy) or when patient continues treatment until progression, death or end of the observation in the study (for mBC patients).

Secondary Objectives – Effectiveness

The effectiveness objectives for this study are as follows:

•Summarize epidemiological information among all included patients: age, BMI, BSA, cigarette smoking, comorbidities (hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, COPD, rheumatoid arthritis, liver disease, and depression)

•Summarize all diagnostic proceedings performed before qualification for anti-HER2 therapy (including: ER/PgR, HER2 status by IHC/ISH)

•Summarize all information about any anticancer therapies administered before qualification or disqualification for anti-HER2 therapy (including: surgery, systemic therapy or radiotherapy)

•Summarize information concerning qualification process for anti-HER2 therapy and the reasons for disqualification

•Summarize all information about anticancer therapies administered concurrently with anti-HER2 therapy (hormonal or chemotherapy)

•Summarize information about timing and types of surgery and radiotherapy in eBC patients that at the start of the study received neoadjuvant anti-HER2 therapy with Herceptin SC.

Other Objectives (anti-HER2 treated subgroup only)

•Disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy

•First disease progression or death from any reason for mBC patients (whatever occurs first during treatment period in the study).

Amendment and Updates to Protocol

None

Study Design

This single cohort, observational, local, multicenter, prospective, primary data collection, non-interventional, Post Authorization Safety Study (NI-PASS) was to assess the safety and tolerance of treatment with anti-HER2 therapy in routine clinical practice.

Secondary goal of the study was to collect information about epidemiological characteristics, diagnostic and therapeutic proceedings, in elderly women (≥70 years old) with HER2-positive early, locally advanced or metastatic breast cancer, according to medical standard of care and reimbursement indications in Poland, following actual National Health Fund (NHF) - Drug Program "Treatment of Breast Cancer" and current version of SPC and about reasons why patients were disqualified from anti-HER2 therapy.

The following patients were enrolled into the study: all 70 years or older patients diagnosed with early, locally advanced or metastatic HER2 positive breast cancer who had agreed to participate in this study conducted in local research centers, regardless of the planned therapeutic proceedings. Recruitment for the study took place after confirmation of HER2 positive breast cancer and prior to qualification for the treatment.

Data were collected from patients treated with anti-HER2 therapies and from patients who were not prescribed (disqualified from) anti-HER2 therapy.

Duration of observation for each patient intended to be from the time of inclusion to the study until maximum 2 years after the last patient enrolled or the date of death (if death occurs first). Data on patients not qualifying for National Health Fund (NHF) - Drug Program "Treatment of Breast Cancer" were collected only on a screening visit and visit 1 and no further observation took place.

For certain analyses, a subgroup of this population was defined as those patients who qualify for and receive anti-HER2 therapy (Herceptin SC or Herceptin IV with or without Perjeta IV) according to records in actual NHF Drug Program "Treatment of Breast Cancer".

Based on information from patients and their medical history, Physicians collected the following data during visits:

•TNM classification of tumor at the time of diagnosis and stage at the time of recruitment

•microscopic diagnostic: verification of the diagnosis of breast cancer - execution of core biopsy (CB) or other possible methods of verification

•IHC/ISH panel (ER/PgR, HER2 status)

•pTNM classification

•WHO/ECOG performance status

•Age, height, weight, BMI, BSA, smoking

•Comorbidities: hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, liver disease, depression and others

•LVEF (left ventricular ejection fraction) - according to the records in actual NHF Drug Program "Treatment of Breast Cancer"

•Assessment of cardiotoxicity and occurrence of congestive heart failure (using CTCAE 4.0 criteria), and for CHF, in addition, assessment based on NYHA criteria

•Type of the previous surgery, radiotherapy, hormonal therapy or/and chemotherapy (including chemotherapy containing anthracyclines) as well as hormonal therapy and chemotherapy concurrent with anti-HER2 treatment

•In patients that start participation in the study receiving neoadjuvant therapy with Herceptin SC information about surgical operations and radiotherapy as well as subsequent change of anti-HER2 treatment will be collected

•Laboratory results and diagnostics required by NHF Drug Program "Treatment of Breast Cancer"

•Data on anti-HER2 treatment dosage and treatment interruptions, discontinuations and reintroductions

•Disease status assessment – disease recurrence, contralateral invasive breast cancer, second primary cancer, unacceptable toxicities or death from any cause

•Occurrence of adverse events - serious and non-serious adverse events (SAEs) and AEs of special interest (AESI)

•Concomitant medications.

If the patient continues treatment with anti-HER2 therapy (Herceptin with Perjeta IV) for more than 2 years (mBC patients according to the actual NHF Drug Program) after the inclusion to the observational study, an information were to be included in the study documentation that the patient is continuing treatment without progression, unacceptable toxicities and is no longer in observation in the study.

The study did not require that patients undergo any additional medical interventions, tests, or procedures.

Setting

In this study we planned to enroll 150 of HER2 positive breast cancer patients across up to 8 sites.

As of September 1, 2019, Roche lost the reimbursement for Herceptin IV, which increased market share of biosimilar for Herceptin. In addition, there was a tendency in many hospitals to reduce the use of the Herceptin SC form resulting from broad access of biosimilar forms and preferential reimbursement conditions system for IV presentation of drugs. Herceptin SC form has been limited in many places to patients who are ineligible for medical reasons to be given IV form (e.g. difficult access to the veins). SC has become an option only at sites with large number of patients after Hospital's Administration approval. These situations prevented the recruitment of the assumed number of patients for Herceptin IV / SC therapy, in addition, after discussions with the Researchers, it was confirmed that the extension of the recruitment period do not ensure that we would achieve the quantitative recruitment goal and do balance in groups of patients treated for eBC and mBC. The balance in these groups would be valuable due to probable existing differences in classification for therapy (one of which is radical in assumption and is limited in number of cycles and the other has a palliative assumption).

As a result of above mentioned reasons study has been prematurely terminated due to Sponsor's decision, with a cut-off date of 30-Sep-2019. A total of 48 patients have been screened with 45 fulfilling the inclusion criteria. Among them 39 patients (30 patients with mBC and 9 patients with eBC.) were included in ITT (IntentionToTreat) population, 35 in SP (Safety Population) and 6 in DDP (Disqualification from Drug Program Population).

First visit of the first patient took place on 17-Sep-2018 while the last visit of the last patient occurred on 30-Sep-2019. The final database lock point took place on 24-Apr-2020.

In total, patients were recruited by 10 physicians in 6 centers in Poland.

Subject and study size (including dropouts)

Elderly women (70 years old or above) diagnosed with HER2-positive breast cancer confirmed by validated immunohistochemistry (IHC) or in situ hybridization (ISH) methods.

The study enrolled only HER2-positive breast cancer patients who were eligible for anti-HER2 therapy as well as patients who were disqualified for anti-HER2 treatment.

Eligible patients scheduled for neoadjuvant, adjuvant or metastatic treatment with Herceptin SC or IV formulation with or without Perjeta IV in real world settings, according to actual NHF Drug Program "Treatment of Breast Cancer" in Poland and current SPC.

Patients must met all of the following criteria for study entry:

•Elderly postmenopausal female patients: ≥70 years of age

•Histologically confirmed HER2 positive breast cancer (all breast cancer stages, all patients)

•ER or PgR receptor status assessed in all patients

•Patients currently qualified for any anticancer treatment (including: surgery, systemic therapy – prior to the first administration of anti-HER2 treatment in NHF Drug Program "Treatment of Breast Cancer" or radiotherapy)

•All patients eligible or disqualified for anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) in accordance with actual reimbursement inclusion criteria in Poland (actual NHF Drug Program "Treatment of Breast Cancer") and current SPC

•Signed, written informed consent to data collection

Patients who met the following criteria were excluded from study entry:

•Patient was participating in any other clinical trial at the moment of enrollment

As no formal hypothesis was tested, all analyses are descriptive in nature. Therefore, sample size was not estimated, instead a number of 150 patients was selected based on calculations from NHF Drug Program "Treatment of the Breast Cancer" report and information received from Polish President of International Society of Geriatric Oncology (SIOG). It was assumed that 100 patients treated with anti-HER2 therapy would be enrolled for subgroup analysis from among all 150 HER2 positive breast cancer patients recruited to the study.

Study has been prematurely terminated due to Sponsor's decision, with a cut-off date of 30-Sep-2019. A total of 48 patients have been screened with 45 fulfilling the inclusion criteria.

Variables and Data Sources

Only variables, obtained according to routine clinical practice and following objectives were collected in this study.

Primary Safety Variables (anti-HER2 treated subgroup only)

•Discontinuations of anti-HER2 treatment

•Adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESIs)

•Dosage of anti-HER2 therapy (number of administered cycles as well as occurrence of interruptions, discontinuations, or reintroductions)

•The treatment plan completion – as patients will normally receive 18 administrations per year, in early or locally advanced breast cancer (neoadjuvant and adjuvant settings) treatment will be considered as complete after 18 administrations or one year of treatment, otherwise plan will be assumed as not completed. For mBC patients, treatment will be assumed as complete if it continues until progression, death or end of the observation in the study.

•Left ventricular ejection fraction assessed in routine clinical practice according to actual NHF Drug Program “Treatment of Breast Cancer” •Occurrence of unacceptable toxicities during anti-HER2 treatment

•Assessment of cardiotoxicity and occurrence of congestive heart failure (based on CTCAE 4.0 criteria) and, in addition, assessment of Congestive Heart Failure (CHF) based on NYHA criteria

Safety information were collected through the course of the study:
•All SAEs, regardless of whether they were related to Herceptin or Perjeta IV treatment
•All AEs regardless of whether they were related to Herceptin or Perjeta IV treatment
•All AESIs regardless of whether they were related to Herceptin or Perjeta IV treatment.

Secondary Effectiveness Variables

•Age, body mass index (BMI), body surface area (BSA), and cigarette smoking

•Comorbidities (hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, liver disease, and depression) and other

•Performance (WHO/ECOG) status

•Histological diagnostic for breast cancer by core biopsy or other verification method

•Progesterone receptor (PgR) status before administration of HER2 therapy

•Estrogen receptor (ER) status before administration of HER2 therapy

•Previous anticancer therapies (surgery, systemic therapy, or radiotherapy) administered before anti-HER2 therapy

•Disqualification of patients from anti-HER2 therapy

•Reasons of disqualification from anti-HER2 therapy (existing comorbidities, prior use of anti-HER2 therapy excluding from drug program (Herceptin, Perjeta IV), presence of adverse events – for example concurrent to prior chemotherapy/systemic therapy or caused by such therapy (such as use of anthracyclines and cardiotoxicity), sociologic issues, economic issues, patient refusal to be treated, others)

•Type of surgery, radiotherapy, hormonal therapy, or chemotherapy (including chemotherapy containing anthracyclines) planned and performed during the observational study

•Concomitant medications.

Other Variables of Interest (anti-HER2 treated subgroup only)

•Disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer, or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy

•First disease progression or death from any reason for mBC patients

Data Sources

Patients' data were collected prospectively during routine visits and subsequently recorded in CRFs. The degree of detail and completeness of data collected was dependent on local clinical practice.This was a non-interventional study and no additional patient's data, assessments, laboratory tests or visits except those collected/ performed as a routine clinical practice were required for the purpose of this study.

Data were collected from 6 oncology centers in Poland

Results

As mentioned earlier due to lost of reimbursement for Herceptin IV, some restriction to access to Herceptin SC and, as a result, the inability to recruit the assumed, statistically significant number of patients, due to Sponsor decision study was prematurely terminated. A total of 48 patients have been screened with 45 fulfilling the inclusion criteria. Among them 39 patients (30 patients with mBC and 9 patients with eBC) are included in ITT (Intention To Treat) population, 35 in SP (Safety Population) and 6 in DDP (Disqualification from Drug Program Population).

Primary objectives of this study were safety objective which are related to the 39 patients from safety population. In this population no cases of discontinuation, interruption or reintroduction of anti-HER2 treatment have been reported.

There were 15 patients (42.9%; 95% Confidence Interval (CI): 28.0% - 59.2%) with AEs occurring on or after the date of the first administration of IMPs – that is treatment emergent AEs. Three patients (8.6%; 95% CI: 2.3% - 23.3%) were affected with serious adverse events (SAEs) and four with severe adverse events (11.4%; 95% CI: 4.1% - 26.7%).

Six patients (17.1%; 95% CI: 7.8% - 33.2%) experienced adverse events related to anti-HER2 treatment (arthralgia, asthenia, diarrhoea, dermatitis, fatigue, leukopenia).

No cardiotoxic adverse events were reported in safety population. There were no AEs leading to death nor Adverse Events of Special Interest reported.

Three patients (8.6%; 95% CI: 2.3% - 23.3%) were affected with serious adverse events (SAEs) – in two cases described as not IMP related. One of this patients experienced a serious related AE (it was arthralgia where causality was connected to trastuzumab SC).

Four patients were affected with severe adverse events (11.4%; 95% CI: 4.1% - 26.7%) All severe AEs were described as not related to IMPs.

Among all AEs reported after the initiation of anti-HER-2 treatment anemia was reported in three patients (8.6% of all study participants), followed by polyneuropathy and asthenia (two patients in each case; 5.7%).

Maximum severity of events was spread across system organ classes (SOCs) with most of patients experiencing AEs of moderate intensity. In five patients adverse events were

evaluated as severe or medically significant, but not immediately life threatening. These were: anemia (three patients), asthenia and syncope (one case each)..

In total eight patients (17.8% of all enrolled) completed the study with six not qualifying to the National Health Fund (NHF) Drug Program, thus ending participation in the study during first visit. One patient qualified to a neoadjuvant therapy with trastuzumab SC participated in the study up until Visit 18, completed the study according to the plan. In one mBC patient a disease progression was reported. Participation of five patients (11.1% of all enrolled) has been terminated early with two being treated with a biosimilar drug (a protocol deviation), and termination dictated by physician decision in case of another two patients. For one patient termination was due to loss to follow-up. The majority of patients (N=32; 71.1%) were still in the treatment at the time the study has been closed.

Mean number of cycles of anti-HER2 therapy during this study were as follow: 7.2 (SD 1.6) cycles of Trastuzumab IV (N=5), 6.2 (SD 4.6) of Trastuzumab SC (N=32) and 9.0 (SD 4.3) of Pertuzumab IV (N=5).

Results of secondary objectives- effectiveness are summarize below. Epidemiological characteristics on ITT population is as follow: 30 patients with eBC with mean age 73.8 y, mean BMI 28.6, mean BSA 1.8 with 22 non-smokers and 3 current smokers and 5 past smokers with length of smoking respectively 26 y and 20 y; 9 patients with mBC with mean age 74.4 y, mean BMI 33.6, mean BSA 1.9 with 8 non-smokers and 1 current smoker with length of smoking 55 y.

Hypertension was the most common comorbidity in the ITT population (N=32; 82.1%), followed by Thyroid disease (N=8; 20.5%), Diabetes type 2 (N=7; 17.9%) and Coronary artery disease (N=6;17.9%). Among other diseases Cataract (N=3), Hypercholesterolemia (N=3) and Blood cholesterol increased (N=2) have been reported more than once.

During the screening assessment more than half of patients (N=23; 59.0%) were fully active with ECOG 0.Two patients were with ECOG 2. Over the course of the study worsening of performance status has been reported in six patients (in one case from 2 to 3, while all the remaining patients had performance deterioration from 0 to 1) and improvement in two patients (in each case from 1 to 0)

Results of diagnostic proceeding before qualification for anti-HER2 therapy performed are as follow: Histologic diagnosis was performed through core cut biopsy in all but one case (excisional biopsy). Breast cancer ImmunoHistoChemistry (IHC) assessment of HER2 receptor status was evaluated in most cases as 3+ (for ITT population N=34; 87.2%). In situ hybridization (ISH) was performed for 8 cases in ITT population.

In ITT populations two thirds of patients had a positive estrogen receptor status (N=27), 26 (66.7%) had positive progesterone status with 25 patients testing positively for both receptors.

Prior to screening 6 patients (15.4%) from ITT therapy undergoing either adjuvant (3 cases) or neoadjuvant treatment. Three patients in total received cyclophosphamide, with the same number treated with paclitaxel, two were treated with doxorubicin and one with epirubicin. One received hormonal therapy prior to screening visit (tamoxifen and letrozole respectively).

During observational study more than three-fourths of patients in the ITT population (N=31; 79.5%) received chemotherapy with paclitaxel and docetaxel being most common in eBC patients and docetaxel in mBC patients.

Hormonal therapy was used in eight eBC (26.7%) and two (22.2%) mBC patients with letrozole used in all eBC cases, while anastrozole treatment used in mBC group.

Prior to screening, in case of ITT population there were 11 patients (out of 39; 28.2%) who underwent tumorectomy (one patient) or mastectomy (10 patients).There was one case of bilateral mastectomy There were reported 6 sentinel lymph node biopsies and 5 axillary lymph node biopsies.

During this study surgery was performed in 9 patients (23.1%; all in eBC group) with six cases of sentinel lymph node biopsy, five mastectomies (one patient underwent bilateral mastectomy), three cases of axillary lymph node biopsy as well as tumorectomy and one quadrantectomy.

Six enrolled patients (13.3% of all enrolled) have not qualified to NHF Drug Program with following reasons: existing comorbidities (N=3), a failure to meet NHF Drug Program inclusion criteria (N=2), patient refusal (N=1) and other reasons given in two cases: a LVEF decreased and too small tumor. These patients form a disqualification from drug program population (DDP).

Discussion

In this study authors plan was to enroll 150 postmenopausal HER2 positive breast cancer patients across up to eight sites, and it was assumed that 100 patients from among that group would be qualified to NHF Drug Program “Treatment of the Breast Cancer”, receive anti-HER2 medication and would be observed for a period of up to two years (early, locally advanced and metastatic breast cancer patients).

Unfortunately due to the reimbursement situation (lost of reimbursement for Herceptin IV) and some restrictions on access to Herceptin SC (as described earlier) study had to be prematurely terminated (as it was impossible to meet the recruitment assumptions) and only 48 patients had been screened with 45 fulfilling the inclusion criteria. Among them 39 patients were included in ITT (Intention To Treat) population, 35 in SP (Safety Population) and 6 in DDP (Disqualification from Drug Program Population). This represents only about 30% of the assumed population.

Gathered data shows that in this safety population there were no cases of discontinuation, interruption or reintroduction of anti-HER2 treatment has been reported. There were no AEs leading to death nor Adverse Events of Special Interest reported. No cardiotoxic adverse events were reported in safety population.

Among 15 patients experiencing treatment emergent AEs only 6 patients (17.1%; 95% CI: 7.8% - 33.2%) experienced adverse events related to anti-HER2 treatment (arthralgia, asthenia, diarrhoea, dermatitis, fatigue, leukopenia). One of this patients experienced a serious related AE (it was arthralgia where causality was connected to trastuzumab SC).

All these AEs are listed in the SPC of trastuzumab and pertuzumab as adverse reactions reported in association with the use of products in clinical registration trials and in post-marketing experience but as this group of patients is so small and statistically not representative in any way, it is not possible to draw any conclusions regarding the safety of the anti-HER2 treatment in elderly patients (≥70 years old) with HER2 positive breast cancer nor notice the difference in the safety of therapy compared to younger patients.

The same situation applies to AEs described as not related to IMPs which were reported in 9 patients (anaemia, upper abdominal pain , mood altered, upper respiratory tract infection, alopecia, syncope, achynolysis, polyneuropathy, asthenia, rash, cough, lymphoedema, fatigue, mental disorder).The number of patients experiencing all AEs mention above is too small to draw any statistically justified conclusion about the frequency and specificity of occurrence and association of these AEs with the age of patients.

Six enrolled patients (13.3% of all enrolled) did not qualified to NHF Drug Program with following reasons: existing comorbidities (N=3), a failure to meet NHF Drug Program inclusion criteria (N= 2), patient refusal (N=1) and other reasons given (N=2): a decreased LVEF and too small tumor. Some of the comorbidities were repeated (Cardiac failure, Coronary artery disease, Hypertension, Type 2 diabetes mellitus, Thyroid disorder, Rheumatoid arthritis) and some of them are considered as civilization diseases of the modern world related to age and lifestyle but not necessarily to the age of 70 and above. Some of the comorbidities were also given as a reason of failure to meet NHF Drug Program inclusion criteria (lymphoma, asthma, Alzheimer's disease, hypertension, arrhythmia). We can summarize that numerous comorbidities (where some of them are simply contraindications to anti-HER2 treatment) influenced the decision of systemic anti-cancer therapy but it should be reminded that, due to small sample size (only 6 patients did not qualified to NHF Drug Program) no binding conclusions about what comorbidities are the most frequent and common for the patient of the age 70 and above and which are the drivers of disqualification can be drawn.

The results of secondary objectives of the study including information about epidemiological characteristics, diagnostic and therapeutic proceedings according to local standards and practice in this population collected for 39 patient (ITT population) were consistent with the epidemiological data of patients qualified for clinical trials and procedures associated with anti-HER2 treatment. Also, there are no characteristic features for a group over 70 years old in these data which are different than for the younger population.

Conclusion

Due to Roche's lost of reimbursement for Herceptin IV and widespread availability and preferential reimbursement model of biosymilars in hospitals, some restriction on Herceptin SC use while conducting the study it was impossible to meet the recruitment assumptions. Due to that fact the study ended prematurely with failure to achieve the planned recruitment of patients (39 patients in ITT population represents only about 30% of the assumed population) and that is why no binding conclusions assessing the diagnostics, therapeutic proceedings and safety of anti-HER2 treatment in population ≥ 70 years old with HER2 positive breast cancer in routine clinical practice in Poland can be drawn. Safety profile of anti-HER treatment in this study was consistent with that described in SPCs, no new safety data were detected. The results don't influence the risk-benefit assessment of the anti-HER2 therapy and do not have power to affect clinical decisions.

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