# EXHIBIT 4



JHU 2177
Merck Sharp v. Johns Hopkins
IPR2024-00625

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| **Claim 1 [pre]** | **Merck's Keytruda (Pembrolizumab)** |
|---|---|
| A method for treating cancer in a patient in need thereof comprising: | Merck's FDA-approved label for Keytruda (pembrolizumab) ("Keytruda Label")[1] instructs physicians to use Keytruda to treat cancer in a patient in need thereof.<br><br>For example, the Keytruda Label indicates that Keytruda is approved for the treatment of cancer in patients having MSI-H or dMMR solid tumors (Indication 1.7),[2] MSI-H or dMMR colorectal cancer (Indication 1.8), and endometrial cancer (Indication 1.15)[3].<br><br>**<u>Indications 1.7 and 1.8 (1.8 and 1.9 in the March 2021 Keytruda Label)</u>** |

[1] While the March 2021, March 2022, and August 2023 Keytruda Labels are cited herein, Hopkins hereby incorporates by reference all Keytruda Labels existing from the earliest issuance date of the asserted patents (March 2021) to present, which have substantially the same relevant information.

[2] Unless specified otherwise, the Indication No. provided corresponds to the Indication No. of the current Keytruda Label (*i.e.*, 08/2023 Keytruda Label).

[3] The revisions in the November 2023 Keytruda Label changed the indication of endometrial carcinoma from Indication 1.15 to Indication 1.16.

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [pre] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)<br>• solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or<br>• colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.<br>This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.8)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.<br>Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.<br>**1.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).<br><br>[03/2021 Keytruda Label at 5.]<br><br>**1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.<br>This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.7)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.<br>Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.<br>**1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC). |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [pre] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | [03/2022 Keytruda Label at 5.]<br><br>**1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options *[see Dosage and Administration (2.1)]*.<br>**1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.<br><br>[08/2023 Keytruda Label at 5.]<br><br>**<u>Indicaiton 1.15</u>**<br><br>In addition, in March 2022, the Keytruda Label was updated to include single-agent Keytruda treatment in patients with MSI-H or dMMR endometrial carcinoma (Indication 1.15).<br><br>**1.15 Endometrial Carcinoma**<br>KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.<br>KEYTRUDA, as a single agent, is indicated for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation *[see Dosage and Administration (2.1)]*.<br><br>[03/2022 Kyetruda Label at 6; *see also* 08/2023 Keytruda Label at 6.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| **Claim 1 [a]** | **Merck's Keytruda (Pembrolizumab)** |
|---|---|
| selecting a patient who has an unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient tumor; and | The Keytruda Label instructs physicians to select for treatment with Keytruda patients who have an unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient tumor.<br>For example, the Dosage and Administration section (Section 2) of the Keytruda Label instructs physicians to select patients having a cancer that is either MSI-H or dMMR for treatment with Keytruda according to Indications 1.7, 1.8, and 1.15.<br><br>**2 DOSAGE AND ADMINISTRATION**<br>**2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, Cervical Cancer, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, TMB-H Cancer, or TNBC**<br>Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:<br>• stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.2)]*.<br>• metastatic NSCLC *[see Clinical Studies (14.2)]*.<br>• first-line treatment of metastatic or unresectable, recurrent HNSCC *[see Clinical Studies (14.4)]*.<br>• metastatic urothelial carcinoma *[see Clinical Studies (14.7)]*.<br>• metastatic gastric cancer *[see Clinical Studies (14.10)]*. If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing.<br>• previously treated recurrent locally advanced or metastatic esophageal cancer *[see Clinical Studies (14.11)]*.<br>• recurrent or metastatic cervical cancer *[see Clinical Studies (14.12)]*.<br>For the MSI-H/dMMR indications, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens *[see Clinical Studies (14.8, 14.9)]*.<br><br>[03/2021 Keytruda Label at 7.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [a] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **2 DOSAGE AND ADMINISTRATION**<br>**2.1 Patient Selection**<br>Patient Selection for Single-Agent Treatment<br>Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:<br>• stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.2)]*.<br>• metastatic NSCLC *[see Clinical Studies (14.2)]*.<br>• first-line treatment of metastatic or unresectable, recurrent HNSCC *[see Clinical Studies (14.3)]*.<br>• previously treated recurrent locally advanced or metastatic esophageal cancer *[see Clinical Studies (14.10)]*.<br>• recurrent or metastatic cervical cancer with disease progression on or after chemotherapy *[see Clinical Studies (14.11)]*.<br>For the MSI-H/dMMR indications, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens *[see Clinical Studies (14.7, 14.8)]*.<br>[03/2022 Keytruda Label at 7.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [a] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **2 DOSAGE AND ADMINISTRATION**<br>**2.1 Patient Selection**<br>Information on FDA-approved tests for patient selection is available at: **http://www.fda.gov/CompanionDiagnostics** .<br>Patient Selection for Single-Agent Treatment<br>Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:<br>• Stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.2)]*.<br>• metastatic NSCLC *[see Clinical Studies (14.2)]*.<br>• first-line treatment of metastatic or unresectable, recurrent HNSCC *[see Clinical Studies (14.3)]*.<br>• previously treated recurrent locally advanced or metastatic esophageal cancer *[see Clinical Studies (14.10)]*.<br>• recurrent or metastatic cervical cancer with disease progression on or after chemotherapy *[see Clinical Studies (14.11)]*.<br>For the MSI-H/dMMR indications, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens *[see Clinical Studies (14.7, 14.8)]*.<br>[08/2023 Keytruda Label at 7.]<br>The Dosage and Administration section of the Keytruda Label refers physicians to FDA's website to find information necessary to test or have tested a biological sample obtained from a patient to determine whether the cancer is MSI-H or dMMR.<br>Information on FDA-approved tests used for patient selection is available at: **http://www.fda.gov/CompanionDiagnostics** .<br>[03/2022 Keytruda Label at 7; *see also* 08/2023 Keytruda Label at 7.]<br>Moreover, Clinical Studies sections 14.7 and 14.8 (or 14.8 and 14.9 in the 03/2021 Keytruda Label) instructs physicians to test or have tested the patient tumor's MSI-H/dMMR status via local PCR, IHC, or third-party tests such as *e.g.*, FoundationOne®CDx and VENTANA MMR |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [a] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | RxDx Panel.<br><br>The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests.<br><br>[03/2021 Keytruda Label at 83; *see also* 03/2022 Keytruda Label at 90.]<br><br>**14.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br><br>The efficacy of KEYTRUDA was investigated in 504 patients with MSI-H or dMMR cancers enrolled in three multicenter, non-randomized, open-label, multi-cohort trials: KEYNOTE-164 (NCT02460198), KEYNOTE-158 (NCT02628067), and KEYNOTE-051 (NCT02332668). All trials excluded patients with autoimmune disease or a medical condition that required immunosuppression. Regardless of histology, MSI or MMR tumor status was determined using polymerase chain reaction (PCR; local or central) or immunohistochemistry (IHC; local or central), respectively.<br><br>[08/2023 Keytruda Label at 98.]<br><br>The FDA's website has a "List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)," from which a physician can select and use or direct the use of a commercially available MSI-H and dMMR biomarker assay to test a patient's biological sample. |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [a] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)**<br>Search: keytruda<br>Export Excel<br>Show 10 entries |

| Diagnostic Name (Manufacturer) | Indication - Sample Type | Drug Trade Name (Generic) NDA / BLA | Biomarker(s) | Biomarker(s) (Details) | PMA / 510(k) / 513(f)(2) / HDE (Approval / Clearance / Grant Date) |
|---|---|---|---|---|---|
| FoundationOne CDx (Foundation Medicine, Inc.) | Solid Tumors - Tissue | Keytruda (pembrolizumab) BLA 125514 | TMB | TMB ≥ 10 mutations per megabase | P170019/S016 (06/16/2020) |
| FoundationOne CDx (Foundation Medicine, Inc.) | Solid Tumors - Tissue | Keytruda (pembrolizumab) BLA 125514 | MSI-High | Microsatellite instability-High (MSI-H) | P170019/S029 (02/18/2022) |
| PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.) | Non-Small Cell Lung Cancer (NSCLC) - Tissue | Keytruda (pembrolizumab) BLA 125514 | PD-L1 | PD-L1 protein expression | P150013 (10/02/2015) |
| PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.) | Cervical Cancer - Tissue | Keytruda (pembrolizumab) BLA 125514 | PD-L1 | PD-L1 protein expression | P150013/S009 (06/12/2018) |
| PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.) | Head and Neck Squamous Cell Carcinoma (HNSCC) - Tissue | Keytruda (pembrolizumab) BLA 125514 | PD-L1 | PD-L1 protein expression | P150013/S014 (06/10/2019) |
| PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.) | Esophageal Squamous Cell Carcinoma (ESCC) - Tissue | Keytruda (pembrolizumab) BLA 125514 | PD-L1 | PD-L1 protein expression | P150013/S016 (07/30/2019) |
| PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.) | Triple-Negative Breast Cancer (TNBC) - Tissue | Keytruda (pembrolizumab) BLA 125514 | PD-L1 | PD-L1 protein expression | P150013/S020 (11/13/2020) |
| Ventana MMR RxDx Panel (Ventana Medical Systems, Inc.) | Solid Tumors | Keytruda (pembrolizumab) BLA 125514 | deficient mismatch repair (dMMR) proteins | MLH1, PMS2, MSH2 and MSH6 | P210001/S001 (03/21/2022) |
| Ventana MMR RxDx Panel (Ventana Medical Systems, Inc.) | Endometrial Carcinoma (EC) - Tissue | Keytruda (pembrolizumab) BLA 125514 in combination with Lenvima (lenvatinib) NDA 206947 | proficient mismatch repair (pMMR) proteins | MLH1, PMS2, MSH2 and MSH6 | P210001/S002 (06/16/2022) |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [a] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | [https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools (last visited on 11/14/2023).]<br><br>For example, the "FoundationOne®CDx (F1CDx) is a qualitative next generation sequencing based *in vitro* diagnostic test that uses targeted high throughput hybridization-based capture technology for detection of substitutions, insertion and deletion alterations (indels) and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) . . . ." *See* SSED PMA P170019/S029 at 2; *see also* SSED PMA P170019/S016 at 2.<br><br>To determine a patient's MSI status, F1CDx employs a fraction based (FB) MSI algorithm to categorize a tumor specimen as MSI-High (MSI-H) or microsatellite stable (MSS). The FB-MSI algorithm calculates the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score) based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. Two FB-MSI score thresholds are applied to classify a tumor specimen as having MSI-H or MSS status. MSI-H status is reported for patients with solid tumors whose samples have FB-MSI scores ≥ 0.0124 while MSS status is reported for patients with solid tumors whose samples have FB-MSI scores ≤ 0.0041. Per the F1CDx assay, a patient whose tumor has an MSI-H score ≥ 0.0124 is reported as eligible for treatment with KEYTRUDA. For patients with solid tumors whose samples have FB-MSI scores >0.0041 and <0.0124, an MSI "Cannot be Determined" result is reported. Patients with this result should be re-tested with a validated orthogonal (alternative) method as these MSI scores represent a range of scores with low reliability. Patients with solid tumors may also receive an MSI status reported as MSI-Cannot Be Determined due to a quality control (QC) failure. Patients with this result should consider re-testing with FoundationOneCDx or an orthogonal (alternative) method, if clinically appropriate.<br><br>[SSED PMA P170019/S029 at 10; *see also* SSED PMA P170019/S016 at 9.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [a] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | *See also, e.g.*, "VENTANA MMR RxDx Panel," generically known as "[i]mmunohistochemistry test, DNA mismatch repair (MMR) [p]rotein assay," which is used for "identifying patients with solid tumors with dMMR status who may benefit from treatment with KEYTRUDA." [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P210001S001 (last visited 11/14/2023).]<br><br>At the time of the Keytruda Label, numerous biomarker assays for determining MSI-H/dMMR status were available, including the Promega OncoMate® MSI Dx Analysis System. *See, e.g.*, https://www.promega.com/products/microsatellite-instability-msi-testing/clinical-msi-testing-ivd/oncomate-msi-dx-analysis-system/.<br><br>Physicians prescribing Keytruda in accordance with the Keytruda Label would have been aware of these microsatellite and MMR markers and would have understood how to test for them in accordance with the Keytruda Label. |

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| [b] administering an effective amount of pembrolizumab to the patient; | The Keytruda Label instructs physicians to use Keytruda (pembrolizumab) to treat cancer in a patient, wherein the cancer is MSI-H or dMMR, by administering an effective amount of Keytruda to a patient.<br><br>For example, the Keytruda Label discloses that Keytruda is a pembrolizumab injection.<br><br>**KEYTRUDA® (pembrolizumab) injection, for intravenous use**<br>**Initial U.S. Approval: 2014**<br><br>[03/2021 Keytruda Label at 1; 03/2022 Keytruda Label at 1; 08/2023 Keytruda Label at 1.]<br><br>The Recommended Dosage section of the Keytruda Label provides the recommended dosages of Keytruda, as well as the duration/timing of treatment based on the indication, wherein the |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | indication is directed to cancer confirmed to be MSI-H/dMMR. |

**2.2 Recommended Dosage**

**Table 1: Recommended Dosage**

| Indication | Recommended Dosage of KEYTRUDA | Duration/Timing of Treatment |
|---|---|---|
| **Monotherapy** | | |
| Adult patients with unresectable or metastatic melanoma | 200 mg every 3 weeks* or 400 mg every 6 weeks* | Until disease progression or unacceptable toxicity |
| Adjuvant treatment of adult patients with melanoma | 200 mg every 3 weeks* or 400 mg every 6 weeks* | Until disease recurrence, unacceptable toxicity, or up to 12 months |
| Adult patients with NSCLC, SCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC | 200 mg every 3 weeks* or 400 mg every 6 weeks* | Until disease progression, unacceptable toxicity, or up to 24 months |
| Adult patients with high-risk BCG-unresponsive NMIBC | 200 mg every 3 weeks* or 400 mg every 6 weeks* | Until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months |
| Pediatric patients with cHL, PMBCL, MSI-H Cancer, MCC, or TMB-H Cancer | 2 mg/kg every 3 weeks (up to a maximum of 200 mg)* | Until disease progression, unacceptable toxicity, or up to 24 months |

* 30-minute intravenous infusion

† Refer to the Prescribing Information for the agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

‡ When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer.

[03/2021 Keytruda Label at 8.]

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **2.2 Recommended Dosage**<br>**Table 1: Recommended Dosage**<br>[illegible] |

| Indication | Recommended Dosage of KEYTRUDA | Duration/Timing of Treatment |
|---|---|---|
| **Monotherapy** | | |
| Adult patients with unresectable or metastatic melanoma | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks* | Until disease progression or unacceptable toxicity |
| Adjuvant treatment of adult patients with melanoma, NSCLC, or RCC | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks* | Until disease recurrence, unacceptable toxicity, or up to 12 months |
| Adult patients with NSCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, MSI-H or dMMR Endometrial Carcinoma, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks* | Until disease progression, unacceptable toxicity, or up to 24 months |
| Adult patients with high-risk BCG-unresponsive NMIBC | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks* | Until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months |
| Pediatric patients with cHL, PMBCL, MSI-H or dMMR Cancer, MCC, or TMB-H Cancer | 2 mg/kg every 3 weeks (up to a maximum of 200 mg)* | Until disease progression, unacceptable toxicity, or up to 24 months |
| Pediatric patients (12 years and older) for adjuvant treatment of melanoma | 2 mg/kg every 3 weeks (up to a maximum of 200 mg)* | Until disease recurrence, unacceptable toxicity, or up to 12 months |

* 30-minute intravenous infusion
† Refer to the Prescribing Information for the agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.
‡ When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer.
§ Patients who experience disease progression or unacceptable toxicity related to KEYTRUDA with neoadjuvant treatment in combination with chemotherapy should not receive adjuvant single agent KEYTRUDA.

[08/2023 Keytruda Label at 8-9; *see also* 03/2022 Keytruda Label at 8-9.]

The Preparation and Administration section of the Keytruda Label provides instructions for preparing and administering Keytruda (pembrolizumab) to patients:

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **2.4 Preparation and Administration**<br>Preparation for Intravenous Infusion<br>• Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.<br>• Dilute KEYTRUDA injection (solution) prior to intravenous administration.<br>• Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. **Mix diluted solution by gentle inversion.** Do not shake. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.<br>• Discard any unused portion left in the vial.<br>Storage of Diluted Solution<br>The product does not contain a preservative.<br>Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:<br>• At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.<br>• Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.<br>Discard after 6 hours at room temperature or after 96 hours under refrigeration.<br>Do not freeze.<br>Administration<br>• Administer diluted solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.<br>• Do not co-administer other drugs through the same infusion line.<br><br>[03/2021 Keytruda Label at 10-11; 03/2022 Keytruda Label at 11; 08/2023 Keytruda Label at 11.]<br><br>The Keytruda Label includes clinical trial results showing that the recommended dosages of Keytruda are therapeutically effective among patients with MSI-H or dMMR solid tumors relevant to Indication 1.7 (or Indication 1.8 for 03/2021 Keytruda Label): |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|

**14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**

The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

**Table 57: MSI-H Trials**

| Study | Design and Patient Population | Number of Patients | MSI-H/dMMR Testing | Dosage | Prior Therapy |
|---|---|---|---|---|---|
| **KEYNOTE-016** NCT01876511 | • prospective, investigator-initiated<br>• 6 sites<br>• patients with CRC and other tumors | 28 CRC<br>30 non-CRC | local PCR or IHC | 10 mg/kg every 2 weeks | • CRC: ≥ 2 prior regimens<br>• Non-CRC: ≥1 prior regimen |
| **KEYNOTE-164** NCT02460198 | • prospective international multi-center<br>• CRC | 61 | local PCR or IHC | 200 mg every 3 weeks | Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb |
| **KEYNOTE-012** NCT01848834 | • retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer | 6 | central PCR | 10 mg/kg every 2 weeks | ≥1 prior regimen |
| **KEYNOTE-028** NCT02054806 | • retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC | 5 | central PCR | 10 mg/kg every 2 weeks | ≥1 prior regimen |
| **KEYNOTE-158** NCT02628067 | • prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC<br>• retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts | 19 | local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts) | 200 mg every 3 weeks | ≥1 prior regimen |
| **Total** | | **149** | | | |

CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **Table 58: Efficacy Results for Patients with MSI-H/dMMR Cancer** |

| Endpoint | KEYTRUDA n=149 |
|---|---|
| **Objective Response Rate** | |
| ORR (95% CI) | 39.6% (31.7, 47.9) |
| Complete response rate | 7.4% |
| Partial response rate | 32.2% |
| **Duration of Response** | |
| Median in months (range) | NR (1.6+, 22.7+) |
| % with duration ≥6 months | 78% |

NR = not reached

**Table 59: Response by Tumor Type**

| | N | Objective Response Rate n (%) | 95% CI | Duration of Response range (months) |
|---|---|---|---|---|
| CRC | 90 | 32 (36%) | (26%, 46%) | (1.6+, 22.7+) |
| Non-CRC | 59 | 27 (46%) | (33%, 59%) | (1.9+, 22.1+) |
| Endometrial cancer | 14 | 5 (36%) | (13%, 65%) | (4.2+, 17.3+) |
| Biliary cancer | 11 | 3 (27%) | (6%, 61%) | (11.6+, 19.6+) |
| Gastric or GE junction cancer | 9 | 5 (56%) | (21%, 86%) | (5.8+, 22.1+) |
| Pancreatic cancer | 6 | 5 (83%) | (36%, 100%) | (2.6+, 9.2+) |
| Small intestinal cancer | 8 | 3 (38%) | (9%, 76%) | (1.9+, 9.1+) |
| Breast cancer | 2 | PR, PR | | (7.6, 15.9) |
| Prostate cancer | 2 | PR, SD | | 9.8+ |
| Bladder cancer | 1 | NE | | |
| Esophageal cancer | 1 | PR | | 18.2+ |
| Sarcoma | 1 | PD | | |
| Thyroid cancer | 1 | NE | | |
| Retroperitoneal adenocarcinoma | 1 | PR | | 7.5+ |
| Small cell lung cancer | 1 | CR | | 8.9+ |
| Renal cell cancer | 1 | PD | | |

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

[03/2021 Keytruda Label at 82-84; *see also* 03/2022 Keytruda Label at 89-90.]

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **14.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>The efficacy of KEYTRUDA was investigated in 504 patients with MSI-H or dMMR cancers enrolled in three multicenter, non-randomized, open-label, multi-cohort trials: KEYNOTE-164 (NCT02460198), KEYNOTE-158 (NCT02628067), and KEYNOTE-051 (NCT02332668). All trials excluded patients with autoimmune disease or a medical condition that required immunosuppression. Regardless of histology, MSI or MMR tumor status was determined using polymerase chain reaction (PCR; local or central) or immunohistochemistry (IHC; local or central), respectively.<br>• KEYNOTE-164 enrolled 124 patients with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with fluoropyrimidine and either oxaliplatin or irinotecan +/- anti-VEGF/EGFR mAb-based therapy.<br>• KEYNOTE-158 enrolled 373 patients with advanced MSI-H or dMMR non-colorectal cancers (non-CRC) who had disease progression following prior therapy. Patients were either prospectively enrolled with MSI-H/dMMR tumors (Cohort K) or retrospectively identified in one of 10 solid tumor cohorts (Cohorts A-J).<br>• KEYNOTE-051 enrolled 7 pediatric patients with MSI-H or dMMR cancers.<br>Adult patients received KEYTRUDA 200 mg every 3 weeks (pediatric patients received 2 mg/kg every 3 weeks) until unacceptable toxicity, disease progression, or a maximum of 24 months. In KEYNOTE-164 and KEYNOTE-158, assessment of tumor status was performed every 9 weeks through the first year, then every 12 weeks thereafter. In KEYNOTE-051, assessment of tumor status was performed every 8 weeks for 24 weeks, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ in KEYNOTE-158) and as assessed by the investigator according to RECIST v1.1 in KEYNOTE-051. |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | Efficacy results are summarized in Tables 69 and 70. |

**Table 69: Efficacy Results for Patients with MSI-H/dMMR Cancer**

| Endpoint | KEYTRUDA n=504* |
|---|---|
| **Objective Response Rate** | |
| ORR (95% CI)† | 33.3% (29.2, 37.6) |
| Complete response rate | 10.3% |
| Partial response rate | 23.0% |
| **Duration of Response** | n=168 |
| Median in months (range) | 63.2 (1.9+, 63.9+) |
| % with duration ≥12 months | 77% |
| % with duration ≥36 months | 39% |

* Median follow-up time of 20.1 months (range 0.1 to 71.4 months)
† Of the 7 pediatric patients from KEYNOTE-051, 1 patient had a radiographic complete response after initial growth of their tumor but is not reflected in the results.
\+ Denotes ongoing response

**Table 70: Response by Tumor Type**

| | N | Objective Response Rate n (%) | 95% CI | Duration of Response range (months) |
|---|---|---|---|---|
| CRC | 124 | 42 (34%) | (26%, 43%) | (4.4, 58.5+) |
| Non-CRC* | 380 | 126 (33%) | (28%, 38%) | (1.9+, 63.9+) |
| Endometrial cancer | 94 | 47 (50%) | (40%, 61%) | (2.9, 63.2) |
| Gastric or GE junction cancer | 51 | 20 (39%) | (26%, 54%) | (1.9+, 63.0+) |
| Small intestinal cancer | 27 | 16 (59%) | (39%, 78%) | (3.7+, 57.3+) |
| Brain cancer | 27† | 1 (4%)‡ | (0%, 19%) | 18.9 |
| Ovarian cancer | 25 | 8 (32%) | (15%, 54%) | (4.2, 56.6+) |
| Biliary cancer | 22 | 9 (41%) | (21%, 64%) | (6.2, 49.0+) |
| Pancreatic cancer | 22 | 4 (18%) | (5%, 40%) | (8.1, 24.3+) |
| Sarcoma | 14 | 3 (21%) | (5%, 51%) | (35.4+, 57.2+) |
| Breast cancer | 13 | 1 (8%) | (0%,36%) | 24.3+ |
| Other§ | 13 | 4 (31%) | (9%, 61%) | (6.2+, 32.3+) |
| Cervical cancer | 11 | 1 (9%) | (0%, 41%) | 63.9+ |
| Neuroendocrine cancer | 11 | 1 (9%) | (0%, 41%) | 13.3 |
| Prostate cancer | 8 | 1 (13%) | (0%, 53%) | 24.5+ |
| Adrenocortical cancer | 7 | 1 (14%) | (0%, 58%) | 4.2 |
| Mesothelioma | 7 | 0 (0%) | (0%, 41%) | |
| Thyroid cancer | 7 | 1 (14%) | (0%, 58%) | 8.2 |
| Small cell lung cancer | 6 | 2 (33%) | (4%, 78%) | (20.0, 47.5) |
| Bladder cancer | 6 | 3 (50%) | (12%, 88%) | (35.6+, 57.5+) |
| Salivary cancer | 5 | 2 (40%) | (5%, 85%) | (42.6+, 57.8+) |
| Renal cell cancer | 4 | 1 (25%) | (0%, 81%) | 22.0 |

* Results include patients in Cohort K of KEYNOTE-158 that were later determined to be pMMR or not MSI-H by central testing
† Includes 6 pediatric patients with brain cancer
‡ In addition to the 1 adult responder, 1 pediatric patient had a radiographic complete response after initial growth of their tumor.
§ Includes tumor type (n): anal (3), HNSCC (1), nasopharyngeal (1), retroperitoneal (1), testicular (1), vaginal (1), vulvar (1), appendiceal adenocarcinoma, NOS (1), hepatocellular carcinoma (1), and carcinoma of unknown origin (1). Includes 1 pediatric patient with abdominal adenocarcinoma.
\+ Denotes ongoing response

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | [08/2023 Keytruda Label at 98-99.]<br><br>The Keytruda Label also includes clinical trial results showing that the recommended dosages of Keytruda are therapeutically effective among patients with MSI-H or dMMR colorectal tumors relevant to Indication 1.8 (Indication 1.9 for 03/2021 Keytruda Label).<br><br>**14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.<br><br>Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks: |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **Table 60: Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-177** |

| Endpoint | KEYTRUDA 200 mg every 3 weeks n=153 | Chemotherapy n=154 |
|---|---|---|
| **PFS** | | |
| Number (%) of patients with event | 82 (54%) | 113 (73%) |
| Median in months (95% CI) | 16.5 (5.4, 32.4) | 8.2 (6.1, 10.2) |
| Hazard ratio* (95% CI) | 0.60 (0.45, 0.80) | |
| p-Value† | 0.0004 | |
| **Objective Response Rate‡** | | |
| ORR (95% CI) | 44% (35.8, 52.0) | 33% (25.8, 41.1) |
| Complete response rate | 11% | 4% |
| Partial response rate | 33% | 29% |
| **Duration of Response‡§** | | |
| Median in months (range) | NR (2.3+, 41.4+) | 10.6 (2.8, 37.5+) |
| % with duration ≥12 months¶ | 75% | 37% |
| % with duration ≥24 months¶ | 43% | 18% |

* Based on Cox regression model
† Two-sided p-value based on log-rank test (compared to a significance level of 0.0234)
‡ Based on confirmed response by BICR review
§ Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm
¶ Based on observed duration of response
\+ Denotes ongoing response
NR = not reached

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

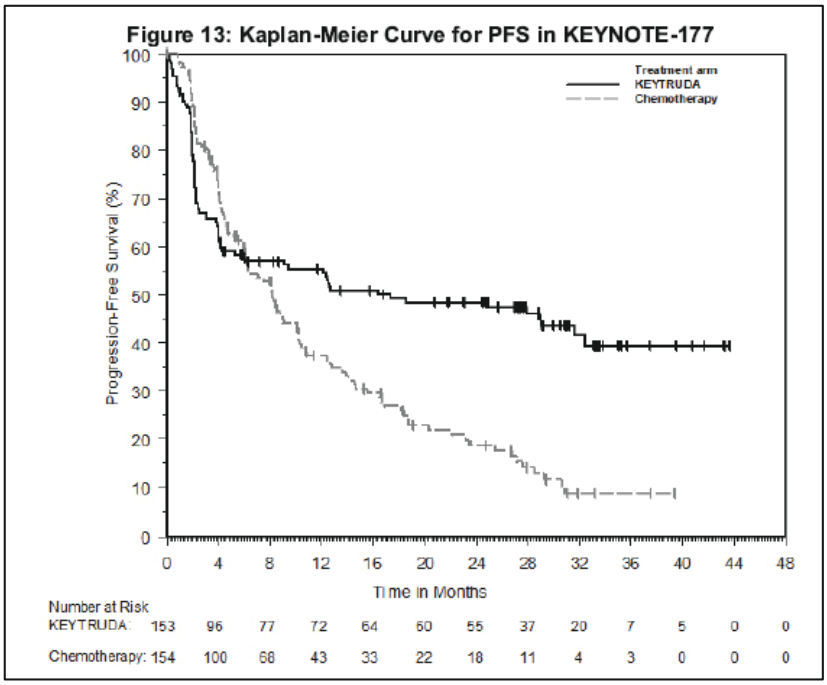
| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| |  <br>[03/2021 Keytruda Label at 84-86; *see also* 03/2022 Keytruda Label at 90-92; *see also* 08/2023 Keytruda Label at 100-101.]<br><br>In March of 2022, the Keytruda Label was updated to include clinical trial results showing that the recommended dosages of single-agent Keytruda are therapeutically effective among patients with MSI-H or dMMR endometrial tumors relevant to Indication 1.15. |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1[b] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma<br>The efficacy of KEYTRUDA was investigated in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial enrolled 90 patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma in Cohorts D and K who received at least one dose of KEYTRUDA. MSI or MMR tumor status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.<br><br>**Table 80: Efficacy Results in Patients with Advanced MSI-H or dMMR Endometrial Carcinoma in KEYNOTE-158**<br>**Endpoint** / **KEYTRUDA n=90***<br>**Objective Response Rate**<br>ORR (95% CI): 46% (35, 56)<br>Complete response rate: 12%<br>Partial response rate: 33%<br>**Duration of Response**: n=41<br>Median in months (range): NR (2.9, 55.7+)<br>% with duration ≥12 months: 68%<br>% with duration ≥24 months: 44%<br>* Median follow-up time of 16.0 months (range 0.5 to 62.1 months)<br>+ Denotes ongoing response<br>NR = not reached<br><br>[03/2022 Keytruda Label at 114-115; *see also* 08/2023 Keytruda Label at 123-124.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| **Claim 1 [c]** | **Merck's Keytruda (Pembrolizumab)** |
|---|---|
| wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status. | The Keytruda Label instructs physicians to use Keytruda to treat cancer in a patient wherein the cancer is MSI-H or dMMR, and treatment with Keytruda results in an outcome that is improved as compared to a corresponding outcome that would be observed from administration of Keytruda to a reference patient whose tumor does not exhibit MSI-H/dMMR status.<br><br>For example, Clinical Studies Section 14.7 of the Keytruda Label (Section 14.8 of the 03/2021 Keytruda Label) demonstrates improved outcome (*e.g.*, progression free survival and/or objective response rate) following treatment with Keytruda in MSI-H/dMMR cancers.<br><br>**14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR. |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **Table 57: MSI-H Trials** |

| Study | Design and Patient Population | Number of Patients | MSI-H/dMMR Testing | Dosage | Prior Therapy |
|---|---|---|---|---|---|
| **KEYNOTE-016** NCT01876511 | • prospective, investigator-initiated<br>• 6 sites<br>• patients with CRC and other tumors | 28 CRC<br>30 non-CRC | local PCR or IHC | 10 mg/kg every 2 weeks | • CRC: ≥ 2 prior regimens<br>• Non-CRC: ≥1 prior regimen |
| **KEYNOTE-164** NCT02460198 | • prospective international multi-center<br>• CRC | 61 | local PCR or IHC | 200 mg every 3 weeks | Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb |
| **KEYNOTE-012** NCT01848834 | • retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer | 6 | central PCR | 10 mg/kg every 2 weeks | ≥1 prior regimen |
| **KEYNOTE-028** NCT02054806 | • retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC | 5 | central PCR | 10 mg/kg every 2 weeks | ≥1 prior regimen |
| **KEYNOTE-158** NCT02628067 | • prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC<br>• retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts | 19 | local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts) | 200 mg every 3 weeks | ≥1 prior regimen |
| **Total** | | **149** | | | |

CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|

**Table 58: Efficacy Results for Patients with MSI-H/dMMR Cancer**

| Endpoint | KEYTRUDA n=149 |
|---|---|
| **Objective Response Rate** | |
| ORR (95% CI) | 39.6% (31.7, 47.9) |
| Complete response rate | 7.4% |
| Partial response rate | 32.2% |
| **Duration of Response** | |
| Median in months (range) | NR (1.6+, 22.7+) |
| % with duration ≥6 months | 78% |

NR = not reached

**Table 59: Response by Tumor Type**

| | N | Objective Response Rate n (%) | 95% CI | Duration of Response range (months) |
|---|---|---|---|---|
| CRC | 90 | 32 (36%) | (26%, 46%) | (1.6+, 22.7+) |
| Non-CRC | 59 | 27 (46%) | (33%, 59%) | (1.9+, 22.1+) |
| Endometrial cancer | 14 | 5 (36%) | (13%, 65%) | (4.2+, 17.3+) |
| Biliary cancer | 11 | 3 (27%) | (6%, 61%) | (11.6+, 19.6+) |
| Gastric or GE junction cancer | 9 | 5 (56%) | (21%, 86%) | (5.8+, 22.1+) |
| Pancreatic cancer | 6 | 5 (83%) | (36%, 100%) | (2.6+, 9.2+) |
| Small intestinal cancer | 8 | 3 (38%) | (9%, 76%) | (1.9+, 9.1+) |
| Breast cancer | 2 | PR, PR | | (7.6, 15.9) |
| Prostate cancer | 2 | PR, SD | | 9.8+ |
| Bladder cancer | 1 | NE | | |
| Esophageal cancer | 1 | PR | | 18.2+ |
| Sarcoma | 1 | PD | | |
| Thyroid cancer | 1 | NE | | |
| Retroperitoneal adenocarcinoma | 1 | PR | | 7.5+ |
| Small cell lung cancer | 1 | CR | | 8.9+ |
| Renal cell cancer | 1 | PD | | |

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

[03/2021 Keytruda Label at 82-84; *see also* 03/2022 Keytruda Label at 89-90.]

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **14.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>The efficacy of KEYTRUDA was investigated in 504 patients with MSI-H or dMMR cancers enrolled in three multicenter, non-randomized, open-label, multi-cohort trials: KEYNOTE-164 (NCT02460198), KEYNOTE-158 (NCT02628067), and KEYNOTE-051 (NCT02332668). All trials excluded patients with autoimmune disease or a medical condition that required immunosuppression. Regardless of histology, MSI or MMR tumor status was determined using polymerase chain reaction (PCR; local or central) or immunohistochemistry (IHC; local or central), respectively.<br>• KEYNOTE-164 enrolled 124 patients with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with fluoropyrimidine and either oxaliplatin or irinotecan +/- anti-VEGF/EGFR mAb-based therapy.<br>• KEYNOTE-158 enrolled 373 patients with advanced MSI-H or dMMR non-colorectal cancers (non-CRC) who had disease progression following prior therapy. Patients were either prospectively enrolled with MSI-H/dMMR tumors (Cohort K) or retrospectively identified in one of 10 solid tumor cohorts (Cohorts A-J).<br>• KEYNOTE-051 enrolled 7 pediatric patients with MSI-H or dMMR cancers.<br>Adult patients received KEYTRUDA 200 mg every 3 weeks (pediatric patients received 2 mg/kg every 3 weeks) until unacceptable toxicity, disease progression, or a maximum of 24 months. In KEYNOTE-164 and KEYNOTE-158, assessment of tumor status was performed every 9 weeks through the first year, then every 12 weeks thereafter. In KEYNOTE-051, assessment of tumor status was performed every 8 weeks for 24 weeks, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ in KEYNOTE-158) and as assessed by the investigator according to RECIST v1.1 in KEYNOTE-051. |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|

Efficacy results are summarized in Tables 69 and 70.

**Table 69: Efficacy Results for Patients with MSI-H/dMMR Cancer**

| Endpoint | KEYTRUDA n=504* |
|---|---|
| **Objective Response Rate** | |
| ORR (95% CI)† | 33.3% (29.2, 37.6) |
| Complete response rate | 10.3% |
| Partial response rate | 23.0% |
| **Duration of Response** | n=168 |
| Median in months (range) | 63.2 (1.9+, 63.9+) |
| % with duration ≥12 months | 77% |
| % with duration ≥36 months | 39% |

* Median follow-up time of 20.1 months (range 0.1 to 71.4 months)
† Of the 7 pediatric patients from KEYNOTE-051, 1 patient had a radiographic complete response after initial growth of their tumor but is not reflected in the results.
\+ Denotes ongoing response

**Table 70: Response by Tumor Type**

| | N | Objective Response Rate n (%) | 95% CI | Duration of Response range (months) |
|---|---|---|---|---|
| CRC | 124 | 42 (34%) | (26%, 43%) | (4.4, 58.5+) |
| Non-CRC* | 380 | 126 (33%) | (28%, 38%) | (1.9+, 63.9+) |
| Endometrial cancer | 94 | 47 (50%) | (40%, 61%) | (2.9, 63.2) |
| Gastric or GE junction cancer | 51 | 20 (39%) | (26%, 54%) | (1.9+, 63.0+) |
| Small intestinal cancer | 27 | 16 (59%) | (39%, 78%) | (3.7+, 57.3+) |
| Brain cancer | 27† | 1 (4%)‡ | (0%, 19%) | 18.9 |
| Ovarian cancer | 25 | 8 (32%) | (15%, 54%) | (4.2, 56.6+) |
| Biliary cancer | 22 | 9 (41%) | (21%, 64%) | (6.2, 49.0+) |
| Pancreatic cancer | 22 | 4 (18%) | (5%, 40%) | (8.1, 24.3+) |
| Sarcoma | 14 | 3 (21%) | (5%, 51%) | (35.4+, 57.2+) |
| Breast cancer | 13 | 1 (8%) | (0%,36%) | 24.3+ |
| Other§ | 13 | 4 (31%) | (9%, 61%) | (6.2+, 32.3+) |
| Cervical cancer | 11 | 1 (9%) | (0%, 41%) | 63.9+ |
| Neuroendocrine cancer | 11 | 1 (9%) | (0%, 41%) | 13.3 |
| Prostate cancer | 8 | 1 (13%) | (0%, 53%) | 24.5+ |
| Adrenocortical cancer | 7 | 1 (14%) | (0%, 58%) | 4.2 |
| Mesothelioma | 7 | 0 (0%) | (0%, 41%) | |
| Thyroid cancer | 7 | 1 (14%) | (0%, 58%) | 8.2 |
| Small cell lung cancer | 6 | 2 (33%) | (4%, 78%) | (20.0, 47.5) |
| Bladder cancer | 6 | 3 (50%) | (12%, 88%) | (35.6+, 57.5+) |
| Salivary cancer | 5 | 2 (40%) | (5%, 85%) | (42.6+, 57.8+) |
| Renal cell cancer | 4 | 1 (25%) | (0%, 81%) | 22.0 |

* Results include patients in Cohort K of KEYNOTE-158 that were later determined to be pMMR or not MSI-H by central testing
† Includes 6 pediatric patients with brain cancer
‡ In addition to the 1 adult responder, 1 pediatric patient had a radiographic complete response after initial growth of their tumor.
§ Includes tumor type (n): anal (3), HNSCC (1), nasopharyngeal (1), retroperitoneal (1), testicular (1), vaginal (1), vulvar (1), appendiceal adenocarcinoma, NOS (1), hepatocellular carcinoma (1), and carcinoma of unknown origin (1). Includes 1 pediatric patient with abdominal adenocarcinoma.
\+ Denotes ongoing response

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | [08/2023 Keytruda Label at 98-99.]<br><br>In addition, Indication 1.7 (Indication 1.8 in the March 2021 Keytruda Label), which was "approved under accelerated approval based on tumor response rate and durability of response," instructs physicians to "[*see Clinical Studies (14.7)*]." *See* 03/2022 Keytruda Label at 5; *see also* 03/2021 Keytruda Label at 5 (Clinical Studies (14.8)).<br><br>Among the studies listed in Clinical Studies Section 14.7 is KEYNOTE-016 (NCT01876511, titled "Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)" ("MSI Clinical Trial"), which compares the efficacy of Keytruda in patients with a tumor that does not exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers (reference patients) to patients with a tumor that does exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers. *See* History of Changes for Study: NCT01876511, Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors, *clinicaltrials.gov archive* (Ex. B to Complaint) at 5.<br><br>**14.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br><br>The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.<br><br>**Table 65: MSI-H Trials**<br><br>**Study** / **Design and Patient Population** / **Number of Patients** / **MSI-H/dMMR Testing** / **Dosage** / **Prior Therapy**<br><br>**KEYNOTE-016** NCT01876511 / • prospective, investigator-initiated • 6 sites • patients with CRC and other tumors / 28 CRC 30 non-CRC / local PCR or IHC / 10 mg/kg every 2 weeks / • CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

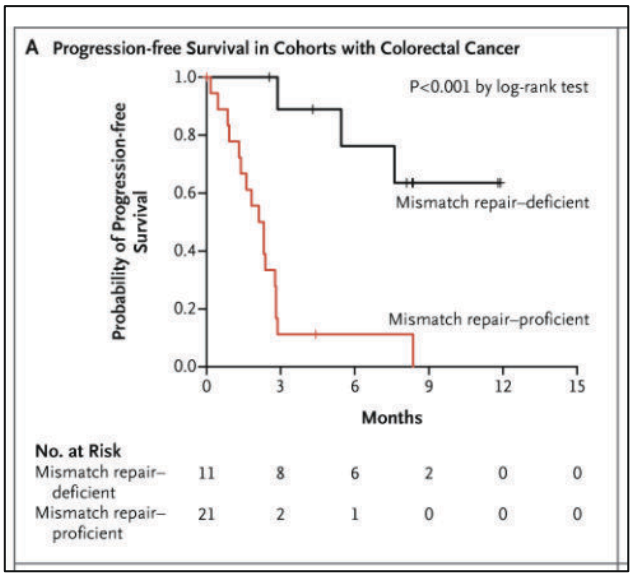
| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | [03/2022 Keytruda Label at 89; *see also* 03/2021 Keytruda Label at 82-83.]<br><br>KEYNOTE-016, as reported in the New England Journal of Medicine article "PD-1 Blockade in Tumors with Mismatch-Repair Deficiency," found that patients with MSI-high tumors exhibited improved objective response rate and progression free survival rate in comparison with patients with mismatch repair proficient tumors. *See* Le et al., *PD-1 Blockade in Tumors with Mismatch-Repair Deficiency*, N ENGL J MED. (2015) ("NEJM Article").<br><br>  <br><br><br>[NEJM Article at Figure 2.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **Table 2**<br>Objective Responses According to RECIST Criteria.<br><br>**Type of Response** / **Mismatch Repair–Deficient Colorectal Cancer (N = 10)** / **Mismatch Repair–Proficient Colorectal Cancer (N = 18)** / **Mismatch Repair–Deficient Noncolorectal Cancer (N = 7)**<br>Complete response — no. (%) / 0 / 0 / 1 (14)*<br>Partial response — no. (%) / 4 (40) / 0 / 4 (57)†<br>Stable disease at week 12 — no. (%) / 5 (50) / 2 (11) / 0<br>Progressive disease — no. (%) / 1 (10) / 11 (61) / 2 (29)<br>Could not be evaluated — no. (%)‡ / 0 / 5 (28) / 0<br>Objective response rate (95% CI) — % / 40 (12–74) / 0 (0–19) / 71 (29–96)<br>Disease control rate (95% CI) — %§ / 90 (55–100) / 11 (1–35) / 71 (29–96)<br>Median duration of response — wk / Not reached / NA¶ / Not reached<br>Median time to response (range) — wk / 28 (13–35) / NA¶ / 12 (10–13)<br><br>*The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.<br>†One patient had a partial response at 12 weeks.<br>‡Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression.<br>§The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more.<br>¶The median time to response was not applicable (NA) because no responses were observed among patients with mismatch repair–proficient colorectal cancer.<br><br>[NEJM Article at Table 2.]<br><br>A physician would understand, based on the studies of KEYNOTE-016 to which Merck directs them, that Keytruda improves the outcomes (*e.g.*, progression free survival, objective response rate) in patients having tumors that exhibit MSI-H or dMMR compared to those patients with tumors that do not.<br><br>The citation to KEYNOTE-016 corresponding to NCT01875511 implicitly encourages physicians to read the NEJM Article discussing the study showing an improved outcome in patients receiving treatment with Keytruda. On information and belief, Merck encouraged physicians to read the NEJM Article publishing the clinical trial results of KEYNOTE-016 and/or touted the clinical outcomes to induce physicians to use Keytruda to practice the claimed |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | method.<br><br>While KEYNOTE-016 was removed from the Keytruda Label in the 03/2023 Keytruda Label update, KEYNOTE-164, cited in later Keytruda Labels (*e.g.*, 08/2023 Keytruda Label), references the NEJM Article. *See, e.g.*, Le at al., *Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164*, J. Clin. Oncol. (2020). A physician would understand, based on the studies of KEYNOTE-016 to which Merck directs them, that Keytruda improves the outcomes in patients having tumors that exhibit MSI-H or dMMR compared to those patients with tumors that do not.<br><br>Accordingly, a physician reading the Keytruda Label would understand that treatment with Keytruda in patients with a tumor that has instability of the one or more microsatellite markers/deficiency of the one or more mismatch repair markers (MSI-H or dMMR) exhibit an improved outcome when compared to a reference patient whose tumors do not exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair marker (MSI-H or dMMR).<br><br>Clinical Studies Section 14.8 of the Keytruda Label (Section 14.9 of the 03/2021 Keytruda Label) also demonstrates an improved outcome (*e.g.*, progression-free survival, objective response rate) following treatment with Keytruda in MSI-H/dMMR colorectal cancers.<br><br>**14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br><br>The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.<br><br>Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks: |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis. Sixty percent of the patients who had been randomized to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including KEYTRUDA. The median follow-up time at the final analysis was 38.1 months (range: 0.2 to 58.7 months). Table 68 and Figure 14 summarize the key efficacy measures for KEYNOTE-177. |

**Table 60: Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-177**

| Endpoint | KEYTRUDA 200 mg every 3 weeks n=153 | Chemotherapy n=154 |
|---|---|---|
| **PFS** | | |
| Number (%) of patients with event | 82 (54%) | 113 (73%) |
| Median in months (95% CI) | 16.5 (5.4, 32.4) | 8.2 (6.1, 10.2) |
| Hazard ratio* (95% CI) | 0.60 (0.45, 0.80) | |
| p-Value† | 0.0004 | |
| **Objective Response Rate‡** | | |
| ORR (95% CI) | 44% (35.8, 52.0) | 33% (25.8, 41.1) |
| Complete response rate | 11% | 4% |
| Partial response rate | 33% | 29% |
| **Duration of Response‡,§** | | |
| Median in months (range) | NR (2.3+, 41.4+) | 10.6 (2.8, 37.5+) |
| % with duration ≥12 months¶ | 75% | 37% |
| % with duration ≥24 months¶ | 43% | 18% |

* Based on Cox regression model
† Two-sided p-value based on log-rank test (compared to a significance level of 0.0234)
‡ Based on confirmed response by BICR review
§ Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm
¶ Based on observed duration of response
\+ Denotes ongoing response
NR = not reached

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

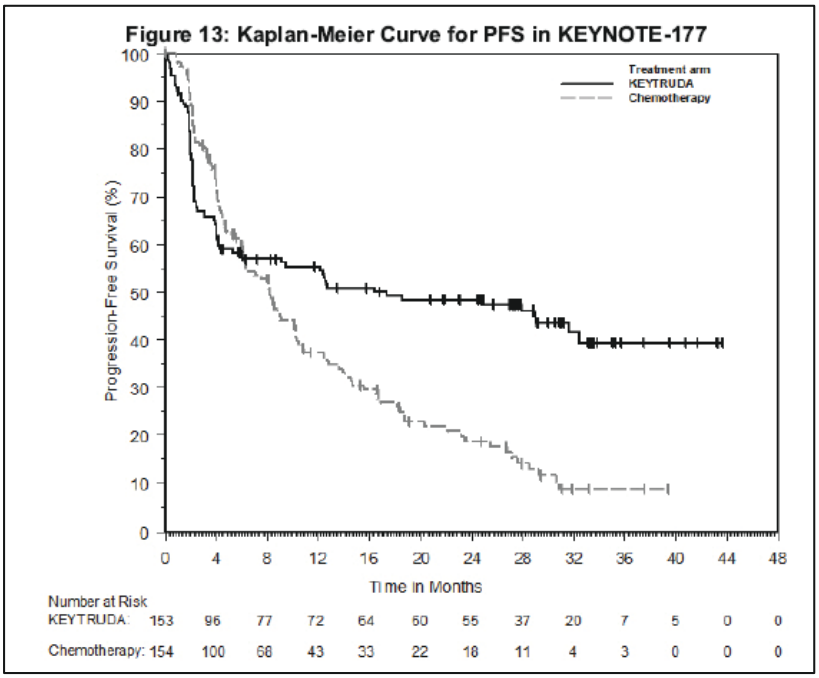
| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| |  <br>[03/2021 Keytruda Label at 84-86; *see also* 03/2022 Keytruda Label at 90-92; *see also* 08/2023 Keytruda Label at 100-101.]<br><br>In March of 2022, the Keytruda Label was updated to include clinical trial results showing that the recommended dosages of single-agent Keytruda are a therapeutically effective among patients with MSI-H or dMMR endometrial tumors relevant to Indication 1.15. Clinical Studies |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 1 [c] | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | Section 14.15 of the Keytruda Label also demonstrates improved outcome (*e.g.*, progression-free survival, objective response rate) following treatment with Keytruda in MSI-H/dMMR cancers.<br><br>As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma<br><br>The efficacy of KEYTRUDA was investigated in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial enrolled 90 patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma in Cohorts D and K who received at least one dose of KEYTRUDA. MSI or MMR tumor status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.<br><br>**Table 83: Efficacy Results in Patients with Advanced MSI-H or dMMR Endometrial Carcinoma in KEYNOTE-158**<br><br>**Endpoint** / **KEYTRUDA n=90***<br>**Objective Response Rate**<br>ORR (95% CI): 46% (35, 56)<br>Complete response rate: 12%<br>Partial response rate: 33%<br>**Duration of Response**: n=41<br>Median in months (range): NR (2.9, 55.7+)<br>% with duration ≥12 months: 68%<br>% with duration ≥24 months: 44%<br>* Median follow-up time of 16.0 months (range 0.5 to 62.1 months)<br>\+ Denotes ongoing response<br>NR = not reached<br><br>[08/2023 Keytruda Label at 123-124; *see also* 03/2022 Keytruda Label at 114-115.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| **Claim 2** | **Merck's Keytruda (Pembrolizumab)** |
|---|---|
| The method of claim 1, wherein the outcome that is improved is an improved objective response rate (ORR), an improved progression-free survival (PFS), or an improved overall survival. | *See* claim 1.<br><br>In addition, the Keytruda Label instructs physicians to use Keytruda to treat cancer in a patient wherein the cancer is MSI-H or dMMR and treatment results in an outcome that is an improved objective response rate (ORR), an improved progression-free survival (PFS), or an improved overall survival.<br><br>For example, Clinical Studies Section 14.7 of the Keytruda Label (Section 14.8 of the 03/2021 Keytruda Label) demonstrates improved objective response rate (ORR) and/or an improved progression-free survival (PFS) following treatment with Keytruda in MSI-H/dMMR cancers.<br><br>**14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR. |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 2 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **Table 57: MSI-H Trials** |

| Study | Design and Patient Population | Number of Patients | MSI-H/dMMR Testing | Dosage | Prior Therapy |
|---|---|---|---|---|---|
| **KEYNOTE-016** NCT01876511 | • prospective, investigator-initiated<br>• 6 sites<br>• patients with CRC and other tumors | 28 CRC<br>30 non-CRC | local PCR or IHC | 10 mg/kg every 2 weeks | • CRC: ≥ 2 prior regimens<br>• Non-CRC: ≥1 prior regimen |
| **KEYNOTE-164** NCT02460198 | • prospective international multi-center<br>• CRC | 61 | local PCR or IHC | 200 mg every 3 weeks | Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb |
| **KEYNOTE-012** NCT01848834 | • retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer | 6 | central PCR | 10 mg/kg every 2 weeks | ≥1 prior regimen |
| **KEYNOTE-028** NCT02054806 | • retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC | 5 | central PCR | 10 mg/kg every 2 weeks | ≥1 prior regimen |
| **KEYNOTE-158** NCT02628067 | • prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC<br>• retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts | 19 | local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts) | 200 mg every 3 weeks | ≥1 prior regimen |
| **Total** | | **149** | | | |

CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 2 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **Table 58: Efficacy Results for Patients with MSI-H/dMMR Cancer** |

| Endpoint | KEYTRUDA n=149 |
|---|---|
| **Objective Response Rate** | |
| ORR (95% CI) | 39.6% (31.7, 47.9) |
| Complete response rate | 7.4% |
| Partial response rate | 32.2% |
| **Duration of Response** | |
| Median in months (range) | NR (1.6+, 22.7+) |
| % with duration ≥6 months | 78% |

NR = not reached

**Table 59: Response by Tumor Type**

| | N | Objective Response Rate n (%) | 95% CI | Duration of Response range (months) |
|---|---|---|---|---|
| CRC | 90 | 32 (36%) | (26%, 46%) | (1.6+, 22.7+) |
| Non-CRC | 59 | 27 (46%) | (33%, 59%) | (1.9+, 22.1+) |
| Endometrial cancer | 14 | 5 (36%) | (13%, 65%) | (4.2+, 17.3+) |
| Biliary cancer | 11 | 3 (27%) | (6%, 61%) | (11.6+, 19.6+) |
| Gastric or GE junction cancer | 9 | 5 (56%) | (21%, 86%) | (5.8+, 22.1+) |
| Pancreatic cancer | 6 | 5 (83%) | (36%, 100%) | (2.6+, 9.2+) |
| Small intestinal cancer | 8 | 3 (38%) | (9%, 76%) | (1.9+, 9.1+) |
| Breast cancer | 2 | PR, PR | | (7.6, 15.9) |
| Prostate cancer | 2 | PR, SD | | 9.8+ |
| Bladder cancer | 1 | NE | | |
| Esophageal cancer | 1 | PR | | 18.2+ |
| Sarcoma | 1 | PD | | |
| Thyroid cancer | 1 | NE | | |
| Retroperitoneal adenocarcinoma | 1 | PR | | 7.5+ |
| Small cell lung cancer | 1 | CR | | 8.9+ |
| Renal cell cancer | 1 | PD | | |

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

[03/2021 Keytruda Label at 82-84; *see also* 03/2022 Keytruda Label at 89-90.]

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 2 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **14.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>The efficacy of KEYTRUDA was investigated in 504 patients with MSI-H or dMMR cancers enrolled in three multicenter, non-randomized, open-label, multi-cohort trials: KEYNOTE-164 (NCT02460198), KEYNOTE-158 (NCT02628067), and KEYNOTE-051 (NCT02332668). All trials excluded patients with autoimmune disease or a medical condition that required immunosuppression. Regardless of histology, MSI or MMR tumor status was determined using polymerase chain reaction (PCR; local or central) or immunohistochemistry (IHC; local or central), respectively.<br>• KEYNOTE-164 enrolled 124 patients with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with fluoropyrimidine and either oxaliplatin or irinotecan +/- anti-VEGF/EGFR mAb-based therapy.<br>• KEYNOTE-158 enrolled 373 patients with advanced MSI-H or dMMR non-colorectal cancers (non-CRC) who had disease progression following prior therapy. Patients were either prospectively enrolled with MSI-H/dMMR tumors (Cohort K) or retrospectively identified in one of 10 solid tumor cohorts (Cohorts A-J).<br>• KEYNOTE-051 enrolled 7 pediatric patients with MSI-H or dMMR cancers.<br>Adult patients received KEYTRUDA 200 mg every 3 weeks (pediatric patients received 2 mg/kg every 3 weeks) until unacceptable toxicity, disease progression, or a maximum of 24 months. In KEYNOTE-164 and KEYNOTE-158, assessment of tumor status was performed every 9 weeks through the first year, then every 12 weeks thereafter. In KEYNOTE-051, assessment of tumor status was performed every 8 weeks for 24 weeks, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ in KEYNOTE-158) and as assessed by the investigator according to RECIST v1.1 in KEYNOTE-051. |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 2 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | Efficacy results are summarized in Tables 69 and 70. |

**Table 69: Efficacy Results for Patients with MSI-H/dMMR Cancer**

| Endpoint | KEYTRUDA n=504* |
|---|---|
| **Objective Response Rate** | |
| ORR (95% CI)† | 33.3% (29.2, 37.6) |
| Complete response rate | 10.3% |
| Partial response rate | 23.0% |
| **Duration of Response** | n=168 |
| Median in months (range) | 63.2 (1.9+, 63.9+) |
| % with duration ≥12 months | 77% |
| % with duration ≥36 months | 39% |

* Median follow-up time of 20.1 months (range 0.1 to 71.4 months)
† Of the 7 pediatric patients from KEYNOTE-051, 1 patient had a radiographic complete response after initial growth of their tumor but is not reflected in the results.
\+ Denotes ongoing response

**Table 70: Response by Tumor Type**

| | N | Objective Response Rate n (%) | 95% CI | Duration of Response range (months) |
|---|---|---|---|---|
| CRC | 124 | 42 (34%) | (26%, 43%) | (4.4, 58.5+) |
| Non-CRC* | 380 | 126 (33%) | (28%, 38%) | (1.9+, 63.9+) |
| Endometrial cancer | 94 | 47 (50%) | (40%, 61%) | (2.9, 63.2) |
| Gastric or GE junction cancer | 51 | 20 (39%) | (26%, 54%) | (1.9+, 63.0+) |
| Small intestinal cancer | 27 | 16 (59%) | (39%, 78%) | (3.7+, 57.3+) |
| Brain cancer | 27† | 1 (4%)‡ | (0%, 19%) | 18.9 |
| Ovarian cancer | 25 | 8 (32%) | (15%, 54%) | (4.2, 56.6+) |
| Biliary cancer | 22 | 9 (41%) | (21%, 64%) | (6.2, 49.0+) |
| Pancreatic cancer | 22 | 4 (18%) | (5%, 40%) | (8.1, 24.3+) |
| Sarcoma | 14 | 3 (21%) | (5%, 51%) | (35.4+, 57.2+) |
| Breast cancer | 13 | 1 (8%) | (0%,36%) | 24.3+ |
| Other§ | 13 | 4 (31%) | (9%, 61%) | (6.2+, 32.3+) |
| Cervical cancer | 11 | 1 (9%) | (0%, 41%) | 63.9+ |
| Neuroendocrine cancer | 11 | 1 (9%) | (0%, 41%) | 13.3 |
| Prostate cancer | 8 | 1 (13%) | (0%, 53%) | 24.5+ |
| Adrenocortical cancer | 7 | 1 (14%) | (0%, 58%) | 4.2 |
| Mesothelioma | 7 | 0 (0%) | (0%, 41%) | |
| Thyroid cancer | 7 | 1 (14%) | (0%, 58%) | 8.2 |
| Small cell lung cancer | 6 | 2 (33%) | (4%, 78%) | (20.0, 47.5) |
| Bladder cancer | 6 | 3 (50%) | (12%, 88%) | (35.6+, 57.5+) |
| Salivary cancer | 5 | 2 (40%) | (5%, 85%) | (42.6+, 57.8+) |
| Renal cell cancer | 4 | 1 (25%) | (0%, 81%) | 22.0 |

* Results include patients in Cohort K of KEYNOTE-158 that were later determined to be pMMR or not MSI-H by central testing
† Includes 6 pediatric patients with brain cancer
‡ In addition to the 1 adult responder, 1 pediatric patient had a radiographic complete response after initial growth of their tumor.
§ Includes tumor type (n): anal (3), HNSCC (1), nasopharyngeal (1), retroperitoneal (1), testicular (1), vaginal (1), vulvar (1), appendiceal adenocarcinoma, NOS (1), hepatocellular carcinoma (1), and carcinoma of unknown origin (1). Includes 1 pediatric patient with abdominal adenocarcinoma.
\+ Denotes ongoing response

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 2 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | [08/2023 Keytruda Label at 98-99.]<br><br>*See also* NEJM Article at *e.g.*, Figure 2 and Tables 1 and 2 (discussing results of study in MSI-H/dMMR patients v. non-MSI-H/dMMR treated with Keytruda).<br><br>Clinical Studies Section 14.8 of the Keytruda Label (Section 14.9 of the 03/2021 Keytruda Label) also demonstrates improved objective response rate (ORR) and/or an improved progression-free survival (PFS) following treatment with Keytruda in MSI-H/dMMR colorectal cancers.<br><br>**14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.<br><br>Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks:<br><br>The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis. Sixty percent of the patients who had been randomized to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including KEYTRUDA. The median follow-up time at the final analysis was 38.1 months (range: 0.2 to 58.7 months). Table 68 and Figure 14 summarize the key efficacy measures for KEYNOTE-177. |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 2 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **Table 60: Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-177** |

| Endpoint | KEYTRUDA 200 mg every 3 weeks n=153 | Chemotherapy n=154 |
|---|---|---|
| **PFS** | | |
| Number (%) of patients with event | 82 (54%) | 113 (73%) |
| Median in months (95% CI) | 16.5 (5.4, 32.4) | 8.2 (6.1, 10.2) |
| Hazard ratio* (95% CI) | 0.60 (0.45, 0.80) | |
| p-Value† | 0.0004 | |
| **Objective Response Rate‡** | | |
| ORR (95% CI) | 44% (35.8, 52.0) | 33% (25.8, 41.1) |
| Complete response rate | 11% | 4% |
| Partial response rate | 33% | 29% |
| **Duration of Response‡§** | | |
| Median in months (range) | NR (2.3+, 41.4+) | 10.6 (2.8, 37.5+) |
| % with duration ≥12 months¶ | 75% | 37% |
| % with duration ≥24 months¶ | 43% | 18% |

* Based on Cox regression model
† Two-sided p-value based on log-rank test (compared to a significance level of 0.0234)
‡ Based on confirmed response by BICR review
§ Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm
¶ Based on observed duration of response
\+ Denotes ongoing response
NR = not reached

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

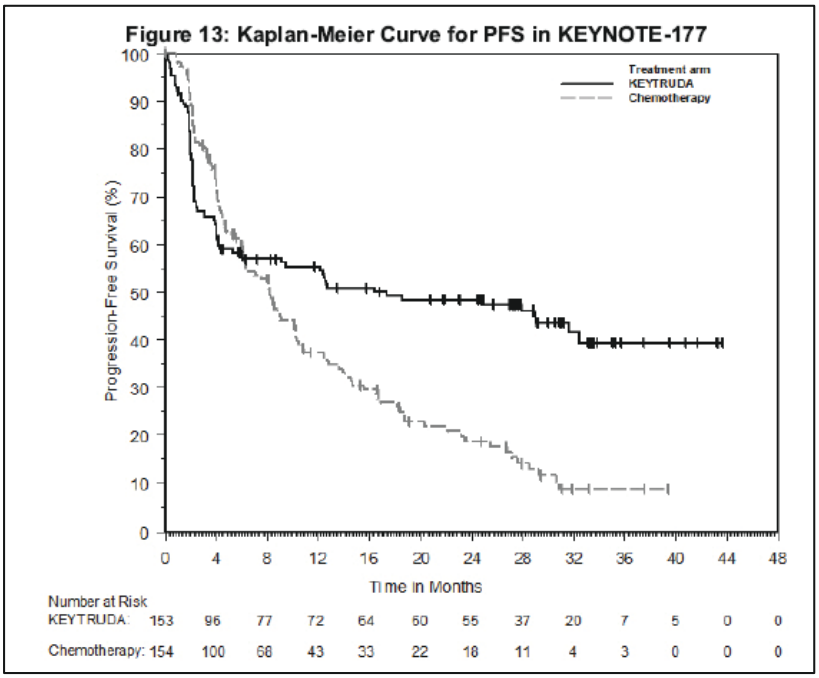
| Claim 2 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| |  <br>[03/2021 Keytruda Label at 84-86; *see also* 03/2022 Keytruda Label at 90-92; *see also* 08/2023 Keytruda Label at 100-101.]<br><br>In March of 2022, the Keytruda Label was updated to include clinical trial results showing that the recommended dosages of single-agent Keytruda are therapeutically effective among patients with MSI-H or dMMR endometrial tumors relevant to Indication 1.15. Clinical Studies Section |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 2 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | 14.15 of the Keytruda Label also demonstrates improved objective response rate (ORR) and/or an improved progression-free survival (PFS) following treatment with Keytruda in MSI-H/dMMR cancers.<br><br>As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma<br><br>The efficacy of KEYTRUDA was investigated in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial enrolled 90 patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma in Cohorts D and K who received at least one dose of KEYTRUDA. MSI or MMR tumor status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.<br><br>**Table 83: Efficacy Results in Patients with Advanced MSI-H or dMMR Endometrial Carcinoma in KEYNOTE-158**<br><br>Endpoint: KEYTRUDA n=90*<br>Objective Response Rate<br>ORR (95% CI): 46% (35, 56)<br>Complete response rate: 12%<br>Partial response rate: 33%<br>Duration of Response: n=41<br>Median in months (range): NR (2.9, 55.7+)<br>% with duration ≥12 months: 68%<br>% with duration ≥24 months: 44%<br>* Median follow-up time of 16.0 months (range 0.5 to 62.1 months)<br>+ Denotes ongoing response<br>NR = not reached<br><br>[08/2023 Keytruda Label at 123-124; *see also* 03/2022 Keytruda Label at 114-115.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| **Claim 4** | **Merck's Keytruda (Pembrolizumab)** |
|---|---|
| The method of claim 2, wherein the outcome is assessed in the patient within approximately 20 weeks after administering pembrolizumab. | *See* claim 2.<br><br>In addition, the Keytruda Label instructs physicians to use Keytruda (pembrolizumab) to treat cancer in a patient wherein the cancer is MSI-H or dMMR and wherein the outcome is assessed in the population of cancer patients at 20 weeks after administering Keytruda.<br><br>For example, the Keytruda Label instructs physicians to assess the objective response rate in patients with MSI-H or dMMR tumors treated with Keytruda in accordance with Indications 1.7 (or 1.8 of the 03/2021 Keytruda Label) and 1.8 (or 1.9 of the 03/2021 Keytruda Label) every 8 or 9 or 12 weeks.<br><br>Assessing the objective response rate in accordance with Indication 1.7 is equivalent to assessing the objective response rate at 20 weeks. For example, physicians assessing the objective response rate in the population of cancer patients every 9 weeks in accordance with the Keytruda Label results in the second assessment at 18 weeks. Physicians following the Keytruda Label will therefore perform substantially the same function as assessing at 20 weeks when assessing at 18-weeks, just assessing two-weeks prior. As another example, physicians assessing the objective response rate in the population of cancer patients every 12 weeks in accordance with the Keytruda Label results in the second assessment at 24 weeks. Physicians following the Keytruda Label will therefore perform substantially the same function as assessing at 20 weeks when assessing at 24-weeks, just assessing four-weeks later. Moreover, physicians following the Keytruda Label will assess the objective response rate in the population of cancer patients in substantially the same way—by analyzing the patient's tumor specimen (via "BICR according to RECIST v1.1")—to obtain substantially the same result, *i.e.*, an objective response rate. Any difference between assessing at 20 weeks verses assessing at 18 or 24 weeks is insubstantial. |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 4 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.<br><br>[03/2021 Keytruda Label at 82; *see also* 03/2022 Keytruda Label at 89.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 4 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **14.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>The efficacy of KEYTRUDA was investigated in 504 patients with MSI-H or dMMR cancers enrolled in three multicenter, non-randomized, open-label, multi-cohort trials: KEYNOTE-164 (NCT02460198), KEYNOTE-158 (NCT02628067), and KEYNOTE-051 (NCT02332668). All trials excluded patients with autoimmune disease or a medical condition that required immunosuppression. Regardless of histology, MSI or MMR tumor status was determined using polymerase chain reaction (PCR; local or central) or immunohistochemistry (IHC; local or central), respectively.<br>• KEYNOTE-164 enrolled 124 patients with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with fluoropyrimidine and either oxaliplatin or irinotecan +/- anti-VEGF/EGFR mAb-based therapy.<br>• KEYNOTE-158 enrolled 373 patients with advanced MSI-H or dMMR non-colorectal cancers (non-CRC) who had disease progression following prior therapy. Patients were either prospectively enrolled with MSI-H/dMMR tumors (Cohort K) or retrospectively identified in one of 10 solid tumor cohorts (Cohorts A-J).<br>• KEYNOTE-051 enrolled 7 pediatric patients with MSI-H or dMMR cancers.<br>Adult patients received KEYTRUDA 200 mg every 3 weeks (pediatric patients received 2 mg/kg every 3 weeks) until unacceptable toxicity, disease progression, or a maximum of 24 months. In KEYNOTE-164 and KEYNOTE-158, assessment of tumor status was performed every 9 weeks through the first year, then every 12 weeks thereafter. In KEYNOTE-051, assessment of tumor status was performed every 8 weeks for 24 weeks, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ in KEYNOTE-158) and as assessed by the investigator according to RECIST v1.1 in KEYNOTE-051.<br>[08/2023 Keytruda Label at 98.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 4 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.<br>Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks:<br>• mFOLFOX6 (oxaliplatin, leucovorin, and FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m$^2$, leucovorin 400 mg/m$^2$ (or levoleucovorin 200 mg/m$^2$), and FU 400 mg/m$^2$ bolus on Day 1, then FU 2400 mg/m$^2$ over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m$^2$ on first infusion, then 250 mg/m$^2$ weekly.<br>• FOLFIRI (irinotecan, leucovorin, and FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m$^2$, leucovorin 400 mg/m$^2$ (or levoleucovorin 200 mg/m$^2$), and FU 400 mg/m$^2$ bolus on Day 1, then FU 2400 mg/m$^2$ over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m$^2$ on first infusion, then 250 mg/m$^2$ weekly.<br>Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of<br><br>[03/2021 Keytruda Label at 84; *see also* 03/2022 Keytruda Label at 90-91; *see also* 08/2023 Keytruda Label at 100.]<br><br>The Keytruda Label also instructs physicians to assess the objective response rate in patients with MSI-H or dMMR endometrial tumors treated with Keytruda in accordance with Indication 1.15 every 9 or 12 weeks.<br><br>Assessing the objective response rate in accordance with Indication 1.15 is equivalent to assessing the objective response rate at 20 weeks. For example, physicians assessing the objective response rate in the population of cancer patients every 9 weeks in accordance with the Keytruda Label results in the second assessment at 18 weeks. Physicians following the Keytruda Label will therefore perform substantially the same function as assessing at 20 weeks when assessing at 18-weeks, just assessing two-weeks prior. As another example, physicians |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 4 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | assessing the objective response rate in the population of cancer patients every 12 weeks in accordance with the Keytruda Label results in the second assessment at 24 weeks. Physicians following the Keytruda Label will therefore perform substantially the same function as assessing at 20 weeks when assessing at 24-weeks, just assessing four-weeks later. Moreover, physicians following the Keytruda Label will assess the objective response rate in the population of cancer patients in substantially the same way—by analyzing the patient's tumor specimen (via "BICR according to RECIST v1.1")—to obtain substantially the same result, *i.e.*, an objective response rate. Any difference between assessing at 20 weeks verses assessing at 18 or 24 weeks is insubstantial.<br><br>As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma<br>The efficacy of KEYTRUDA was investigated in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial enrolled 90 patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma in Cohorts D and K who received at least one dose of KEYTRUDA. MSI or MMR tumor status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.<br><br>[03/2022 Keytruda Label at 114; 08/2023 Keytruda Label at 123.] |

| Claim 6 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| The method of claim 1, wherein the cancer is a metastatic cancer. | *See* claim 1. |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 6 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | In addition, the Keytruda Label instructs physicians to use Keytruda to treat cancer in a patient wherein the cancer is MSI-H or dMMR and is a metastatic cancer.<br><br>For example, the Keytruda Label indicates that Keytruda may be used to treat the following metastatic cancers including *e.g.*, metastatic MSI-H/dMMR solid tumors (Indication 1.7) or metastatic MSI-H/dMMR colorectal cancer (Indication 1.8).<br><br>**Indications 1.7 and 1.8 (1.8 and 1.9 in the March 2021 Keytruda Label)**<br><br>**1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)<br>• solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or<br>• colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.<br>This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.8)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.<br>Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.<br>**1.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).<br><br>[03/2021 Keytruda Label at 5.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 6 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.<br>This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.7)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.<br>Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.<br>**1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).<br>[03/2022 Keytruda Label at 5.]<br>**1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options *[see Dosage and Administration (2.1)]*.<br>**1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.<br>[08/2023 Keytruda Label at 5.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| **Claim 7** | **Merck's Keytruda (Pembrolizumab)** |
|---|---|
| The method of claim 1, wherein the cancer is a metastatic colorectal cancer. | *See* claim 1.<br><br>In addition, the Keytruda Label instructs physicians to use Keytruda to treat cancer in a patient wherein the cancer is MSI-H or dMMR and is a metastatic colorectal cancer.<br><br>For example, the Keytruda Label indicates that Keytruda may be used to treat metastatic MSI-H/dMMR cancers (Indication 1.7) and metastatic colorectal cancer (Indication 1.8).<br><br>**<u>Indications 1.7 and 1.8 (1.8 and 1.9 in the March 2021 Keytruda Label)</u>**<br><br>**1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)<br>• solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or<br>• colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.<br>This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.8)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.<br><u>Limitations of Use</u>: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.<br>**1.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).<br><br>[03/2021 Keytruda Label at 5.] |

**EXHIBIT 4**

**INFRINGEMENT OF U.S. PATENT NO. 11,339,219 BY KEYTRUDA**

| Claim 7 | Merck's Keytruda (Pembrolizumab) |
|---|---|
| | **1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.<br>This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.7)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.<br>Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.<br>**1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).<br>[03/2022 Keytruda Label at 5.]<br><br>**1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**<br>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options *[see Dosage and Administration (2.1)]*.<br>**1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**<br>KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.<br>[08/2023 Keytruda Label at 5.] |