Non-Interventional Study (NIS) Protocol

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Comparative, multicenter study estimating association between germline DNA-repair genes mutations and PD-L1 expression level in breast cancer

Sponsor:

Tatarstan Cancer Center

The following Amendment(s) have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

NON-INTERVENTIONAL STUDY PROTOCOL SYNOPSIS

Comparative, multicenter study estimating association between germline DNA-repair genes mutations and PD-L1 expression level in breast cancer

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Study Site(s), number of subjects planned:

It is estimated that 240 patients will be entered into the study from 2 centers (Tatarstan Cancer Center and Republican State Clinical Oncological Dispensary in Ufa) in approximately 1 year.

Total planned Study period:

First subject in	January 2018
Last subject in	January 2019
Study Database lock	March 2019
Final Study Report	July 2019

Medicinal Products (type, dose, mode of administration) and concomitant medication

Not applicable. This is an observational study; therefore, patients are not assigned to a particular treatment by study protocol. Treatment will be according to current clinical practice.

Rationale for this Non-Interventional Study (NIS)

Currently there is no precise data concerning the prevalence and types DNA-repair genes mutations, which lead to Homologous Recombination-deficiency, and its correlation with PD-L1 expression in BC.

Objectives of this Non-Interventional Study

Primary objective

To reveal association between the presence of germline DNA-repair genes mutations and PD-L1 expression level in tumour and immune cells in breast cancer (to reveal the differences of PD-L1 high tumor rate between patients with hereditary BC who have clinically significant germline mutations in DNA-repair genes (HR- deficiency) and patients with sporadic BC without such mutations).

Secondary objectives

- To study the frequency of germline mutations forming the familial breast cancer in Tatarstan and Bashkortostan republics.

- To estimate the relation of the frequency of PD-L1 expression in tumour or/and immune cells with disease stage, receptor status (ER, PR, HER2neu), morphological type, Grade

- To estimate the relation of number of tumour-infiltrating lymphocytes (TILs) with disease stage, receptor status (ER, PR, HER2neu), morphological type, Grade and presence of clinically significant mutations in genes of DNA-repair system.

Study design

This is a multicentre, non-interventional, prospective study to be carried out in representative oncology departments / institutions in order to determine the association between the presence of germline DNA-repair genes mutations and PD-L1 expression level in tumour and immune cells in breast cancer. No additional procedures besides those already used in the routine clinical practice will be applied to the patients. Treatment assignment will be done according to the current practice.

It is planned to enroll approximately 240 subjects in Russian Federation.

PD-L1 expression in tumor and immune cells in FFPE tumor tissue samples is the primary variable in this study.

Genetic testing of germline mutations in DNA-repair system genes (NGS) in blood samples receiving on Screening/ Baseline Visit and PD-L1 expression testing (IHC) in FFPE tumor tissue samples will be carried out in Republican Clinical Oncological Dispensary, Kazan.

The investigated group will consist of patients with clinical features of hereditary BC and revealed pathogenic germline mutations in DNA-repair genes (TP53 MLH1 MSH2 MSH6 PMS2 EPCAM APC MUTYH CDKN2A CDK4 ATM KIT PDGFRA CDH1 CTNNA1 PRSS1 SPINK1 BRCA1 BRCA2 FANCI FANCL PALB2 RAD51B RAD51C RAD54L RAD51D CHEK1 CHEK2 CDK12 BRIP1 PPP2R2A BARD1 PARP1 STK11 XRCC3). The control group will consist of patients with sporadic BC without mutations in these genes.

The PD-L1 expression level in tumor and immune cells and number of TILs in FFPE tissue samples received prior to start of any antitumor treatment will be estimated in both groups.

Target subject population

Target study population will be women 18 years and older with BC diagnosed before enrolment into the study, consented to participate in this non-interventional study, who visit the oncology hospitals/departments in Kazan and Ufa.

Study variable(s):

Primary variable:

PD-L1 expression in tumor and immune cells in FFPE tumor tissue samples estimated by ICH is the primary variable in this study. The primary variable value will be represented as "PD-L1 high" and "PD-L1 low". PD-L1 expression for both TC and IC in the tumor microenvironment will be determined by the percentage of cells expressing PD-L1 at any intensity above background staining. PD-L1 will be defined as high if either ≥ 25% of TC or ≥25% of IC expressed PD-L1, and PD-L1 was defined as low if both < 25% of TC and <25% of IC expressed PD-L1.

Secondary variables:

<u>Patient characteristics:</u>

- Age
- ethnicity
- Family oncological history with pointed localization of cancer (BC, OC, Prostate cancer, Pancreatic cancer or other localizations) and relation degree
- Individual oncological history: BC, OC, pancreatic cancer or other localizations

<u>Disease information/ diagnostic procedures:</u>

- Disease stage and TNM classification
- Morphological classification, Grade (1/2/3)

- Receptor status: ER, PR, HER2neu
- Extent of the disease
- Profile of germline mutations in DNA-repair system genes
- Number of TILs
- PD-L1 expression in tumor and immune cells in FFPE tumor tissue samples estimated by ICH as “PD-L1 high” or “PD-L1 low” based on 50% cut-off. PD-L1 will be defined as high if either ≥ 50% of TC or ≥ 50% of IC expressed PD-L1, and PD-L1 was defined as low if both< 50% of TC and< 50% of IC expressed PD-L1.
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Statistical methods

A Non-Interventional Study is a study in which epidemiological methods including other methods that can be used to analyse human population health data.

All statistical analyses will be performed by statistical software system.

A comprehensive Statistical Analysis Plan will be prepared before database lock.

TABLE OF CONTENTS **PAGE**

LIST OF TABLES

LIST OF FIGURES

LIST OF ATTACHMENTS

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this NIS Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ADR	Adverse Drug Reaction
Assessment	An observation made on a variable involving a subjective judgement (assessment)
CRF	Case Report Form
LEC	Local Ethics Committee
PD-L1	Ligand of programed depth receptor
GCP	Good Clinical Practice
NIS	Non-Interventional Study
NISA	Non-Interventional Study Agreement
NISP	Non-Interventional Study Protocol
NISR	Non-Interventional Study Report
BC	Breast Cancer
OC	Ovarian Cancer
PI	Principal Investigator responsible for the conduct of a NIS at a site
PRO	Patient Reported Outcomes
PS	Performance Status
Variable	A characteristic of a property of a subject that may vary eg, from time to time or between subjects
WHO	World Health Organization
TILs	Number of tumor-infiltrating lymphocytes
IHC	Immunohistochemistry
NGS	Next generation sequencing
ER	Estrogen receptor
PR	Progesterone receptor

1. INTRODUCTION

1.1 Background

Breast cancer (BC) occupies the first place among malignancy in females (29.9% of all tumors in female patients in Russian Federation in 2015) [1].
One of the most perspective direction of the oncotherapy is anticancer immunotherapy – employment of inhibitors of immune checkpoints. Immune checkpoints inhibitors (such as anti-PD-1 and anti-PD-L1 antibodies) have shown good clinical efficiency in clinical research to cure such malignant tumor with high mutation load, as melanoma, lung cancer, and others.
One of the hypothesis of such effect states that, usually, more cancer neoantigens are synthetized in the tumors with high mutation load (driven by genome instability), causing severe lymphoid infiltration [2-3]. This situation is balanced by overexpression of such inhibitors of the immune response as PD-1 and PD-L1 [4 - 6].
Breast cancer – is relatively heterogenic tumor, with different genetic, morphological and phenotypic forms.
Despite relatively low expression of PD-L1 in BC in general, there are reasons to believe that genetic instability, driven by mutations in genes involved in DNA repair, can increase the immunogenicity and, thus, the expression of PD-L1 in BC.
To date, it is widely accepted that 5-10% of BC cases are represented by hereditary types, i.e. mediated by germline pathogenic mutations in genes of DNA reparation pathways. Hereditary breast cancer (HBC), as well as ovarian cancer (OC), caused by mutations in genes BRCA1, BRCA2, CHEK2, TP53 и PTEN, and others. Thus, one of the promising directions here is to understand the inter-relation among germline pathogenic mutations associated with HBC, and activity of PD-L1. It would allow to optimize selection of anti-PD-L1 therapy, by forming group of patients (matching criteria of HBC) with high level of PD-L1 expression in cancer cells and tumor-infiltrating lymphocytes.

1.2 Rationale for the proposed study:

It is important to mention, that nearly all information, accumulated on the HBC and OC in Russia is based on the analysis of the females of Slavic origin [7-8]. There are reasons to assume that representatives of other ethnic groups (total number of nationalities in Russian Federation exceeds 100) in Russia, have different from Slavs spectrum if founder-mutations in BRCA1/2 genes. Thus, generally accepted diagnostic procedures aimed on the detection of the most frequent in Slavs founder-mutations should result in high number of false-positive results [7].
For example, in the pool if patients with BC in Bashkortostan republic, mutation
5382insC BRCA1 are found in less than 4% of cases [11]. Among, patients in Sakha republic (Yakutia), typical for West and East European (Slavs) populations mutations 5382insC, 4153delA, C61G in BRCA1 was not detected at al. Such kind of discrepancy, suggests the domination of East-Eurasian component and low number of West-European lines of mtDNA and Y-chromosomes in the population of eastern regions of Russia [10, 12].
Also, currently there are no comprehensive studies in Russia on the frequencies of mutations in other than BRCA1/2 genes involved in DNA reparation.

Here we propose complex and comprehensive research program aimed to detect relation among presence of germline pathogenic mutations in the DNA repair network genes (including BRCA1/2) and frequency of high PD-L1 expression in cancer cells and tumor-infiltrating lymphocytes in BC.
Understanding of inter-relation of presence of germline pathogenic mutations in BC and expression of PD-L1 can become one of the important approaches to identify group of patients, responsive to therapy by inhibitors of immune checkpoints or to combined therapy by target (PARP inhibitors) and immunotherapeutic drugs.

2. NIS OBJECTIVES

2.1 Primary objective

To reveal association between the presence of germline DNA-repair genes mutations and PD-L1 expression level in tumour and immune cells in breast cancer (to reveal the difference of PD-L1 high tumor rate between patients with hereditary BC who have clinically significant germline mutations in DNA-repair genes (HR- deficiency) and patients with sporadic BC without such mutations).

2.2 Secondary objectives

- To study the frequency of germline mutations forming the familial breast cancer in Tatarstan and Bashkortostan republics.

- To estimate the relation of the frequency of PD-L1 expression in tumor or/and immune cells with disease stage, receptor status (ER, PR, HER2neu), morphological type, Grade

- To estimate the relation of number of tumor-infiltrating lymphocytes (TILs) with disease stage, receptor status (ER, PR, HER2neu), morphological type, Grade and presence of clinically significant mutations in genes of DNA-repair system.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This is a multicentre, non-interventional, prospective study to be carried out in representative oncology departments / institutions in order to determine the interrelation between the presence of germline DNA-repair genes mutations and PD-L1 expression level in tumour and immune cells in breast cancer. No additional procedures besides those already used in the routine clinical practice will be applied to the patients. Treatment assignment will be done according to the current practice.

It is planned to enroll approximately 240 subjects in 2 centers (Tatarstan Cancer Centre and Republican Clinical Oncological Dispensary Ufa.

PD-L1 expression in tumor and immune cells in FFPE tumor tissue samples estimated by IHC is the primary variable in this study. The primary variable value will be represented as “PD-L1 high” and “PD-L1 low”.

Genetic testing of germline mutations in DNA-repair system genes (NGS) in blood samples receiving on Screening/ Baseline Visit and PD-L1 expression testing (IHC) in FFPE tumor tissue samples will be carried out in Tatarstan Cancer Centre, Kazan.

The PD-L1 expression level in tumor and immune cells and number of TILs in FFPE tissue samples received prior to start of any antitumor treatment will be estimated in both groups.

The only one visit is planned for all patients in this study.

Information regarding patient demographics, the disease characteristics, and diagnostic tests results will be taken from the medical records.

Information about familial and individual oncological history will be received on the visit.

Material and methods:

IHC testing of PD-L1 expression level in tumor tissue samples will be conducted using VENTANA PD-L1 (SP263) Rabbit Monoclonal Primary Antibody. PD-L1 expression for both TC and IC in the tumor microenvironment will be determined by the percentage of cells expressing PD-L1 at any intensity above background staining. PD-L1 will be defined as high if either ≥ 25% of TC or ≥ 25% of IC expressed PD-L1, and PD-L1 was defined as low if both, <25% of TC and, <25% of IC expressed PD-L1.

Mutations analysis:

The germline mutations in follow panel of genes will be analysed by NGS:

TP53 MLH1 MSH2 MSH6 PMS2 EPCAM APC MUTYH CDKN2A CDK4 ATM KIT PDGFRA CDH1 CTNNA1 PRSS1 SPINK1 BRCA1 BRCA2 FANCI FANCL PALB2 RAD51B RAD51C RAD54L RAD51D CHEK1 CHEK2 CDK12 BRIP1 PPP2R2A BARD1 PARP1 STK11 XRCC3

DNA from tissue samples will be extracted using a QIAamp DNA Blood Mini Kit. DNA concentration will be measured on the spectrophotometer NanoVue Plus («GE Healthcare»). Preparing sequencing library will be performed using NimblGen SepCapEZ Choice («Roche»).

Sequencing will be performed on the Illumina MiSeq («Illumina»).

Bioinformatic analysis will be conducted as follows:

1. Trimming the adapter sequences and low-quality reads and using Cutadapt and Trimmomatic.

2. Mapping reads to a reference genome sequence (GRch37/hg19) using the algorithm BWA-MEM.

3. Quality control of input data, alignment, concentration and coverage of target regions using FastQC, BAMQC and NGSrich. Expected covering target regions - by up to 400x-600x, the proportion of target regions covered above 100x - at least 95%, which will detect somatic mutation content of about 1%.

4. Search for the nucleotide variation germinal mutations using GATK HaplotypeCaller + UnifiedGenotyper (to produce a combined VCF-file).

5. Search for the nucleotide variation of somatic mutations via Mutect2 + Strelka (to produce a combined VCF-file).

6. Processing consensus VCF-files using the program SnpSift (filter - read depth more than 10).

7. Annotation using SnpEff (analysis of all transcripts), ANNOVAR (allele frequency analysis ExAC, 1000G and ESP6500, algorithms the functional significance SIFT, PolyPhen2, Mutation Taster, FATMM, CADD, DANN, Eigen) and Alamut Batch (effect on splicing, database dbSNP, ClinVar, HGMD Professional), BIC database.

This pipeline has the following characteristics in the analysis our target panel of genes (exons + 50 bp flanking intron regions) with sample NA12878-GIABv3.2 (Precision FDA platform):

Precision: 100%

Recall: 100%

F-Measure:100%

Study Flow Chart

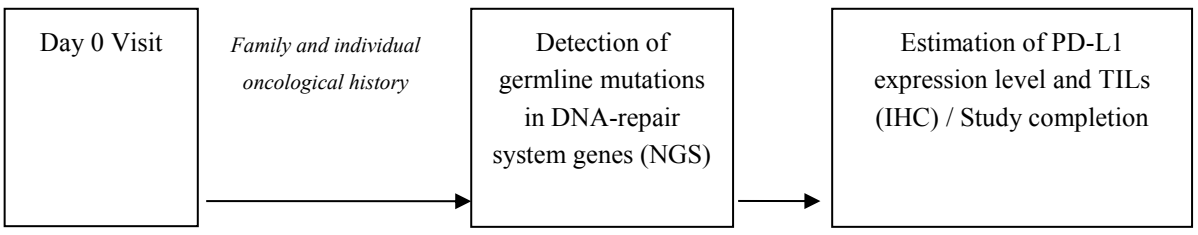

Table 1 Study Plan

Study procedures	Screening/ Baseline Visit (day 0)	Biomarker analysis	
		Detection of presence/absence of germline mutations in DNA-repair system genes (NGS) **(1-3 months after day 0)**	**Estimation of PD-L1 expression level and TILs (IHC)** **(1 month after NGS results)**
Informed consent	**X**		
Patient demographics	**X**		
Medical history	**X**		
Inclusion / Exclusion criteria	**X**		
Receiving of blood samples for NGS	**X**		
Genetic testing		**X**	
Request of FFPE tumor tissue samples for IHC	**X**		
IHC			**X**
Disease information	**X**		

4. SELECTION OF SUBJECT POPULATION

4.1 Investigators

Patients will be recruited by the specialists working at the Tatarstan Cancer Center in Kazan and at the Republican State Clinical Oncological Dispensary in Ufa.

4.2 Inclusion criteria

The subject population must fulfil all of the following criteria:

1. The voluntary obtained informed consent signed by both the subject and the investigator.

2. Females 18 years age or more.

3. Histologically confirmed BC with known hormone receptors and HER2neu receptors status, Grade of tumor, diagnosed before enrolment into the study.

4. Availability of FFPE tissue samples received prior to any type of antitumor treatment start. Tumour tissue samples must be satisfied IHC requirements for PD-L1 testing.

5. Ability of blood samples receiving for NGS germline mutations testing.

6. Completed medical records (stage, receptors status, demographic data)

4.3 Exclusion criteria

1. Any evidence of uncontrolled system pathology, active infections, active bleeding diathesis, renal graft, including virus hepatitis B, C or HIV.

2. Patients participating in clinical studies

3. Any medical condition, which on the opinion of the investigator may interfere the patient's participation in the study. The decision of patient exclusion can be made based on corresponding section in medical records (which must be completed prior to the visit in line with local standard) or on a visit information. It can include but not limited any medical conditions impeding sign informed concerns (for example mental disorder).

5. DISCONTINUATION OF SUBJECTS

5.1 Criteria for Discontinuation

Subjects may be discontinued from the NIS at any time. Specific reasons for discontinuing a subject from this NIS are:

1. Voluntary discontinuation by the subject who is at any time free to discontinue his / her participation in the NIS, without prejudice to further treatment

2. Incorrect enrolment e.g., the patient does not meet the required inclusion/exclusion criteria for the study.

5.2 Procedures for discontinuation

Subjects who discontinue should be asked about the reason(s) for their discontinuation. If possible, they should be seen and assessed by the investigator according to current practice.

6. THERAPEUTIC STRATEGY

6.1 Therapeutic strategy of a Non-Interventional Study

The assignment of a subject to a particular therapeutic strategy is not decided in advance by a protocol but falls within current practice.

7. STUDY CONDUCT

7.1 Restrictions during the study

No specific restrictions are applicable for this non-interventional study.

8. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

8.1 Primary variable

PD-L1 expression in tumor and immune cells in FFPE tumor tissue samples estimated by ICH is the primary variable in this study. The primary variable value will be represented as "PD-L1 high" or "PD-L1 low". PD-L1 expression for both TC and IC in the tumor microenvironment will be determined by the percentage of cells expressing PD-L1 at any intensity above background staining. PD-L1 will be defined as high if either ≥ 25% of TC or ≥ 25% of IC expressed PD-L1, and PD-L1 was defined as low if both< 25% of TC and< 25% of IC expressed PD-L1.

The following data to describe the primary objective will be collected:

The "PD-L1 high" cases rate in both patients with hereditary BC with pathogenic germline mutations in DNA-repair system genes and patients with sporadic BC without germline mutations in these genes.

8.2. Secondary variables

The secondary variables for this study are defined as:

<u>Patient characteristics:</u>

- Age
- ethnicity (Tatar, Bashkir, Slavic etc)
- Family oncological history with pointed localization of cancer (BC, OC, Prostate cancer, Pancreatic cancer or other localizations) and relation degree
- Individual oncological history: BC, OC, pancreatic cancer or other localizations

Disease information/ diagnostic procedures:

- Disease stage and TNM classification
- Morphological classification, Grade (1/2/3)
- Receptor status: ER, PR, HER2neu
- Extent of the disease
- Profile of germline mutations in DNA-repair system genes
- Number of TILs
- PD-L1 expression in tumor and immune cells in FFPE tumor tissue samples estimated by ICH as "PD-L1 high" or "PD-L1 low" based on 50% cut-off. PD-L1 will be defined as high if either ≥ 50% of TC or ≥ 50% of IC expressed PD-L1, and PD-L1 was defined as low if both< 50% of TC and< 50% of IC expressed PD-L1.

9. SAFETY ASSESSMENT

9.1 Definitions

9.1.1 Definition of an adverse event (AE)

"Adverse Event" or "AE" means a development of any untoward medical occurrence or the deterioration of a preexisting medical condition in a patient or clinical trial subject and which does not necessarily have a causal relationship with this treatment.

Adverse Event might be an unfavorable symptom (e.g. nausea, chest pain), factor (e.g. tachycardia, enlarged liver) or abnormal research result (e.g. deviation of laboratory rates, alteration of electrocardiogram) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following information should be reported: the use of medication during pregnancy (irrespectively of whether the pregnancy termination is known), and/or lactation, suicide and attempted suicide, suspected drug interactions.

9.1.2 Definition of serious adverse event (SAE)

A SAE is an AE, occurring at any dose or study phase that fulfils one or more of the following:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality/birth defect?

Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

NOTE.

- The Term "threat to life" with respect to SAEs means that there was an immediate risk of lethal outcome in the patient at the time of this event. This definition does not refer to event which hypothetically could result in lethal outcome, in that case, that if it had occurred at more severe form.

Medical events that are important, but do not result in lethal outcome or events that are directly life-threatening or requiring hospitalization, can also be considered as serious adverse events in those cases when, in accordance with sound clinical or scientific opinions, it is hazardous for the patient (or patient) and when in order to prevent one of the outcomes mentioned above medical or surgical intervention may be required. In this case, the event is considered as serious. Examples of such events are common or malignant tumor, allergic bronchospasm requiring intensive therapy in the emergency care department or at home, hematological disorders or convulsions that do not result in hospitalization or the development of drug dependency or drug abuse.

9.2 Non-interventional studies without special safety assessment

The active collection of any safety data will not be performed due to the non-interventional type of the study. Spontaneous reports of events related to safety will be reported in accordance with the pharmacovigilance regulatory requirements in the post-marketing period. It is imperative that all investigators participating in the study must be familiarized with this section of the Protocol. Primary investigator is responsible for training of co-investigators involved in the study upon the procedures of processing of spontaneously reported safety events, as well as with national pharmacovigilance regulatory requirements in Russia.

9.3 Non-interventional studies with special safety assessment

The active collection of any safety data will not be performed due to the non-interventional type of the study.

9.4 Report on safety information

9.4.1 Reports on adverse events

Safety monitoring will be carried out in accordance with the local pharmacovigilance requirements, used in standard medical practice in the Russian Federation.

9.4.2 Reports on unexpected adverse reactions at drug administration

Since it is not planned to research any study drug or vaccine, and monitoring of patients receiving standard therapy with drugs approved for use in the Russian Federation will be carried out. Safety monitoring and report of adverse events, including adverse reactions, not specified in the package inserts, will be performed in accordance with local pharmacovigilance requirements, applicable for standard medical practice in the Russian Federation.

9.4.3. Register of spontaneous reports of adverse events

The following principles of AEs registration, reported for patients participating in the study, should be applied: the investigator must report AEs within the pharmacovigilance procedures and in accordance with local regulatory requirements:

1. To the Federal Service on Surveillance in Healthcare: In written form to address: Russian Federation, 109074, Moscow, Slavyanskaya sq., 4, build. 1. Special form available at the moment on the following site should be used: http://www.roszdravnadzor.ru/i/upload/files/1308641445.19876-26263.doc.
2. To the correspondent pharmaceutical company, i.e. marketing company owning registration certificate on the correspondent drug, according to the local regulatory requirements.
3. In case if spontaneous AE is connected to the AstraZeneca drug, the investigator should submit information about AE to the Patient Safety department of AstraZeneca (in business and non-business hours) within 24 hours from the moment of adverse event information receipt via any of the following ways:
   - E-mail: AdverseEvents.ru@astrazeneca.com
   - Send a message and /or fill (Attachment 4 to the protocol) the AE Reporting Form;
   - Tel.: 8 (495) 799 56 99, Fax +7 (495) 799 56 98.

10. ETHICAL CONDUCT OF THE NON-INTERVENTIONAL STUDY

The Non-Interventional Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs.

The Investigator will perform the NIS in accordance with the regulations and guidelines governing medical practice and ethics in the country of the NIS and in accordance with currently acceptable techniques and know-how.

10.1 Ethics review

The final protocol of the Non-Interventional Study, including the final version of the Subject Informed Consent Form, must be approved or given a favourable opinion in writing by the Local Ethics Committee.

The Local Ethics Committee must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

10.1 Subject Informed consent

The Investigator at each site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the NIS. Subjects must also be notified that they are free to discontinue from the NIS at any time. The subjects should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated subject informed consent must be obtained before any specific procedure for the NIS is performed, including:

- Interview with the investigator
- Fulfil the questionnaires
- CRFs completion.

The Investigator must store the original, signed Subject Informed Consent Form. A copy of the signed Subject Informed Consent Form must be given to the subject.

10.2 Subject data protection

The Subject Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorise the collection, use and transmission of their personal data by the Investigator and by those persons who need that information for the purposes of the NIS.

The Subject Informed Consent Form will explain that NIS data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

11. STUDY MANAGEMENT

11.1 Monitoring, Quality Control and Archiving

The sponsor will carry out Monitoring and quality control in each centre to:

- Provide information and support to the investigator(s)

- Confirm that the research team is complying with the protocol and that data are being accurately recorded in the case report forms (CRFs)
- Ensure that the subject informed consent forms are signed and stored at the investigator's site
- Ensure that the CRFs are completed properly and with adequate quality.

11.1 Training of study site personnel

Investigators should be trained in conduction of the study. New information about the study should be timely given to doctors.

Investigators should be trained in the local regulatory pharmacovigilance procedures requirements. If information about AE, emerged against the background of the use of any investigational drug or vaccine becomes known to Investigator, Investigator must collect and transmit such information to mentioned above contacts within the time-frames regulated by local pharmacovigilance requirements.

11.1 NIS timetable and end of study

Before the first subject is enrolled in the NIS and any NIS related procedures are undertaken the following should be fulfilled

- Written approval of the NIS by the Ethics Committee and/or Regulatory Authorities, according to local regulations

The planned timetable for the NIS is estimated to be as follows:

First subject in	January 2018
Last subject in	January 2019
Study Database lock	March 2019
Final Study Report	July 2019

12. DATA MANAGEMENT

12.1 Collection, monitoring, processing of data and archiving

Each enrolled patient would be assigned with unique identification number (the least available from the pre-designed sequence). The individual Case Report Form (CRF), specially designed for this study, will be completed for each patient enrolled.

The collection of data from out-patient medical records or disease histories for hospitalised patient, as well as collection of data received by a physician during the routine patient examination will be performed. Any special data collection procedures are not stipulated within the framework of this study. All patient data will be recorded by the participating physician both in the source documents and in the CRF. Source documents are kept by physician.

Signed Informed Consents will be kept by the physician during the study and after the study completion.

Database will have to be completed, and then passed appropriate quality check, considered to be full and accurate, and then will be locked. Collected data will be analyzed.

Essential study documents must be retained by the participating physician for as long as needed to comply with local and international regulations. No source documents, containing patients' personal data, should be taken away from the physician.

12.2 Reporting and publication of data

- Investigators will prepare a Non-Interventional Study Report within 6 months after completion of the last subject.

- The results from the NIS will be presented to the Investigators as a Study report at Q4, 2019.

In accordance with the Declaration of Helsinki, both authors and publishers have ethical obligations. In publication of the results of the NIS, the authors are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available.

13. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

13.1 Statistical evaluation – general aspects

This is prospective non-interventional study designed as a case-control type for exact assessment of influence of the mutations in DNA repair genes presence on PD-L1 expression in BC. Case-control studies are often used for comparison of influence a predictive factor on a outcome. The primary variable (PD-L1 expression) and explored risk factor (mutations in DNA repair genes presence) will have nominal value: high/low and yes/no respectively.

A Non-Interventional Study is a study in which epidemiological methods including other methods that can be used to analyse human population health data.

All statistical analyses will be performed by means of the statistical software system.

A comprehensive Statistical Analysis Plan will be prepared before database lock.

13.2 Description of outcome variables in relation to objectives and hypotheses

The following measures will be analyzed:

- Proportion and number of PD-L1 high cases in investigational group.
- Proportion and number of PD-L1 high cases in control group.
- Proportion of PD-L1 high cases in different morphological variants patient's subgroups.
- Proportion of PD-L1 high cases in different receptor status (ER, PR, HER2neu) patients subgroups.
- Number of TILs in depends on germline mutation status, morphological variant, Grade, receptor status (ER, PR, HER2neu).
- The frequency of germline mutations forming the familial breast cancer in Tatarstan and Bashkortostan republics.
- Proportion of different BC subtypes in both investigational and base groups.
- Demographic characteristics, familial and individual history for all the screened patients.

13.3 Description of analysis sets

All Enrolled set will consist of all the subjects who signed informed consent to enter the study. Patient disposition and baseline characteristics and demography as well as analysis of the primary and secondary objectives will be based on the set.

All patients will be enrolled in 2 groups 1:1. The analyses of primary objective will be conducted based on the results in these groups:

- The investigated group will be consists of patients with clinical features of hereditary BC (according to NCCN breast and/or ovarian cancer genetic assessment guidelines V1.2017[22]) and revealed clinically significant (pathogenic) germline mutations in DNA-repair genes (TP53 MLH1 MSH2 MSH6 PMS2 EPCAM APC MUTYH CDKN2A CDK4 ATM KIT PDGFRA CDH1 CTNNA1 PRSS1 SPINK1 BRCA1 BRCA2 FANCI FANCL PALB2 RAD51B RAD51C RAD54L RAD51D CHEK1 CHEK2 CDK12 BRIP1 PPP2R2A BARD1 PARP1 STK11 XRCC3) regardless morphological type, grade, receptor status and extent of the disease.

- The control group will be consisting of patients with sporadic BC without germline mutations in DNA-repair genes (TP53 MLH1 MSH2 MSH6 PMS2 EPCAM APC MUTYH CDKN2A CDK4 ATM KIT PDGFRA CDH1 CTNNA1 PRSS1 SPINK1 BRCA1 BRCA2 FANCI FANCL PALB2 RAD51B RAD51C RAD54L RAD51D CHEK1 CHEK2 CDK12 BRIP1 PPP2R2A BARD1 PARP1 STK11 XRCC3) regardless morphological type, grade, receptor status and extent of the disease.

13.4 Method of statistical analysis

Considering the study objectives, the analysis strategy will be as follows:

A descriptive analysis approach will be used to analyse the study population, baseline data and clinical outcomes.

Descriptive statistics will include n, mean, median, standard deviation, minimum and maximum for continuous variables and n, frequency and percentage for categorical values. Proportion will be assessed together with 95% confidence interval, if applicable.

The assess of differences in pd-l1 high cases frequency between two groups and association of germline ddr-gene mutations and pd-l1 expression level will be performed by logistic regression with odds ratio calculation with 95% confidence interval

14. DETERMINATION OF SAMPLE SIZE

Today the data of PD-L1 expression level in breast cancer are limited. There are a few number of studies, which evaluated the frequency of PD-L1 expression in different breast cancer variants and the data of PD-L1 expression level in these studies are very differentiated depends on diagnostic approach, clone of antibodies and cut-off[17-21]. We have calculated 2 variants of sample size based on minimal and maximal literature quantity data, using the Chi-squared statistic (or z test). Due to the absence of exact data about PD-L1 expression in hereditary and sporadic breast cancer we calculated the sample size based on data from general BC population (mainly is represented by sporadic BC) and TNBC (significant part of which is represented by hereditary BC). In the articles used as basis for calculation[17-21] the authors assessed PD-L1 expression in tumor cells and the cut-off for PD-L1 positivity was 5%. In 2 studies estimated PD-L1 expression in total BC population as 4% and in TNBC as 11% the SP142 clone was used for IHC. We have found the only one study assessing concordance between SP142 and SP263 antibodies clones for IHC (on a subset of cases including BC) and the concordance was 95%. We are planning to assess the PD-L1 expression in both tumor and immune cells and use the 25% of PD-L1 positive cells as cut-off.

Considering the listed above we assume that the sample size will be near to a mean value between these two calculations.

Near 120 patients with breast cancer who have mutations in DNA-repair system genes and near 120 patients with breast cancer without mutations will be enrolled to the study in 2 centers:

Tatarstan Cancer Center, Kazan and Bashkortostan Clinical Oncology Center, Ufa. We will need to test near 390 patients for enrolling 240 patients (expected screen failure rate 35-40%). This data are based on the results of own pivotal study which has shown the frequency of clinically significant mutations in genes of DNA-repair system in familial BC 65%.

1. If α (two-tailed) =0,05, β =0,2, subject ratio in groups (q_1 and q2)=0,5/0,5, frequency of BC cases with high PD-L1 expression in sporadic BC group (based on the data in general population of BC[19]) P_0=0,217, frequency of BC cases with high PD-L1 expression in hereditary BC group (based on the data in TNBC population, significant part of the letter is represented by HBC[20]) P_1=0,559, that OR 4.574, RR= 2.576

The standard normal deviate for $\alpha = Z_\alpha = 1.960$
The standard normal deviate for $\beta = Z_\beta = 0.842$
Pooled proportion = $P = (q_1*P_1) + (q_0*P_0) = 0.388$
$A = Z_\alpha\sqrt{P(1-P)(1/q_1 + 1/q_0)} = 1.911$
$B = Z_\beta\sqrt{P_1(1-P_1)(1/q_1) + P_0(1-P_0)(1/q_0)} = 0.768$
$C = (P_1-P_0)^2 = 0.117$
Total group size = $N = (A+B)^2/C = 61$
Continuity correction (added to N for Group 0) = $CC = 1/(q_1 * |P_1-P_0|) = 6$
That sample size can be calculated as:

Sample size (with continuity correction)

	N	Outcome+	Outcome-
Group 1:	37	21	16
Group 0:	37	8	29
Total:	74	29	45

Sample size (without continuity correction)

	N	Outcome+	Outcome-
Group 1:	31	17	14
Group 0:	31	7	24
Total:	62	24	38

2. If α (two-tailed) =0,05, β =0,2, subject ratio in groups (q_1 and q2)=0,5/0,5, frequency of BC cases with high PD-L1 expression in sporadic BC group (based on the data in general population of BC[17]) P_0=0,04, frequency of BC cases with high PD-L1 expression in hereditary BC group (based on the data in TNBC population, significant part of the letter is represented by HBC[18]) P_1=0,11, that OR 2,966, RR=2,750

The standard normal deviate for $\alpha = Z_\alpha = 1.960$
The standard normal deviate for $\beta = Z_\beta = 0.842$
Pooled proportion = $P = (q_1 * P_1) + (q_0 * P_0) = 0{,}075$
$A = Z_\alpha \sqrt{P(1-P)(1/q_1 + 1/q_0)} = 1.032$
$B = Z_\beta \sqrt{P_1(1-P_1)(1/q_1) + P_0(1-P_0)(1/q_0)} = 0.439$
$C = (P_1-P_0)^2 = 0.005$
Total group size = $N = (A+B)^2/C = 442$
Continuity correction (added to N for Group 0) = $CC = 1/(q_1 * |P_1-P_0|) = 29$
That sample size can be calculated as:

Sample size (with continuity correction)

	N	Outcome+	Outcome-
Group 1:	250	28	222
Group 0:	250	10	240
Total:	500	38	462

Sample size (without continuity correction)

	N	Outcome+	Outcome-
Group 1:	221	24	197
Group 0:	221	9	212
Total:	442	33	409

3. Our assumption. If α (two-tailed) =0,05, β =0,2, subject ratio in groups (q_1 and q2)=0,5/0,5, frequency of BC cases with high PD-L1 expression in sporadic BC group P_0=0,14, frequency of BC cases with high PD-L1 expression in hereditary BC group P_1=0,30, that OR 2,633, RR=2,114

The standard normal deviate for $\alpha = Z_\alpha = 1.960$
The standard normal deviate for $\beta = Z_\beta = 0.842$
Pooled proportion = $P = (q_1 * P_1) + (q_0 * P_0) = 0{,}220$
$A = Z_\alpha \sqrt{P(1-P)(1/q_1 + 1/q_0)} = 1.624$
$B = Z_\beta \sqrt{P_1(1-P_1)(1/q_1) + P_0(1-P_0)(1/q_0)} = 0.684$
$C = (P_1-P_0)^2 = 0.026$

Total group size = N = $(A+B)^2/C$ = 208
Continuity correction (added to N for Group 0) = CC = $1/(q_1 * |P_1-P_0|)$ = 13
That sample size can be calculated as:

Sample size (with continuity correction)

	N	Outcome+	Outcome-
Group 1:	117	35	82
Group 0:	117	16	101
Total:	234	51	183

Sample size (without continuity correction)

	N	Outcome+	Outcome-
Group 1:	104	31	73
Group 0:	104	15	89
Total:	208	46	162

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Attachment 1.[23]
TNM classification of BC

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor

Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1	Tumor ≤ 20 mm in greatest dimension
T1mi	Tumor ≤ 1 mm in greatest dimension
T1a	Tumor > 1 mm but ≤ 5 mm in greatest dimension
T1b	Tumor > 5 mm but ≤ 10 mm in greatest dimension
T1c	Tumor > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumor > 20 mm but ≤ 50 mm in greatest dimension
T3	Tumor > 50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional lymph nodes (N)	
Clinical	
NX	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures

N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence*of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s), with or without level I, II axillary node involvement, or in clinically detected * ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s), with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)
*"Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis on the basis of fine-needle aspiration (FNA) biopsy with cytologic examination.	
Pathologic (pN)*	
pNX	Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically. *Note:* Isolated tumor cell clusters (ITCs) are defined as small clusters of cells ≤ 0.2 mm, or single tumor cells, or a cluster of < 200 cells in a single histologic cross-section; ITCs may be detected by routine histology or by immunohistochemical (IHC) methods; nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated
pN0(i-)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) ≤ 0.2 mm (detected by hematoxylin-eosin [H&E] stain or IHC, including ITC)
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (reverse transcriptase polymerase chain reaction [RT-PCR])
pN0(mol+)	Positive molecular findings (RT-PCR) but no regional lymph node metastases detected by histology or IHC

pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes and/or in internal mammary nodes, with metastases detected by sentinel lymph node biopsy but not clinically detected†
pN1mi	Micrometastases (> 0.2 mm and/or > 200 cells, but none > 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes (at least 1 metastasis > 2.0 mm)
pN1b	Metastases in internal mammary nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected†
pN1c	Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected†
pN2	Metastases in 4-9 axillary lymph nodes or in clinically detected‡ internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least 1 tumor deposit > 2.0 mm)
pN2b	Metastases in clinically detected‡ internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in ≥ 10 axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected‡ ipsilateral internal mammary lymph nodes in the presence of ≥ 1 positive level I, II axillary lymph nodes; or in > 3 axillary lymph nodes and in internal mammary lymph nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected†; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ≥ 10 axillary lymph nodes (at least 1 tumor deposit > 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected‡ ipsilateral internal mammary lymph nodes in the presence of ≥ 1 positive axillary lymph nodes; or in > 3 axillary lymph nodes and in internal mammary lymph nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected†
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
*Classification is based on axillary lymph node dissection, with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel	

node"—for example, pN0(sn). † "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination. ‡ "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis on the basis of FNA biopsy with cytologic examination.	
Distant metastasis (M)	
M0	No clinical or radiographic evidence of distant metastasis
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven > 0.2 mm

Attachment 2.[23]

Staging of BC according to TNM

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0

	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Attachment 3.

Clinical features of hereditary BC according to NCCN breast and/or ovarian cancer genetic assessment guidelines V1.2017[22]

- Anyone with a family history of one or more of the following:
  - A blood relative with a known mutation in a gene that increases cancer risk
  - A blood relative with two or more primary breast cancers
  - Two or more relatives with breast cancer on the same side of the family with at least one diagnosed before age 50
  - A blood relative with ovarian cancer
  - A close blood relative with breast cancer before age 45
  - A blood relative with male breast cancer
- Anyone of Ashkenazi Jewish ancestry with breast, ovarian, or pancreatic cancer at any age.
- Anyone with a cancer diagnosis and one or more of the following:
  - A blood relative with a known mutation in a gene that increases cancer risk

    - Breast cancer at or before the age of 50
    - Triple-negative breast cancer at or before the age of 60
    - Ovarian, fallopian tube, or primary peritoneal cancer at any age
    - Male breast cancer at any age
- Anyone with breast cancer at any age and one or more of the following:
    - A blood relative with a known mutation in a gene that increases cancer risk
    - An Ashkenazi Jewish ancestor
    - A close blood relative with breast cancer before age 50
    - A close blood relative with ovarian cancer
    - A second primary breast cancer
- Two or more close blood relatives with breast cancer with at least one diagnosed before age 50
- Anyone with a personal or family history of three or more of the following, especially if any of the cases are diagnosed before age 50:
    - Pancreatic cancer
    - Prostate cancer
    - Melanoma
    - Sarcoma
    - Adrenal cancer
    - Brain tumors
    - Leukemia
    - Uterine cancer
    - Thyroid cancer
    - Kidney cancer
    - Diffuse gastric cancer
    - Colon cancer

Attachment 4. AE Reporting Form

AstraZeneca

ФОРМА СООБЩЕНИЯ О НЕЖЕЛАТЕЛЬНОМ ЯВЛЕНИИ

Local / AZ ref: _____

Первичное сообщение: **Повторное сообщение:**

1. Сведения о пациенте

Информация о пациенте (название ЛПУ, номер карты)

Дата рождения или возраст ☐ Муж. ☐ Жен.

Вес кг Рост см

Национальность

Сообщено ли в регуляторные инстанции ☐ да ☐ нет

Заполняется сотрудниками АстраЗенека
Когда было получено извещение_____
Соответствует ли извещение критериям срочного отчета? ☐ да ☐ нет

2. Сведения о лице, предоставившем данные о нежелательном явлении

ФИО

Адрес

Почтовый индекс

Страна Номер телефона

Профессия:
☐ Врач ☐ Провизор/фармацевт ☐ Другой медицинский работник
☐ Не связан с медициной* *Подробнее _____

Подпись: **Дата:**

3. Название ЛС	Серия	Показание к применению	Доза и кратность приема	Способ введения	Дата начала приема	Дата окончания приема	Действия в отношении ЛС

4. Описание нежелательного явления (диагноз или симптомы/синдромы)	Дата возникновения НЯ	Продолжительность НЯ или дата его прекращения	Выраженность НЯ	Исход НЯ*
			☐Слабая☐Сред.☐Сильная	
			☐Слабая☐Сред.☐Сильная	

Проявления НЯ уменьшились после отмены или уменьшения дозы ЛС? ☐ да ☐ нет ☐неизвестно

Проявления НЯ возобновились после возобновления приема ЛС? ☐ да ☐ нет ☐неизвестно

*** Исход**
1 = Полное выздоровление
2 = Улучшение
3 = Без улучшения
4 = Выздоровление с остаточными явлениями
5 = Летальный исход
6 = Неизвестно

5. Информация о проведенном обследовании и лечении

Связано ли НЯ с приемом данного ЛС? ☐ да ☐ нет **Обоснование**

6. Является ли нежелательно явление серьезным? ☐ да ☐ нет **Если да, отметьте подходящие из перечисленных ниже признаков**

Смерть	Представляет угрозу для жизни	Госпитализация / продление госпитализации	Длительная или постоянная нетрудоспособность/ инвалидность	Врожденная аномалия/ врожден. дефект	Значимое медицинское событие
☐	☐	☐	☐	☐	☐

В случае смерти указать причину:

Дата смерти: _____

В случае смерти – было ли произведено вскрытие?
☐ да ☐ нет (если «да», укажите результат)

7. Анамнез и сопутствующие заболевания
(в том числе, вредные привычки, непереносимость лекарственных средств, аллергические реакции, профвредности и др.)

8. Сопутствующая терапия (исключая ЛС, применявшиеся для данного нежелательного явления)	Показание	Суточная доза	Способ введения	Начало приема	Окончание приема

Сотрудник АЗ, первым узнавший о НЯ	**ФИО**	**Дата**	**Телефон**	**Факс**	**e-mail:**
Сотрудник АЗ, подавший данный отчет в Корпоративную Базу Данных	**ФИО**	**Дата**	**Телефон**	**Факс**	**e-mail:**