SPONSOR:

Merck Sharp & Dohme Limited
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(hereafter referred to as the Sponsor or MSD)

TITLE:

A *R*etrospective *E*valuation of *P*D-*L1* expression on primary non-small *c*ell lung cancer samples and *a*ssociated involved hilar or mediastinal lymph nodes (N1 or N2) (*REPLICA*).

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List of Abbreviations (Optional)

AE	*Adverse event*
CAC	*Clinical Adjudication Committee*
EMA	*European Medical Association*
FDA	*Food and Drug Administration*
GPRD	*General Practice Research Database*
ICD-9	*International Classification of Disease, 9th Modification*
IEC	*Independent Ethics Committee*
ISERP	*Independent Safety Epidemiology Review Panel*
PASS	*Post-Authorization Safety Surveillance*
SAP	*Statistical Analysis Plan*
SOP	*Standard Operating Procedure*

PROTOCOL SUMMARY

Title	A Retrospective Evaluation of PD-L1 expression on primary non-small cell lung cancer samples and associated involved hilar or mediastinal lymph nodes (N1 or N2) (REPLICA).
Vendor/Collaborator	N/A
Rationale	The aim of this study is to evaluate whether there is heterogeneity of PD-L1 expression, between the primary NSCLC tumours and the associated hilar/ mediastinal lymph nodes (LNs) from the same patient at the time of lung resection.
Primary Objective(s)	Correlation of PD-L1 expression in the primary site (lung) and associated hilar or mediastinal LNs (N1 and N2)
Study Design	Samples (primary tumour and hilar/mediastinal LNs, N1 or N2) from 500 consecutive chemotherapy naïve patients who have undergone lung resection and hilar/ mediastinal lymphadenectomy for NSCLC (squamous and non-squamous cell cancer) without primary systemic treatment or Radiotherapy have been collected and will be analysed for PD-L1 expression. All tissue samples will be anonymized.
Study Population	1000 samples from 500 patients
Study Duration	9 months
Exposure and Outcome	Analysis of expression of PD-L1 in the primary tumor and in the associated metastatic lymph nodes
Statistical Methods	As the data is categorical, There are 3 possible outcomes: ➢ A (<1%) ➢ B (≥1-49%) ➢ C (≥50%) An **analysis of proportion** will be performed
Sample Size and Power Calculations	1000 samples from 500 patients will be analysed. No power calculations will be used in the analysis.
Limitations	This is a retrospective study with archival tissue samples collected and preserved by different staff members. Some variations in collection and storage may have occurred.

1 Background and Rationale

1.1 Background

Immunotherapy has changed the landscape in treating non-small cell lung cancer. Recently published data shows that about one quarter of non-small cell lung cancer (NSCLC) patients show overexpression of programmed death ligand (PD-L1) protein which is defined as membranous PD-L1 expression on more than 50% of tumour cells regardless of staining intensity (1,2). These patients show higher response rates and better progression free survival (PFS).

Possible PD-L1 intratumour heterogeneity (3) as well as expressional differences between the primary tumor and metastatic sites (LNs or visceral metastases) may play a role in responses seen with immunotherapy.

There is confusion on how PD-L1 expression (homogeneous vs heterogeneous) can affect selection of patients and response to treatment
Also the dynamic of PD-L1 expression in different sites of disease is unknown and this may have implications on biopsy, and staging and also on treatment choice (immunotherapy alone vs immunotherapy and chemotherapy (treatment with high toxicity to be probably reserved for patients with significant heterogeneous expression) vs Immunotherapy and local treatment for sites with low expression of PDL1 (surgery, RT, RFA) (4)

There is no data regarding the possible difference of expression of PD-L1 between the primary tumour and the hilar/ mediastinal lymph nodes

1.2 Rationale

This study will give information on the expression of PD-L1 between primary tumour and involved LNs. Therefore, the study may shed some light in terms of appropriateness of sampling from primary tumour or lymph nodes and may be a step towards a better understanding of potential prognostic factors for anti-PD1/anti-PDL1 therapies. This will help to understand the possible differences in PD-L1 expression and implication in treatment planning.

Objectives and Hypotheses

2.1 Primary Objective(s) & Hypothesis(es)

- To analyse the correlation of PD-L1 expression in the primary site (lung) and associated hilar/mediastinal LNs (N1 and N2) in NSCLC looking at all variables in both primary tumour and hilar/ mediastinal LN.

2.2 Secondary objective(s) & hypothesis

- Correlate the PD-L1 expression with:
  - Histology

- Tumour size
- tumour location
- Predominant adenocarcinoma subtype
- Lymphovascular invasion

- Clinical characteristics
- age
- sex
- smoking history
- PET SUV data if available

3 METHODOLOGY

3.1 Summary of Study Design

Samples (primary tumour and hilar/mediastinal LNs) from 500 patients who underwent lung resection and hilar and/or mediastinal lymphadenectomy for NSCLC (squamous and non-squamous cell cancer) without primary systemic treatment or Radiotherapy will be collected and analysed for PD-L1 expression. The samples will include core biopsies or will include looking at 2 areas of the resected material to mirror core biopsies. These will be included to reflect real world practice as many samples are taken as core biopsies

Expression of PD-L1 will be analysed on tumour samples in both primary tumours and hilar/ mediastinal LNs using the 22C3 pharmdx DAKO assay (5).

This is a retrospective observational study with no Investigational Medicinal Product involvement. Two researchers will identify the archived cases from GSTT/KCL tissue bank+/- satellite centre to be identified in due course checking all the cases fulfil the inclusion/exclusion criteria starting from 1st Jan 2018 going back up to five years until 500 unique cases of NSCLC eligible samples are identified. All samples will be anonymized and ethics approval obtained. Most of the patients involved in the analysis have had a tissue bank/research consent form signed at the time of the lung surgery (consent form attached as an appendix). As soon as all the required samples are identified (tumours from primary site and involved LNs), they will be anonymized and sent to the lab for PD-L1 analysis.

Once all the cases are identified, histology slides will be retrieved and reviewed to check the quality and quantity of the tumour, using the standard NHS Quality Assurance method (this is the standard procedure for pathology labs), and select a representative block for primary tumour and metastatic tumour in the lymph node, respectively. Each primary and associated lymph node that has more than 100 neoplastic cells in the selected block, will be tested. When metastasis is present in more than one lymph node, the node furthest away from the primary tumour with more than 100 neoplastic cells will be used and the number of involved nodes recorded.

Three blocks will be taken from each resection and the pathologist will take the block with the highest percentage of tumour cells (following H&E) while the lymph node sample would have to have at least 100 cells – a minimum of 100 cells is required for an accurate assessment of PD-L1 expression according to the 22C3 pharmdx DAKO assay. There is no evidence to suggest the station of the LN affects PD-L1 expression. The LN furthest from the primary tumour will be chosen for analysis if there are N1 and N2 available (LNs a few mms from the primary may have the same pattern of disease as the primary).

The selected blocks will be retrieved and processed using DAKO PD-L1 immunohistochemistry 22C3 pharmDx Kit. PD-L1 stained slides will be reviewed by two pathologists independently, using the recommended scoring system. For cases where there is discrepancy, the two histopathologists will review the stains jointly and the consensus score will be used for data analysis.

The tumour proportion score (TPS) will be documented for each sample according to the following categories:

- PD-L1 negative: <1%
- ≥ 1-49%
- ≥ 50%

Materials:

500 unique samples from the primary tumour and 500 samples from matched involved LNs retrieved at the time of surgery will be evaluated for PD-L1 expression. Levels of PD-L1 expression in the primary tumour and matched LNs will be reported by appropriately trained pathologists. In total 1000 retrospective paraffin-embedded samples will be tested and reported for PD-L1 expression

3.2 Study Population

The study population includes 500 consecutive patients (preliminary and interim analysis after the first 100 samples) with early stage non small cell lung cancer, adenocarcinoma or squamous cell carcinoma or large cell carcinoma NOS (not otherwise specified) who underwent an anatomical lung resection and mediastinal lymph node dissection at Guy's Hospital and for which adequate tissue and consent is available. No patient received any induction treatment (chemotherapy or radiotherapy).

Patient with a diagnosis of neuroendocrine tumors (carcinoid, small cell lung cancer) will be excluded

Patients with no lymphadenectomy performed will be excluded

3.3 Inclusion Criteria

- Histological diagnosis of non-small cell carcinomas, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma NOS (not otherwise specified)
- Surgical resected primary lung tumour with lymph node (N1 and/or N2) metastasis
- Adequate quantity and quality of tumour tissue for research (section 3.1)
- Documented ethical approval for use of the sample and associated clinical data.
- Available clinical and demographic data

3.4 Exclusion Criteria

- Histology subtype other than NSCLC (described above)
- Pathology samples that do not meet the criteria to be defined in the laboratory manual.
- Cases for whom the mandatory set of required demographic, clinical, treatment and outcome data are not available
- Patients treated with neoadjuvant therapy or prior radiotherapy.

4 Variables and Epidemiological Measurements

This is a retrospective non-interventional study; Expression of PD-L1 between the primary tumour and the LNs will be analysed using the FDA approved 22C3 pharmdx DAKO assay. Clinical, demographical and pathological variables will be collected (see table in section7.1).

4 Variables and Epidemiological Measurements

This is a retrospective non-interventional study; Expression of PD-L1 between the primary tumour and the LNs will be analysed using the FDA approved 22C3 pharmdx DAKO assay. Clinical, demographical and pathological variables will be collected (see table in section7.1).

Standard statistical methods will be used to compare the PD-L1 expression between primary tumour and metastatic tumour, and to evaluate associations between PD-L1 expression in primary and metastatic tumour, and tumor histology. Variables that will be looked at include:

- sex
- age
- history of smoking
- performance status
- site of disease
- tumour location (upper or lower lobes),
- tumour cell type,
- maximum diameter of the tumour
- visceral pleural invasion
- lympho-vascular invasion

4.2 Outcomes

The primary outcome will be the expression of PDL1 in the primary tumor and in the hilar/ mediastinal lymph nodes.

The secondary outcome will be to correlate the expression of PD-L1 of primary tumor and involved lymph node with clinical (age, sex, smoking history, PET SUV data when available) and pathological variables (histology, size, predominant subtype, lymphovascular invasion).

4.3 Covariates

N/A

5 STUDY PROCEDURES

5.1 General Informed Consent

Patients involved in the analysis have previously signed a tissue bank/research consent form at the time of the lung surgery allowing research to be carried out on samples taken during surgical procedures. Because all the samples will be anonymized and the pathologist/researcher will not have access to the clinical data all tumors samples retrospectively collected can be used. A template of the consent form is included in Section 12

6 Safety Reporting and Related Procedures

6 Safety Reporting and Related Procedures

Adverse Event Reporting Language for Non-Interventional Study Protocols

Introduction

This is a non-interventional study based on secondary use of data collected from healthcare professionals or consumers for other purposes, including samples previously collected for other purposes.. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

6.1 Adverse Event Reporting/ Adverse Device Event (ADE) Reporting:

6.1.1 INVESTIGATOR RESPONSIBILITY:

Although adverse events are not actively solicited in this study, there are certain circumstances in which individual adverse events will be reported. For example, during review of medical records or physician notes (paper or electronic), to collect data as required by the protocol, if a notation of a serious adverse reaction (SAR), including death, or a non-serious adverse reaction (NSAR) to any MSD product is identified, the event must be reported according to Table 1. Similarly, if the investigator becomes aware of any device event, adverse device event (ADE) or incident with 22C3 pharmdx DAKO assay, the event must be reported according to Table 1. The investigator must evaluate each incident, device event and adverse device event for causality and record causality on the medical device form for each device event reported.

Similarly, pre-specified Health Outcomes of Interest (HOIs) that meet criteria for SAR/NSAR, special situations, and any spontaneously reported AEs must be reported according to Table 1.

Table 1: AE Reporting Timeframes and Process for Investigators and Vendors

EVENT TYPE	**INVESTIGATOR TIMEFRAMES**
	Investigator to MSD [
SAR Pre-specified HOI that meets criteria of SAR Serious Special Situation, regardless of causality Incident	24 hours from receipt
Device Event Adverse Device Event	1 BD/3 CD from receipt
NSAR Pre-specified HOI that meets criteria of NSAR Non-serious Special Situation, regardless of causality	10 CD from receipt
Spontaneously reported adverse events for MSD products-submit using above timeframes	
If the investigator elects to submit AEs for **non-MSD products**, they should be reported to the market authorisation holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.	
Follow-up to any event-submit using above timeframes	
BD-Business Day; CD-Calendar Day	
AE reports from investigators must be transmitted via fax, secure email (if available), or entered directly into vendor's electronic data collection (EDC) platform, if utilised. **Investigator to MSD:** Applies to studies that do not have a vendor managing AEs.	

Submitting AE Reports to MSD UK and Ireland Pharmacovigilance Department: All AEs must be submitted to MSD UK and Ireland PV department via FAX # 0032 2402 5990 , in English using an AE form (attached) for reporting to worldwide regulatory agencies as appropriate All incidents, device events and adverse device events must be submitted per the procedures above using the medical device form.

6.2 DEFINITIONS

6.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

6.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

6.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalisation, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalisation.

6.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 6.2.3.

6.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent

6.2.6 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are pre-specified clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnosis, treatment or procedures. Examples of HOIs include syncope or hypoglycaemia collected as study endpoints. HOIs must be assessed as part of AE collection and may meet criteria for AE reporting. Specifically, the investigator must assess each HOI for serious criteria and causality. If the HOI meets criteria specified in the protocol for AE reporting, then it must be reported as such.

6.2.7 Sponsor's Product

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

6.2.8 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form for each reported event in relationship to a Sponsor's product.

Secondary Data Collection
Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed should be reported as NSAR/SARs. During review of secondary data, causality should never be assigned retrospectively.

6.2.9 Medical Device

Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,
-

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

6.2.10 Device Event

Any malfunction [1] or deterioration in the characteristics or performance of a device, including inadequacies in the labeling or instructions for use, that led to or could have led to an untoward event for the user or any person. Examples include broken threads of IUD, bent needle, leakage or breakage.

- Device Events do not necessarily need to involve a user or any other person.

[1] Malfunction

The failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

6.2.11 Adverse Device Event

- Any adverse health outcome related to the use of a device or device-like features of a drug delivery system

Examples of Adverse Device Events:

- Changes in bleeding patterns or flow while on IUD
- Mild infection while using dental implant

6.2.12 Incident (including malfunction):

- Any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.

  Note: Not all medical device incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- A Medical device **incident** associated with a device happened

- AND

- The Medical device **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health

A serious deterioration in state of health can include any of the following:

- Life-threatening illness, even if temporary in nature
- Permanent impairment of a body function or permanent damage to a body structure
- Any indirect harm as a consequence of an incorrect diagnostic or IVD test results when used within instructions for use
- Fetal distress, fetal death or any congenital abnormality or birth defects
- Condition necessitating medical or surgical intervention, including hospitalization or prolongation of existing hospitalization to prevent one of the above

- An other important medical event/considered medically significant.

- **Examples of Reportable Medical Device Incidents**
-
- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse
- A participant's study treatment is interrupted or compromised by a medical device failure
- A misdiagnosis due to medical device failure leads to inappropriate treatment
- A participant's health deteriorates due to medical device failure

6.2.13 Indirect Harm

In the majority of cases, diagnostic devices IVDs and IVF/ART medical devices will, due to their intended use, not directly lead to physical injury or damage to health of people (harm). These devices are more likely to lead to indirect harm rather than to direct harm. Harm may occur as a consequence of the medical decision, action taken/not taken on the basis of information or result(s) provided by the device or as a consequence of the treatment of cells (e.g. gametes and embryos in the case of IVF/ART devices) or organs outside of the human body that will later be transferred to a patient.

Examples of indirect harm include:

- misdiagnosis
- delayed diagnosis
- delayed treatment
- inappropriate treatment
- absence of treatment
- transfusion of inappropriate materials
-

Indirect harm may be caused by

- imprecise results
- inadequate quality controls
- inadequate calibration
- false positive or
- false negative results

6.3 Sponsor Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory agencies, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7 Statistical Analysis Plan

7.1 Statistical Methods

7.1 Statistical Methods

This is a non-interventional study;
Expression of PD-L1 between the primary tumour and the LNs will be analysed using the FDA approved 22C3 pharmdx DAKO assay.
Clinical, demographical and pathological variables will be collected (see below).

A database analysis of our thoracic surgery unit registry at Guy's hospital has been conducted to identify all patients with pathologically confirmed NSCLC with N1 or N2 disease without any induction treatment. Data has been collected retrospectively from hospital records and from a prospectively compiled computerized database.
Clinical records have already been analysed for:

- sex
- age
- history of smoking
- performance status
- site of disease
- tumour location (upper or lower lobes),
- tumour cell type,
- maximum diameter of the tumour
- visceral pleural invasion
- lympho-vascular invasion

As the data is categorical,
There are 3 possible outcomes:

- A (<1%)
- B (≥1-49%)
- C (≥50%)

Therefore an **analysis of proportion** will be performed.
In the limited case series or case reports in the literature there is a finding of 10 to 20% non-matching of PD-L1 expression.
If we use an effect size of 0.15 with an alpha (α) of 0.05 and a (1-β) of 0.95 then using a 1 tailed binomial test we get a total sample size of 119 (with a low critical n=69).
125 patients per group (n=4) according to the anatomical location will be considered:

- left upper lobe
- left lower lobe
- right upper/middle lobe
- right lower lobe

Therefore a total of 500 patients will be enrolled in this study for analysis.

Tumour and lymph node samples will be tested for PD-L1 expression.

In the database, all potential factors which may affect PDL1 expression were measured at the time of diagnosis and evaluated as categorical variables. Factors that significantly correlate with heterogenous PDL1 expression in univariate analysis (at $p<0.10$) were tested for their independent role in multivariate analysis using the Cox proportional hazards model.
The stepwise backward procedure based on the likelihood ratio was used to assess the significance of covariates included in the model.
Hazard ratios and 95% confidence intervals were calculated. A p value < 0.05 was considered statistically significant. All analyses were conducted using the SPSS (SPSS Inc., USA) software package.
PDL1 expression will be correlated with clinical and pathological variables.

Variable	Primary tumor	LN
Pathological Variables		
Histology		
Tumor size (max diameter)	X	-
Tumour location		
Predominant subtype	X	-
Lymphovascular invasion	X	-
PD-L1 expression	X	X
Clinical Characteristics		
Age		
Sex		
Smoking		
PET SUV data (if available)		

Sample Size
Archival tissue samples from primary lung non-small cell carcinomas and involved hilar/ mediastinal LNs (N1 and/or N2 lymph nodes) from 500 resected cases.
500 samples from the primary site and 500 samples from the associated involved LNs.

An interim analysis after the first 100 samples will be performed
3 categories of PD-L1 expression:

- <1%
- ≥ 1-49%
- ≥ 50%

7.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, hazard ratios, incidence rates, test/retest reliability)

To analyse the correlation of PD-L1 expression in the primary site (lung) and associated hilar/mediastinal LNs (N1 and N2) in NSCLC

7.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

Correlate the PD-L1 expression with:

- Histology
- Tumour size
- Tumour location
- Predominant adenocarcinoma subtype
- Lymphovascular invasion

Clinical characteristics

- age
- sex
- smoking history
- PET SUV data if available

7.1.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

- NA

7.2 Bias

7.2.1 Methods to Minimize Bias

- Samples will be collected chronologically from January 2018 backwards from the first 500 eligible patients.

7.2.3 Limitations

This is a retrospective study with archival tissue samples collected and preserved by different staff members. Some variations in collection and storage may have occurred.
Alimitation of this study is if only resection samples are available

7.3 Sample Size and Power Calculations

500 samples from the primary site and 500 samples from the associated involved hilar/mediastinal LNs. The power calculation has been explained above in 7.1

8 ADMINISTRATIVE AND REGULATORY DETAILS

8.1 Confidentiality

8.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

8.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject has agreed to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

8.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognises that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicentre study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

8.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

8.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's R&D department.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-centre study (including multinational). When more than one study site is open in an EU country, MSD, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-centrestudy, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarises the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

8.5 Quality Management System

Data collected will be collected by the investigators. Two qualified pathologists will review the anonymised slides and record PD-L1 expression independently.

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good

Pharmacoepidemiology Practice, and all applicable local laws, rules and regulations relating to the conduct of the study.

8.6 Data Management

The data will be collected and stored in the thoracic surgery database at Guy's Hospital. The data will be entirely anonymized and will be analyzed by the investigator used SPPS software package. The investigators will provide a final study report to MSD that shall be made of descriptive data, tables and data listings, and contain all relevant adverse experiences as a line listing or table. Any Study subject level data submitted to MSD will only be coded with a number and no other personal identifiers such as birth date or Study subject initials

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

For an outsourced study the institutional policies of the vendor should be followed for development of data management plans. However, the vendor should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

9 Publications

Data will be presented at National and International conference and published on Pubmed indexed journals.

10 References

1. Pembrolizumab versus docetaxel for pre- viously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE- 010): a randomised controlled trial. Herbst RS, Baas P, Kim DW, et al. Lancet 2016;387:1540-50.

2. Pembrolizumab for the treatment of non– small-cell lung cancer. Garon EB, Rizvi NA, Hui R, et al. N Engl J Med 2015; 372:2018-28.

3. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. Gerlinger M, Rowan AJ, Horswell S et al. N Engl J Med. 2012 Mar 8;366

4. Temporal and spatial discordance of programmed cell death-ligand 1 expression and lymphocyte tumor infiltration between paired primary lesions and brain metastases in lung cancer. Mansfield AS, Aubry MC, Moser JC, Harrington SM, Dronca RS, Park SS, Dong H. Ann Of Onc 2016 (27) 1953-1958

5. Quantitative and pathologist-read comparison of the heterogeneity of programmed death-ligand 1 (PD-L1) expression in non-small cell lung cancer. Rehman JA, Han G, Carvajal-Hausdorf DE, Wasserman BE, et al. Mol Pathol 2016 Nov 11.

11 Appendices

12 Attachments

Guy's and St Thomas' NHS
NHS Foundation Trust

KING'S HEALTH PARTNERS
Pioneering better health for all

NHS Number:

Name:

Hospital Number:

Date of Birth:

Research Biobank
Adult consent form for cells & tissue surplus to diagnostic requirement

I confirm that I have read patient information leaflet 'Donating cells and tissue for research to improve health care – information for patients' and have had an opportunity to ask questions.

I agree to the following:	**Please initial box if you agree**
Any cells or tissue obtained during my diagnosis, surgery and any subsequent procedures may be kept for future research. Including samples left over from previous diagnostic tests	
These samples may be used for genetic research	
These samples may be used for research involving animals	
These samples may be used to create cell lines	
Specific individuals contracted to GSTT may look at relevant sections of my medical notes to obtain information about my condition.	
My samples and data will be stored and used anonymously.	
My GP can be contacted for information relevant to my condition and ongoing treatment in the event that I stop attending GSTT.	
I understand that I can withdraw my consent at any time without giving a reason. Any unused samples taken for research purposes will be destroyed.	

Name of Patient _____ Name of Person taking Consent _____

Date _____ Date _____

Signature Patient / Representative _____ Signature of Person taking Consent _____

Date: April 2015, Version 2 Biobank Copy REC No: 12/EE/0493

13 SIGNATURES

Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 6 – Safety Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME	SIGNATURE	DATE
_____	_____	_____