SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	In vitro diagnostic immunohistochemistry (IHC) test for detection of PD-L1 in formalin-fixed, paraffin-embedded (FFPE) human tissue sections
Device Trade Name:	PD-L1 IHC 22C3 pharmDx
Device Procode:	PLS
Applicant's Name and Address:	Dako North America, Inc. 6392 Via Real Carpinteria, CA 93013
Date(s) of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P150013/S001

Date of FDA Notice of Approval: October 24, 2016

The PD-L1 IHC 22C3 pharmDx (P150013) was approved on October 2, 2015 for the qualitative detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue using EnVision FLEX visualization system on the Autostainer Link 48. PD-L1 protein expression is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining. The indication for use of the device as approved in P150013 is to aid in identifying patients with NSCLC whose tumors are considered PD-L1 positive if TPS $\geq$ 50% and for whom safety and efficacy of KEYTRUDA® (pembrolizumab) have been established. The SSED to support the indication is available on the CDRH website and is incorporated by reference here.

The current supplement was submitted to expand the indication for the PD-L1 IHC 22C3 pharmDx to identify patients, who have PD-L1 staining in $\geq$ 1% of tumor cells, for treatment with KEYTRUDA® (pembrolizumab). If the PD-L1 IHC 22C3 pharmDx test result shows that TPS $\geq$ 1%, then patients who have had at least one prior systemic therapy are eligible for treatment with Keytruda®. If the test result shows TPS $\geq$ 50%, then patients with metastatic NSCLC with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC are eligible for treatment with Keytruda®.

II. INDICATIONS FOR USE

For in vitro diagnostic use.

PD-L1 IHC 22C3 pharmDx is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue using EnVision FLEX visualization system on the Autostainer Link 48. PD-L1 protein expression is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. The specimen should be considered to have PD-L1 expression if TPS ≥1% and high PD-L1 expression if TPS ≥50%.

PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA® (pembrolizumab). See the KEYTRUDA® product label for expression cutoff values guiding therapy in specific clinical circumstances.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PD-L1 IHC 22C3 pharmDx labeling.

V. DEVICE DESCRIPTION

Device Kit Components

PD-L1 IHC 22C3 pharmDx contains optimized reagents required to complete an immunohistochemical (IHC) staining procedure for formalin-fixed and paraffin-embedded (FFPE) specimens using the EnVision FLEX visualization system and the Dako Autostainer Link 48 with DakoLink software 4.0.3. Wash buffer and hematoxylin are required, but not included in the kit. Deparaffinization is performed using the PT Link. Coverslipping can be manual or automated. The kit contains the reagents necessary to perform 50 tests in up to 15 individual runs. An overview of the kit components is shown in the table below.

Table 1: Overview of PD-L1 IHC 22C3 pharmDx Components

Reagent	Description	Qty x Vol
Peroxidase-Blocking Reagent	Buffered solution containing hydrogen peroxide, detergent and 0.015 mol/L sodium azide.	1 x 34.5 mL
Monoclonal Mouse anti-PD-L1, Clone 22C3	Monoclonal mouse anti-PD-L1 antibody in a buffered solution, containing stabilizing protein(3 µg/mL protein concentration) , and	1 x 19.5 mL

Reagent	Description	Qty x Vol
	0.015 mol/L sodium azide.	
Negative Control Reagent	Monoclonal mouse control IgG antibody in a buffered solution, containing stabilizing protein, and 0.015 mol/L sodium azide.	1 x 15 mL
Linker, Anti-Mouse	Rabbit secondary antibody against mouse immunoglobulins in a buffered solution containing stabilizing protein and 0.015 mol/L sodium azide.	1x 34.5 mL
Visualization Reagent-HRP	Dextran coupled with peroxidase molecules and goat secondary antibody molecules against rabbit and mouse immunoglobulins in a buffered solution containing stabilizing protein and an antimicrobial agent.	1 x 34.5 mL
DAB+ Buffered Substrate	Buffered solution, containing hydrogen peroxide and an antimicrobial agent.	15 x 7.2 mL
DAB+ Chromogen	3,3'-diaminobenzidine tetrahydrochloride in an organic solvent.	1 x 5 mL
DAB Enhancer	Cupric sulfate in water.	1 x 34.5 mL
Target Retrieval Solution Low pH (50X)	Buffered solution, pH 6.1, containing detergent and an antimicrobial agent.	6 x 30 mL
Cell Line Control Slides	Each slide contains sections of two pelleted, formalin-fixed paraffin-embedded cell lines: NCI-H226 with moderate PD-L1 protein expression (positive control), and MCF-7 with negative PD-L1 protein expression (negative control).	3 x 5 slides

PD-L1 IHC 22C3 pharmDx comes with individually labeled reagent components that are recognized together. The kit components can only be used on the specified instrument with the PD-L1 IHC 22C3 pharmDx protocol. The DakoLink software has been designed to recognize and group PD-L1 IHC 22C3 pharmDx reagents, mandating that the reagents are run together.

Specimen Preparation

Non-small cell lung carcinoma (NSCLC) specimens must be handled to preserve the tissue for IHC staining. Standard methods of tissue processing should be used for all specimens. Only formalin-fixed, paraffin-embedded (FFPE) tissues are suitable for use. Tissue specimens should be cut into sections of 4-5 µm, mounted on charged microscope slides and stored in the dark at 2-8 °C until staining, which should be performed within 6 months of sectioning.

Test Controls and Calibrators

Control cell line slides listed in the above table should be used to verify the staining procedure. One control slide should be stained with the Primary Antibody to PD-L1 in each staining run. The evaluation of the Control Slide cell lines supplied in the kit indicates the validity of the staining run. They should not be used as an aid in interpretation of patient results. Additional information about the use of controls are avalailable in the product labeling.

Principles of Procedure

PD-L1 IHC 22C3 pharmDx contains optimized reagents required to complete an IHC staining procedure on FFPE specimens using the Autostainer Link 48. Following deparaffinization of the tissue sections, rehydration and target retrieval, the slides are incubated with the primary monoclonal antibody to PD-L1 (Clone 22C3) or the Negative Control Reagent. Specimens are then incubated with a linker antibody specific to the host species of the primary antibody, and then are incubated with the ready-to-use Visualization Reagent consisting of secondary antibody molecules and horseradish peroxidase (HRP) molecules coupled to a dextran polymer backbone. The enzymatic conversion of the subsequently added DAB+ Chromogen results in precipitation of a visible reaction product at the site(s) of antigen. The color of the chromogenic reaction is modified by a chromogen enhancement reagent, DAB Enhancer. The specimen may then be counterstained with hematoxylin and coverslipped.

Staining protocol

The PD-L1 IHC 22C3 pharmDx is designed to be run on the Autostainer Link 48 with DakoLink software according to the following staining protocol:

Peroxidase-Blocking Reagent (2 drop zones x 150µL): 5 minutes (± 1 minute);
Rinse in buffer;
Monoclonal Mouse anti-PD-L1 (or Negative Control Reagent) (2 drop zones x 150 µL): 30 minutes (± 1 minute);
Rinse in buffer;
Linker, anti-Mouse Ig (2 drop zones x 150µL): 30 minutes (± 1 minute);
Rinse in buffer;
Visualization Reagent (2 drop zones x 150µL): 30 minutes (± 1 minute);
Rinse in buffer: 5 minutes;
DAB+ solution (2 drop zones x 150µL): 2 x 5 minutes (± 1 minute);
Rinse in buffer;

DAB+ Enhancer (2 drop zones x 150µL): 5 minutes (± 1 minute);
Rinse in buffer;
Hematoxylin (2 x 150µL): 5 minutes (± 1 minute);
Rinse in deionized water;
Rinse in buffer: 5 minutes;
Rinse in deionized water;
Remove slides from autostainer and place in bath of reagent water.

Interpretation of PD-L1 Staining

Interpretation of specimens should be performed by a pathologist using a light microscope. An objective of 10-40X magnification is appropriate. To successfully score PD-L1 IHC 22C3 pharmDx stained specimens, it is critical that the appropriate cells are evaluated and proper cellular localization is identified. All viable tumor cells on the entire slide must be evaluated and included in the PD-L1scoring assessment. A minimum of 100 viable tumor cells must be present for the specimen to be considered adequate for PD-L1 evaluation. Only viable tumor cells should be scored. Any perceptible membrane staining should be included in the scoring. Cytoplasmic staining should be considered non-specific staining. Tumor associated immune cells such as infiltrating lymphocytes or macrophages are not included in the scoring for the determination of PD-L1 positivity using the assay.

The Tumor Proportion Score (TPS), which determines the PD-L1 expression of the specimen, is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity (i.e., ≥1+). . The specimen should be considered PD-L1 positive if TPS ≥ 1%. The specimen should be considered PD-L1 high expression if TPS is ≥ 50%. The PD-L1 IHC 22C3 pharmDx Interpretation Manual for NSCLC is available to users to assist in the interpretation of assay results.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There is no other FDA-cleared or -approved alternative class III immunohistochemistry assays available for detection of PD-L1 in formalin-fixed, paraffin embedded (FFPE) non-small cell lung carcinoma (NSCLC) tissues for the selection of patients to be treated with KEYTRUDA® (pembrolizumab).

VII. MARKETING HISTORY

PD-L1 IHC 22C3 pharmDx was approved under P150013 on October 2, 2015 for selection of NSCLC patients eligible for treatment with KEYTRUDA® (pembrolizumab). The device is currently marketed in the United States.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect PD-L1 test results, and subsequently improper patient management decisions in non-small cell lung carcinoma (NSCLC) treatment.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Since approval of the original PMA (P150013), there have been no changes to the device design including reagent formulation or kit configuration. Preclinical studies were performed using the PD-L1 IHC 22C3 pharmDx kit to support the analytical performance of device at the 1% cut-off (TPS ≥1%). These studies were conducted to characterize the assay, demonstrate the impact of pre-analytical variables on assay performance, verify precision and robustness of the assay, and establish assay stability. Please refer to the Summary of Safety and Effectiveness Data (SSED) for P150013 for a summary of the results for the 50% cut-off (TPS ≥ 50%).

1. Analytical Sensitivity

Analytical sensitivity of PD-L1 IHC 22C3 pharmDx was tested on 127 unique cases of FFPE non-small cell lung carcinoma (NSCLC) tissue using one production lot. The specimens were chosen at random and represented the full range of PD-L1 expression. Assessment of PD-L1 expression demonstrated staining across a range of 0-100% positive tumor cells and 0-3 staining intensity. The rate of positivity when the TPS was ≥ 1% was 56%.

2. Analytical Specificity

a. Western Blot

Western blot analysis was performed on tumor cell lysates (NCI-H226 and MCF7) and with varying concentrations of purified PD-L1. By the IHC assay, NCI-H226 is PD-L1 positive and MCF7 is negative for PD-L1. The Western blot results indicated that Monoclonal Mouse anti-PD-L1 clone 22C3 specifically detected purified PD-L1 protein and there was low cross-reactivity to other proteins in the cell lysates.

b. Immunoreactivity in Human Tissues

See Summary of Safety and Effectiveness Data for P150013.

3. Robustness

Robustness of PD-L1 IHC 22C3 pharmDx was tested using one lot of the device and 24 NSCLC specimens (12 positive and 12 negative). The robustness conditions tested were the following:

- Tissue Thickness
  - 3 µm
  - 4 µm - standard
  - 5 µm

- Microscope Slide Type
  - Fisherbrand™ Superfrost™ Plus
  - Dako FLEX IHC Microscope Slides (Dako code K8020)
- Target Retrieval Solution: Time
  - 18 minutes
  - 20 minutes-standard
  - 22 minutes
- Target Retrieval Solution: Temperature
  - 95°C
  - 97°C -standard
  - 99°C
- Target Retrieval Solution: pH
  - pH 5.8
  - pH 5.9
  - pH 6.1-standard
  - pH 6.4
- Target Retrieval Solution: Re-use
  - Use 1
  - Use 2
  - Use 3

As compared to the standard condition, no significant difference in results was observed for the experimental conditions listed above.

4. Precision

The objective of the precision study was to demonstrate the PD-L1 IHC 22C3 pharmDx assay produces consistent, repeatable and reproducible results. Summaries and results of the repeatabilitystudies are presented Table 2. Negative percent agreement (NPA) or average negative agreement (ANA), positive percent agreement (PPA) or average positive agreement (APA) and overall agreement (OA) were determined for the ≥ 1% cutoff. Data were evaluated using a percentile bootstrap method to calculate confidence intervals for the average agreements. For the studies which resulted in 100% agreement, confidence intervals were calculated using the Wilson Score method based on the number of independent pair-wise comparisons (effective degrees of freedom). See SSED for P150013 for performance data at the 50% cut-off.

Table 2: Repeatability of PD-L1 IHC 22C3 pharmDx Tested at One Site (TPS ≥ 1%)

Study	Method	Agreement (95% CI)
Inter-instrument	Each of 24 non-small cell lung carcinoma specimens (12 positive and 12 negative) with a range of PD-L1 IHC expression was tested on each of six Autostainer Link 48 instruments.	NPA 100% (94.0-100%) PPA 100% (94.0-100%) OA 100% (96.9-100%)
Inter-operator	Each of 24 non-small cell lung carcinoma specimens (12 positive and 12 negative) with a range of PD-L1 IHC expression was tested using six analysts on one Autostainer Link 48 instrument.	NPA 100% (93.9-100%) PPA 100% (94.0-100%) OA 100% (96.9-100%)
Inter-day	Each of 24 non-small cell lung carcinoma specimens (12 positive and 12 negative) with a range of PD-L1 IHC expression was tested on six non-consecutive days on the Autostainer Link 48 instrument.	NPA 100% (94.0-100%) PPA 100% (94.0-100%) OA 100% (96.9-100%)
Inter-lot	Each of 24 non-small cell lung carcinoma specimens (13 positive and 11 negative) with a range of PD-L1 IHC expression was tested with three replicates and each of three reagent lots on the Autostainer Link 48 instrument.	ANA 98.3% (95.9-100%) APA 97.9% (94.6-100%) OA 98.1% (95.3-100%)
Intra-run	Each of 24 non-small cell lung carcinoma specimens (12 positive and 12 negative) with a range of PD-L1 IHC expression was tested with six replicates within a run on the Autostainer Link 48 instrument.	NPA 100% (94.0-100%) PPA 100% (93.8-100%) OA 100% (96.8-100%)
Intra-day	Each of 24 non-small cell lung carcinoma specimens (12 positive and 12 negative) with a range of PD-L1 IHC expression was tested on two runs within a day, repeated over three days, on the Autostainer Link 48 instrument.	NPA 100% (91.0-100%) PPA 100% (91.2-100%) OA 100% (95.4-100%)
Inter-observer	Three different observers scoring 48 PD-L1 stained NSCLC slides. Slides were blinded and randomized prior to scoring.	ANA 91.7% (82.6-98.0%) APA 95.8% (91.5-99.0%) OA 94.4% (88.9-98.6%)
Intra-observer	One observer scoring 48 PD-L1stained NSCLC slides 3 times. Slides were blinded and randomized prior to scoring, as well as a two week wash out period between reads .	ANA 95.7% (88.4-100%) APA 98.0% (95.0-100%) OA 97.2% (93.1-100%)

5. External Reproducibility

The objective of this study was to evaluate PD-L1 IHC 22C3 pharmDx with respect to Inter-Day, Inter-Laboratory, Inter- and Intra- Observer reproducibility on formalin-fixed, paraffin embedded (FFPE) human NSCLC tissue specimens when using the device at the cut-point of TPS ≥1%. The study was a blinded and randomized reproducibility study performed at three external sites.The study was divided into Part A (Inter-Day and Inter-Laboratory endpoints) and Part B (Inter- and Intra-Observer endpoints). Three (3) additional "wildcard" specimens were

added to each reading to minimize recall bias and were not used in the data analysis. The results are summarized in the Table 3 below:

Table 3: Reproducibility of the PD-L1 IHC 22C3 pharmDx at Three External Sites (TPS ≥ 1%)

Study	Method	Agreement (95% CI)
Inter-site	Each of 36 NSCLC specimens (20 positive and 16 negative) with a range of PD-L1 IHC expression was tested on five non-consecutive days. Inter-site analysis was performed between three sites on a total of 2700 pair-wise comparisons.	ANA 94.8% (90.3-98.4%) APA 95.5% (91.2-98.7%) OA 95.2% (95.4-100%)
Intra-site (inter-day)	Each of 36 NSCLC specimens (20 positive and 16 negative) with a range of PD-L1 IHC expression was tested on five non-consecutive days at each of three study sites. Intra-site analysis was performed for three sites on a total of 1080 pair-wise comparisons.	ANA 96.2% (94.1-97.5%) APA 96.7% (95.0-97.9%) OA 96.5% (95.2-97.4%)
Inter-observer	Scoring of 62 NSCLC specimens (34 positive and 28 negative) with a range of PD-L1 IHC expression was performed by three pathologists, one at each of three study sites, on three non-consecutive days. Inter-observer analysis was performed between three sites on a total of 1674 pair-wise comparisons.	ANA 85.8 (79.3-91.8%) APA 88.2% (82.2-93.3%) OA 87.1% (81.0-92.6%)
Intra-observer	Scoring of 62 NSCLC specimens (34 positive and 28 negative) with a range of PD-L1 IHC expression was performed by three pathologists, one at each of three study sites, on three non-consecutive days. Intra-observer analysis was performed for three sites on a total of 558 pair-wise comparisons.	ANA 93.7% (90.0-96.1%) APA 94.8% (91.6-96.7%) OA 94.3% (92.0-95.9%)

6. Stability Studies

a. Cut Section Stability

Based on real time results, NSCLC tissue sections should be stained within 6 months of sectioning. See SSED for P150013.

b. Block Stability

See SSED for P150013.

c. PD-L1 IHC 22C3 pharmDx Stability

Based on a real time stability study with three lots of PD-L1 IHC 22C3 pharmDx components, the following results were supported for transport simulation, working stability and in-use/on-board stability:

Total Shelf Life (Includes Margin of Safety):
11 months at 2-8 °C

Finished Good Shelf Life:
9 months at 2-8 °C

In-Use/On-Board Stability Testing
Eighteen cycles to room temperature

Working/Reconstituted Stability Testing
DAB Substrate-Chromogen Solution: 5 Days at 2-8 °C, protected from light.
Target Retrieval Solution: 5 days at room temperature in a PT-Link with up to 3 uses for 3-in-1 pretreatment.

B. Animal Studies

None

C. Additional Studies

1. **Primary vs. Metastatic Tumor**
   Expression data from 23 scorable pairs of primary and metastatic NSCLC tissues were analyzed. The results showed a similar dynamic range of PD-L1 expression in primary and metastatic NSCLC specimen pairs, with 87% (20/23 specimen pairs) having the same diagnostic determination using either TPS ≥50% or TPS ≥1% as the cut off.

2. **Impact on Ischemia/Fixation**
   See SSED for P150013.

3. **Intra-Case Heretogeneity**
   Multiple (2-5) specimen blocks per case were tested with PD-L1 IHC 22C3 pharmDx for a total of 20 individual cases. The results showed that 100% (20 of 20 sets) and 85% (17 of 20 sets) of NSCLC intra-case specimens obtained diagnostically concordant scores at ≥ 50% and ≥ 1% TPS, respectively.

4. **Intra-Block Heretogeneity**
   The first and 50th consecutive tissue sections cut from a NSCLC FFPE tissue block from a total of 20 blocks were tested with PD-L1 IHC 22C3 pharmDx. The results showed that 100% (20 of 20 pairs) at the 50% TPS cutoff and 95% (19 of 20 pairs) at the 1% TPS cutoff of the section pairs obtained diagnostically concordant scores.

5. Control Cell Line Validation
See SSED for P150013.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The clinical performance of PD-L1 IHC 22C3 pharmDx for TPS ≥ 1% was based on a Phase 2/3 multicenter, open-label, randomized clinical study conducted to assess the safety and efficacy of KEYTRUDA® (pembrolizumab) in patients with advanced NSCLC (KEYNOTE-010 or KN010). This global trial included US, Canada, Western and Eastern Europe, Asia, Australia, and South America. Patients were determined to be PD-L1 positive by a clinical trial assay (CTA), and had progression of disease following treatment with platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations were eligible to participate only if they had disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA® (pembrolizumab). Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR (according to RECIST 1.1 as assessed by blinded independent central review) and duration of response. The efficacy evaluation was performed in patients with positive PD-L1 expression at TPS ≥ 1% and who had progression of disease following treatment with platinum-containing chemotherapy. This clinical study was used to support approval of KEYTRUDA® (pembrolizumab) under sBLA125514/S08. A bridging study was also conducted to support the performance of PD-L1 IHC 22C3 pharmDx in selecting PD-L1 positive NSCLC patients for treatment with KEYTRUDA® (pembrolizumab).

A. Study Design

The clinical study was a global, multicenter, open-label, randomized Phase 2/3 clinical study to assess the safety and efficacy of KEYTRUDA® (pembrolizumab) treatment in patients with advanced NSCLC who were PD-L1 positive as determined by TPS ≥ 1% using a CTA. A total of 1,034 subjects were randomized in a 1:1:1 ratio to receive pembrolizumab at 10 mg/kg Q3W or 2 mg/kg Q3W or docetaxel at 75 mg/m2 Q3W. Subjects were stratified by Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1) and geographic region of the enrolling site (East Asia [Japan, Korea, and Taiwan] vs. non-East Asia) prior to randomization. Per protocol, the extent of tumor PD-L1 expression (strongly positive [TPS ≥ 50%] vs. weakly positive [TPS = 1-49%]) was added as a third stratification factor based on prior data. A total of 441 subjects were randomized prior to the implementation of the PD-L1 stratification factor and 593subjects were randomized thereafter.

1. Inclusion and Exclusion Criteria
Enrollment in the study was limited to patients who met the following inclusion criteria:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥18 years of age on day of signing informed consent.

3. Have a life expectancy of at least 3 months.
4. Have a histologically or cytologically confirmed diagnosis of non-small cell lung cancer (NSCLC) and have at least one measurable lesion as defined by RECIST 1.1. The target lesion(s) should also have bi-dimensional measurability for irRC evaluation on study.
5. Have a performance status of 0 or 1 on the ECOG Performance Scale.
6. Have provided tissue for PD-L1 biomarker analysis from a newly obtained formalin fixed tumor tissue from a recent biopsy of a tumor lesion not previously irradiated; no systemic antineoplastic therapy may be administered between the PD-L1 biopsy and initiating study medication. Although patients using tyrosine kinase inhibitors prior to treatment on this protocol may continue using these until it is time to begin the appropriate wash out period for these medications. For patients in whom obtaining a new tumor biopsy will be medically inappropriate, the investigator may appeal to the Sponsor's study clinical director, and if there is agreement, the investigator may submit an archival formalin-fixed, paraffin-embedded tumor specimen for PD-L1 analysis. The tissue sample must be received and evaluated by the central vendor prior to randomization. Fine needle aspirates are not acceptable. Needle or excisional biopsies, or resected tissue is required.
7. Have a PD-L1 positive (either strongly or weakly) tumor as determined by IHC at a central laboratory. If a patient's initial tumor specimen is not classified as PD-L1 positive by the central laboratory, a newly obtained specimen (different from the sample previously submitted) may be submitted for testing. If the newer specimen is classified as PD-L1 positive by the central laboratory, the patient meets this eligibility criterion.

Subjects were excluded from the trial based on the following exclusion criteria:

1. Has received prior therapy with docetaxel for NSCLC.
2. Is currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of the first dose of trial treatment. The 30 day window should be applied to the last dose of an antineoplastic investigational agent or last use of an investigational device with antineoplastic intent.
3. Has received prior systemic cytotoxic chemotherapy, antineoplastic biological therapy (e.g., cetuximab), major surgery within 3 weeks of the first dose of trial treatment; received thoracic radiation therapy of > 30 Gy within 6 months of the first dose of trial treatment; received prior tyrosine kinase inhibitor therapy or completed palliative radiotherapy within 7 days of the first dose of trial treatment.
4. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or has participated in another MK-3475 clinical trial.

2. Follow-up Schedule

Tumor assessments were performed at baseline and every 9 weeks thereafter.

3. Clinical Endpoints

A primary objective of the study was to evaluate the anti-tumor activity of KEYTRUDA® (pembrolizumab) in patients with NSCLC who had at least one prior systemic therapy and whose tumors were positive for PD-L1 expression. The primary efficacy endpoints were overall survival (OS) (i.e., the time from randomization to death due to any cause) and progression free survival (PFS) (i.e., time from randomization to documented PD or death due to any cause, whichever occurred first) per RECIST 1.1 based on blinded independent radiologists' review. The secondary objectives for this trial were overall response rate (ORR) and response duration per RECIST 1.1 based on blinded independent radiologists' review.

With regard to safety, information about adverse events was collected from time of signed informed consent throughout the treatment period and least 30 days after their last dose of study drug or until initiation of a new anti-cancer treatment, whichever occured first. The safety analysis was performed in all patients who had received at least 1 dose of study treatment.

With regard to effectiveness, the intention-to-treat (ITT) population in the overall positive (TPS $\geq$ 1%) and high expression (TPS $\geq$ 50%) PD-L1 populations served as the primary populations for the efficacy analyses in this trial.

4. Bridging Study

A bridging study for KEYNOTE-010 was conducted to establish the clinical performance of the PD-L1 IHC 22C3 pharmDx (commercial ready assay or CRA) for patients randomized according to the CTA. Retrospective testing of banked FFPE NSCLC tissue samples from patients screened for the clinical study was done with the CRA and evaluated against clinical performance endpoints based on clinical trial enrollment using the CTA. Samples stored as cut tissue sections that had reached the 6-month stability limit at the time of the bridging study were considered out of the stability window (OSW) and were excluded from the bridging study primary analysis. Only samples within the stability window (WSW) were considered as part of primary analysis. The CTA was used to screen 2,699 patients in this trial. Of these, 1,034 were enrolled in the trial using the CTA. A total of 1,944 samples were retested with the CRA. Of these, 1,007 were within the stability window and therefore included in the agreement analysis . Sample accountability for the bridging study is shown in Table 4.

Table 4: Sample Accountability - Agreement Analysis Data Set

Detail	Number
Total patients screened	2699
No CTA testing (no CRA testing)	477
CTA testing with no CRA testing	278
CRA testing, OSW (includes not evaluable CRA)	873
CRA testing, WSW - not evaluable PD-L1 results	61
CRA testing, WSW with CTA testing OSW	3
Agreement Analysis Data Set	1007

Statistical analysis was performed on specimen samples that were within the stability window for banked specimens. Conditioning on CTA results negative percent agreement (NPA) and positive percent agreement (PPA) estimates were calculated for TPS $\geq$ 1% (cut-off for PD-L1 positive) along with two-sided 95% confidence intervals. The results are shown in Table 5.

Table 5: Performance Summary (TPS ≥ 1%)

CTA	CRA		Total	Performance Characteristic
	Negative	Positive		
Negative	294	17	311	NPA=94.5% [91.4%-96.6%]
Positive	139	557	696	PPA=80.0% [76.9%-82.8%]
Total	433	574	1,007	

B. Accountability of PMA Cohort

The PMA cohort consisted of a total of 1,034 previously treated NSCLC patients who were enrolled in the study based on PD-L1 testing with a CTA. Out of the 1,034 patients, tumor tissue from 1,019 patients was tested with the PD-L1 IHC 22C3 pharmDx test; test results showed 413 patients with positive PD-L1 expression (TPS ≥1%), 94 patients with negative PD-L1 expression (TPS < 1%) and 497 patients with unknown PD-L1 expression status (476 patients were not included because the tissue sections were outside the 6 month stability window and 21 patients had unevaluable tumor tissue.

C. Study Population Demographics and Baseline Parameters

Study enrollment occurred at 198 centers in 24 countries. Out of the 413 patients with positive PD-L1 expression (TPS $\geq$ 1%) by PD-L1 IHC 22C3 pharmDx, 115 were enrolled in the US. The baseline characteristics for the 413 patients are shown in the table below.

Table 6: Baseline Characteristics

Characteristics	n (%)
Subjects in population	413
Gender	
Male	241 (58.4)
Female	172 (41.6)
Age (Years)	
< 65	231 (55.9)
>=65	182 (44.1)
Race	
Asian	62(15)
Black Or African American	14 (3.4)
White	317 (76.8)
Ethnicity	
Hispanic Or Latino	26 (6.3)
Not Hispanic Or Latino	349 (84.5)
Region	
Non-East Asian	365 (88.4)
East Asia	48 (11.6)
US	115 (27.8)
Non-US	298 (72.2)
ECOG	
0	119 (28.8)
1	292 (70.7)
2	1 (0.2)
3	1 (0.2)
Histology	
Squamous	92 (22.3)
Non-Squamous	283 (68.5)
Smoking Status	
Never	88 (21.3)
Current/Former	320 (77.5)
Brain Metastases	
Yes	65 (15.7)
No	348 (84.3)
Number of Unique Prior Systemic Therapies	
1	289 (70)
2	82(19.9)
3 or more	32 (7.7)
EGFR Mutation	37 (9)
ALK Gene Rearrangement	4 (1.0)

D. Safety and Effectiveness Results

1. Safety Results

   In the trial, grade ≥ 3 adverse events (AE) occurred in 46.6% and 45.5% of the patients enrolled in the pembrolizumab 2 mg/kg and 10 mg/kg arms, respectively, and 45% of the patients in the docetaxel. In general, the incidence and types of AEs were similar between the two pembrolizumab arms. The most common grade ≥ 3 AEs in both treatment arms were fatigue, pneumonia and dyspnea. Grade ≥ 3 pneumonitis was reported in 2.1% of patients enrolled in each the pembrolizumab arms. Grade ≥ 3 myelosuppression was the most common AE in the docetaxel arm. Four patients died possibly due to pembrolizumab related pneumonitis, 2 in the 2 mg/kg and 2 in the 4 mg/kg arm. A direct causal relationship is not certain due to other existing co-morbid conditions. Safety of the drug was also addressed in the original drug approval.

2. Effectiveness Results

   Efficacy evaluation was performed in patients with positive PD-L1 expression (TPS ≥ 1%) and with PD-L1 high expression (TPS ≥ 50%) as determined by the PD-L1 IHC 22C3 pharmDx who had progression of disease following treatment with platinum-containing chemotherapy. Efficacy results are shown in Table 7 and Figure 1 for TPS ≥ 1% and Table 8 for TPS ≥ 50%.

Table 7: Efficacy Results of All Randomized Patients (TPS ≥ 1%)

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value(stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	266 (77%)	255 (74%)	257 (75%)
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Hazard ratio* (95% CI)	0.88 (0.73,1.04)	0.79 (0.66, 0.94)	---
p-Value (stratified log-rank)	0.068	0.005	---
Objective response rate			
ORR† (95% CI)	18% (14, 23)	19% (15, 23)	9% (7, 13)
p-Value (Miettenen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 20.1+)	NR (2.1+, 17.8+)	6.2 (1.4+, 8.8+)

* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model

† All responses were partial responses

NR = not reached

Table 8: Efficacy Results of All Randomized Patients (TPS ≥ 50%)

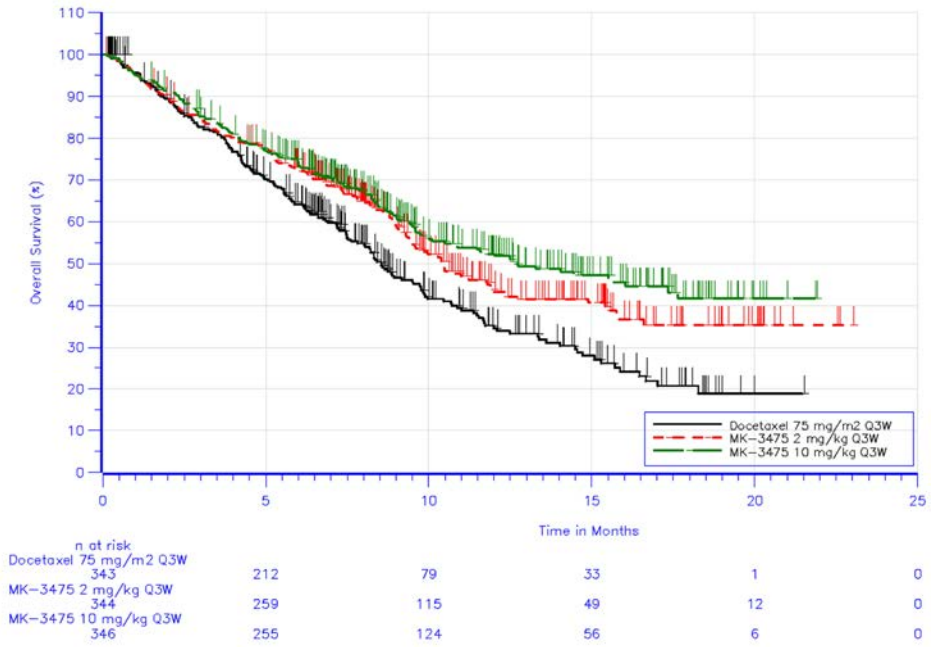
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=139	KEYTRUDA 10 mg/kg every 3 weeks n=151	Docetaxel 75 mg/m^2 every 3 weeks n=152
OS			
Deaths (%)	58 (42%)	60 (40%)	86 (57%)
Median in months (95% CI)	14.9 (10.4, NR)	17.3 (11.8, NR)	8.2 (6.4, 10.7)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	89 (64%)	97 (64%)	118 (78%)
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Objective response rate			
ORR† (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
p-Value (Miettenen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 16.8+)	NR (2.1+, 17.8+)	8.1 (2.1+, 8.8+)

* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model

† All responses were partial responses

NR = not reached

Figure 1: Kaplan-Meier of Overall Survival Subjects with TPS ≥1%, ITT Population



Additional sensitivity analyses were performed to assess the robustness of efficacy results using the CRA. Table 9 describes the range of efficacy results observed in the robustness analyses taking into account CRA results as opposed to CTA results, as well as missingness of CRA results.

Table 9: HR|CRA+ from the Analysis of Overall Survival Subjects with CRA Positive (TPS ≥ 1%)

		HR Estimates and 95% Confidence Intervals based on Multiple				
		IF=1.0	**IF=0.8**	**IF=0.5**	**IF=0.3**	**IF=0**
MK 2mg/kg vs. Docetaxel	V1	0.67(0.53,0.86)	0.67(0.53,0.86)	0.68(0.53,0.87)	0.68(0.53,0.87)	0.68(0.53,0.87)
	V2	0.67(0.53,0.86)	0.68(0.53,0.86)	0.68(0.53,0.87)	0.68(0.53,0.87)	0.68(0.54,0.87)
	V3	0.67(0.48,0.95)	0.67(0.48,0.95)	0.68(0.48,0.95)	0.68(0.48,0.95)	0.68(0.49,0.96)
MK 10mg/kg vs. Docetaxel	V1	0.61(0.48,0.79)	0.62(0.48,0.79)	0.62(0.48,0.79)	0.62(0.49,0.80)	0.62(0.49,0.80)
	V2	0.61(0.48,0.78)	0.62(0.48,0.79)	0.62(0.49,0.79)	0.62(0.49,0.80)	0.63(0.49,0.80)
	V3	0.61(0.44,0.87)	0.62(0.44,0.87)	0.62(0.44,0.87)	0.62(0.44,0.87)	0.62(0.44,0.88)

Estimation conducted on log hazard scale and then estimate and CI back-transformed to HR scale.
V1 is a Bayesian imputation, V2 additionally uses the lower bound of P(CTA+|CRA+), and V3 additionally uses a random draw for LHR|CTA-,CRA+ from the estimate of the asymptotic distribution of LHR|CTA+,CRA+.
IF: Inflation Factor; IF=1.0 indicates HR|CRA+,CTA-=HR|CRA+,CTA+, IF=0 indicates HR|CRA+,CTA-=1.

3. Subgroup Analyses
   Results for all groups analyzed are shown in the tables above.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

To support the clinical performance of PD-L1 IHC 22C3 pharmDx to select previously untreated patients with PD-L1 TPS $\geq$ 50% for treatment with KEYTRUDA® (pembrolizumab), data from clinical study KEYNOTE 024 (KN024) were used. The trial was a randomized (1:1), open-label, multicenter, controlled trial. Key eligibility criteria were metastatic NSCLC, PD-L1 expression TPS of 50% or greater using the PD-L1 IHC 22C3 pharmDx Kit, and no prior systemic treatment for metastatic NSCLC. Patients were not eligible for the trial if they had: EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or received more than 30 Gy of thoracic radiation within the prior 26 weeks. Patients were randomized to receive KEYTRUDA 200 mg every 3 weeks (n=154) or investigator's choice platinum-containing chemotherapy (n=151; including pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin. Non-squamous patients could receive pemetrexed maintenance). Patients were treated with KEYTRUDA until unacceptable toxicity or disease progression, or up to 35 administrations. Subsequent disease progression could be retreated for up to 1 additional year. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed every 9 weeks. Patients on chemotherapy who experienced progression of disease were offered KEYTRUDA.

Among the 305 patients in KN024, baseline characteristics were: median age 65 years (54% age 65 or older); 61% male; 82% White and 15% Asian; and 35% and 65% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous

(18%) and non-squamous (82%); M1 (99%); and brain metastases (9%). The major efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR) using Response Evaluation Criteria on Solid Tumors Version 1.1 (RECIST 1.1). Additional efficacy outcome measures were overall survival (OS) and objective response rate (ORR) as assessed by BICR using RECIST 1.1. Table 10 summarizes key efficacy measures for the entire intent to treat (ITT) population.

Table 10: Efficacy Results in KN024

Endpoint	KEYTRUDA 200 mg every 3 weeksn=154	Chemotherapy n=151
PFS*		
Number (%) patients with event	73 (47%)	116 (77%)
Hazard ratio† (95% CI)	0.50 (0.37,0.68)	---
p-Value‡	<0.001	---
Median in months (95%	10.3	6.0
OS		
Number (%) patients with event	44 (29%)	64 (42%)
Hazard ratio† (95% CI)	0.60 (0.41,0.89)	---
p-Value‡	0.005	---
Median in months (95%	Not reached	Not reached
ORR*		
ORR % (95% CI)	45% (37, 53)	28% (21, 36)
Complete response %	4%	1%
Partial response %	41%	27%
p-Value (Miettenen-Nurminen)	0.001	
Median duration of response in months	NR (1.9+, 14.5+)	6.3 (2.1+, 12.6+)

* Assessed by BICR using RECIST 1.1

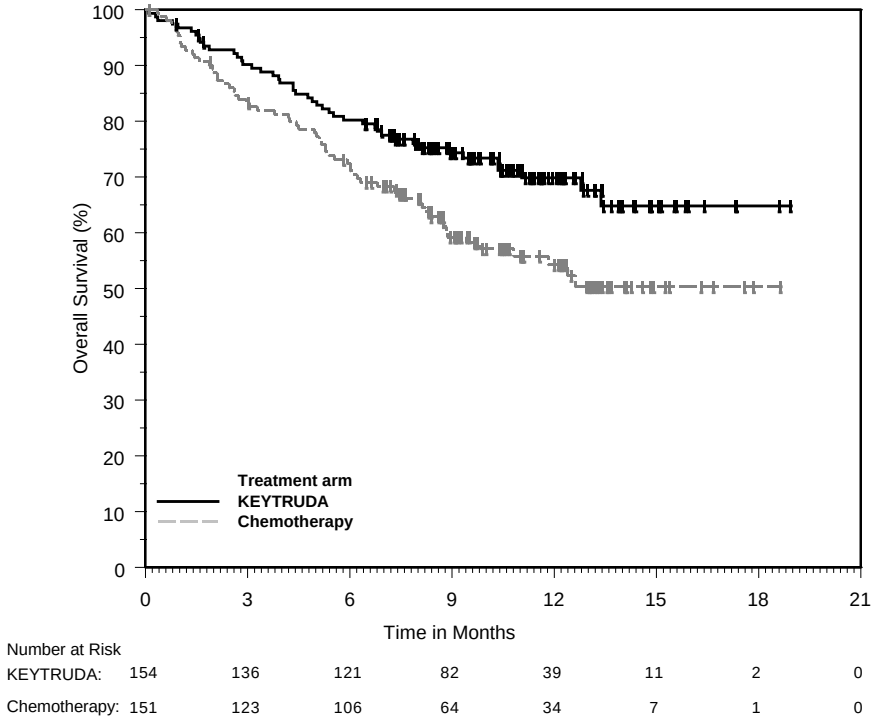
† Hazard ratio (KEYTRUDA vs. chemotherapy) based on stratified Cox proportional hazard model

‡ Based on stratified Log rank test

NA = not available

Among the 69 patients randomized to KEYTRUDA 200 mg with an objective response, response durations ranged from 1.9+ to 14.5+ months. Eighty-eight percent of these responders had a response duration of 6 months or longer (based on Kaplan-Meier estimation). Kaplan-Meier curves for OS are presented in Figure 2.

Figure 2: Kaplan-Meier Curve for Overall Survival in KN 024



Number at Risk

KEYTRUDA:	154	136	121	82	39	11	2	0
Chemotherapy:	151	123	106	64	34	7	1	0

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Hematology and Pathology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

KEYTRUDA® (pembrolizumab) demonstrated a statistically significant improvement in OS for NSCLC patients who were previously treated, in the pembrolizumab arm compared the docetaxel arm for the TPS $\geq$ 1% and TPS $\geq$ 50% groups. In addition, KEYTRUDA® (pembrolizumab) demonstrated a clinically meaningful improvement in PFS, OS and ORR in patients with metastatic NSCLC with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC and whose tumors had high PD-L1 expression (TPS $\geq$ 50%).

The performance of the PD-L1 IHC 22C3 pharmDx was also supported by the analytical validation studies.

B. Safety Conclusions

The PD-L1 IHC 22C3 pharmDx is an *in vitro* diagnostic device, which involves tumor specimens collected from patients with NSCLC. The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above. Risks of the PD-L1 IHC 22C3 pharmDx are associated with failure of the device to perform as expected or failure to correctly interpret test results. As PD-L1 IHC 22C3 pharmDx is intended for use to identify patients for KEYTRUDA® (pembrolizumab) therapy, if incorrect, or false, results are reported, then NSCLC patients may not receive the proper treatment. Patients with false positive results may undergo treatment with KEYTRUDA® (pembrolizumab) without much clinical benefit, and may experience adverse reactions associated with KEYTRUDA® (pembrolizumab) therapy. Patients with false negative results may not be considered for treatment with KEYTRUDA® (pembrolizumab), and therefore, may receive other treatment options. There is also a risk of delayed results, which may lead to a delay in treatment with KEYTRUDA® (pembrolizumab).

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the clinical study, which were used to support panel track PMA supplement approval as described above.

The clinical benefit of PD-L1 IHC 22C3 pharmDx was investigated in a multicenter, open-label, randomized clinical study conducted to assess the safety and efficacy of KEYTRUDA® (pembrolizumab) in patients with advanced NSCLC. Archived clinical study samples were retrospectively tested at a US based reference laboratory with PD-L1 IHC 22C3 pharmDx. KEYTRUDA® (pembrolizumab) demonstrated a robust overall response rate with a clinically meaningful duration of response in NSCLC patients with positive PD-L1 expression (TPS $\geq$ 1%) as determined by the PD-L1 IHC 22C3 pharmDx. The trial results showed that that the OS benefit in PD-L1 expression TPS $\geq$ 1% was significant. Additionally, the trial showed benefits in PFS and ORR in the PD-L1 positive groups. The response rate in patients with positive PD-L1 expresssing NSCLC is better than what would be expected of available therapy and represents an improvement on a surrogate endpoint that is reasonably likely to predict clinical benefit.

Additional factors to be considered in determining probable risks and benefits for the PD-L1 IHC 22C3 pharmDx included: analytical performance of the device, and the availability of alternative tests. The primary risks associated with the PD-L1 IHC 22C3 pharmDx are the possibility of inaccurate, or false, results that may lead to mismanagement of patient treatment. The performance of the device is supported by analytical validation studies. The PD-L1 IHC 22C3 pharmDx is currently FDA-approved for the selection of previously treated NSCLC patients with high PD-L1 expression (TPS $\geq$ 50%) for treatment with KEYTRUDA. Thus, the probable benefits are based on evaluation that the test performs consistently and provides clinically relevant results for evaluating PD-L1 status (TPS $\geq$ 1%) in NSCLC patients who are being considered for KEYTRUDA.

1 Patient Perspectives
This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for device indication (stated above) the probable benefits outweigh the probable risks.

D. Overall Conclusions

The performance data presented in this summary support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the open-label, randomized clinical study support the use of the PD-L1 IHC 22C3 pharmDx as an aid in selecting patients with previously treated NSCLC with PD-L1 TPS ≥ 1% who may be eligible for treatment with KEYTRUDA® (pembrolizumab). These patients showed a statistically significant improvement in OS when treated with KEYTRUDA® (pembrolizumab). Additionally, the data support the clinical performance of the PD-L1 IHC 22C3 pharmDx as an aid in selecting patients with metastatic NSCLC whose tumors have high PD-L1expression (TPS ≥50%) with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC who may be eligible for treatment with KEYTRUDA® (pembrolizumab).

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on October 24, 2016. The final conditions of approval cited in the approval order are described below.

In the precision studies, limited numbers of samples from the intended use specimen type were evaluated using PD-L1 IHC 22C3 pharmDx. Additional testing of samples and analyses should be conducted for a comprehensive characterization of the performance of your device. The results from these studies will be included in the labeling.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.