

EXHIBIT 15

EXHIBIT 15: INFRINGEMENT OF U.S. PATENT NO. 11,325,975 BY KEYTRUDA

Claim 1 [pre]	Merck's Keytruda (Pembrolizumab)
A method for treating cancer in a patient in need thereof wherein the patient has been determined to have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, comprising:	Merck's FDA-approved label for Keytruda (pembrolizumab) ("Keytruda Label") instructs physicians to use Keytruda (pembrolizumab) to treat cancer in a patient in need thereof wherein a tumor sample obtained from the patient has been determined to exhibit a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status. The Keytruda Label instructs physicians to determine whether a tumor sample from a patient in need of a cancer treatment exhibits MSI-high or MMR deficiency status. For example, the Keytruda label indicates that Keytruda is approved for the treatment of patients with solid tumors and endometrial tumors that are MSI-H or MMR deficient as determined by an FDA-approved test: 1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer 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 <i>Dosage and Administration</i> (2.1)]. 1.15 Endometrial Carcinoma KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation [see <i>Dosage and Administration</i> (2.1)]. 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 <i>Dosage and Administration</i> (2.1)]. Label at 5-6 (highlighting added). The Dosage and Administration section of the Keytruda Label instructs physicians to test the patient's tumor sample for MSI-H/dMMR status to select patients for single treatment with Keytruda according to Indications 1.7 and 1.15.

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	2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection <u>Patient Selection for Single-Agent Treatment</u> Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in: • stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation [see <i>Clinical Studies (14.2)</i>]. • metastatic NSCLC [see <i>Clinical Studies (14.2)</i>]. • first-line treatment of metastatic or unresectable, recurrent HNSCC [see <i>Clinical Studies (14.3)</i>]. • previously treated recurrent locally advanced or metastatic esophageal cancer [see <i>Clinical Studies (14.10)</i>]. • recurrent or metastatic cervical cancer with disease progression on or after chemotherapy [see <i>Clinical Studies (14.11)</i>]. 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 <i>Clinical Studies (14.7, 14.8)</i>]. Label at 7 (highlighting added). The Dosage and Administration section of the Keytruda Label refers physicians to a website to find information necessary to test or have tested a biological sample obtained from a patient to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient: <u>Additional Patient Selection Information</u> Information on FDA-approved tests for patient selection is available at: http://www.fda.gov/CompanionDiagnostics . Label at 8.

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Claim 1 [a]	Merck's Keytruda (Pembrolizumab)
administering an effective amount of an anti-PD-1 antibody to the patient;	The Keytruda Label instructs physicians to administer an effective amount of pembrolizumab, an anti-PD-1 antibody, to a patient. The Keytruda Label discloses that Keytruda is an anti-PD-1 antibody. -----INDICATIONS AND USAGE----- KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated: Label at 1. The Indications and Usage Section of the Keytruda Label lists Indication 1.7 for the treatment of cancer in a population of patients wherein the cancer is an unresectable or metastatic MSI-H or dMMR solid tumor and the tumor has progressed following a prior treatment. 1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer 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)]. Label at 5. The Indications and Usage Section of the Keytruda Label also lists Indication 1.15 for the treatment of cancer in a population of patients wherein the cancer is an advanced endometrial carcinoma that is MSI-H or dMMR and wherein the tumor has progressed following a prior treatment.

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Claim 1 [a]	Merck's Keytruda (Pembrolizumab)
	1.15 Endometrial Carcinoma KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation [see <i>Dosage and Administration</i> (2.1)]. 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 <i>Dosage and Administration</i> (2.1)]. Label at 6. The Recommended Dosage section of the Keytruda Label provides the recommended dosages of Keytruda as well as the duration/timing of treatment by the indication, wherein the indication is directed to cancer confirmed to be MSI-high/MMR deficient.

Claim 1 [a]

Merck's Keytruda (Pembrolizumab)

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 or RCC	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, 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* or 400 mg every 6 weeks*	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.

§ 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.

Label at 8-9 (highlighting added).

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

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Claim 1 [a]	Merck's Keytruda (Pembrolizumab)
	2.4 Preparation and Administration <u>Preparation for Intravenous Infusion</u> • 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. • Dilute KEYTRUDA injection (solution) prior to intravenous administration. • 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. • Discard any unused portion left in the vial. <u>Storage of Diluted Solution</u> The product does not contain a preservative. Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either: • 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. • 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. Discard after 6 hours at room temperature or after 96 hours under refrigeration. Do not freeze. <u>Administration</u> • 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. • Do not co-administer other drugs through the same infusion line. Label at 11. The Keytruda Label includes clinical trial results showing that the recommended dosages of Keytruda are a therapeutically effective amount of pembrolizumab among patients with MSI-H or dMMR tumors whose tumors had progressed following a prior treatment.

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Claim 1 [a]

Merck's Keytruda (Pembrolizumab)

14.7 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 65: MSI-H Trials

Study	Design and Patient Population	Number of Patients	MSI-H/dMMR Testing	Dosage	Prior Therapy
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
KEYNOTE-164 NCT02460198	- prospective international multi-center - 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 - 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

Claim 1 [a]

Merck’s Keytruda (Pembrolizumab)

Efficacy results are summarized in Tables 66 and 67.

Table 66: 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 67: 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

Label at 89-90 (highlighting added).

The Keytruda Label includes clinical trial results showing that the recommended dosages of Keytruda are a therapeutically effective amount of pembrolizumab among patients with MSI-H

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Claim 1 [a]	Merck's Keytruda (Pembrolizumab)
	or dMMR endometrial tumors relevant to Indication 1.15. 14.15 Endometrial Carcinoma <u>As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma</u> 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. Among the 90 patients evaluated, the baseline characteristics were: median age of 64 years (range: 42 to 86); 83% White, 8% Asian, and 3% Black; 12% Hispanic or Latino; 39% ECOG PS of 0 and 61% ECOG PS of 1; 96% had M1 disease and 4% had M0 disease at study entry; and 51% had one and 48% had two or more prior lines of therapy. Nine patients received only adjuvant therapy and one patient received only neoadjuvant and adjuvant therapy before participating in the study. Efficacy results are summarized in Table 80.

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Claim 1 [a]	Merck's Keytruda (Pembrolizumab)																		
	Table 80: Efficacy Results in Patients with Advanced MSI-H or dMMR Endometrial Carcinoma in KEYNOTE-158 <table> <tr> <th>Endpoint</th><th>KEYTRUDA n=90*</th></tr> <tr> <td>Objective Response Rate</td><td></td></tr> <tr> <td>ORR (95% CI)</td><td>46% (35, 56)</td></tr> <tr> <td>Complete response rate</td><td>12%</td></tr> <tr> <td>Partial response rate</td><td>33%</td></tr> <tr> <td>Duration of Response</td><td>n=41</td></tr> <tr> <td>Median in months (range)</td><td>NR (2.9, 55.7+)</td></tr> <tr> <td>% with duration ≥12 months</td><td>68%</td></tr> <tr> <td>% with duration ≥24 months</td><td>44%</td></tr> </table> * Median follow-up time of 16.0 months (range 0.5 to 62.1 months) + Denotes ongoing response NR = not reached Label at 111, 114-115 (highlighting added).	Endpoint	KEYTRUDA n=90*	Objective Response Rate		ORR (95% CI)	46% (35, 56)	Complete response rate	12%	Partial response rate	33%	Duration of Response	n=41	Median in months (range)	NR (2.9, 55.7+)	% with duration ≥12 months	68%	% with duration ≥24 months	44%
Endpoint	KEYTRUDA n=90*																		
Objective Response Rate																			
ORR (95% CI)	46% (35, 56)																		
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% with duration ≥12 months	68%																		
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Claim 1 [b]	Merck's Keytruda (Pembrolizumab)
[b] 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 the anti-PD-antibody, wherein the reference patient has a tumor that does not	The Keytruda Label instructs physicians that treatment of a patient with a tumor determined to be MSI-high or MMR deficient with Keytruda in accordance with the Keytruda Label 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-high or MMR deficient status. For example, Indication 1.7 was “approved under accelerated approval based on tumor response rate and durability of response [see <i>Clinical Studies</i> (14.7)].” Label at 5.

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Claim 1 [b]	Merck's Keytruda (Pembrolizumab)												
exhibit a MSI-high or a MMR deficiency status; and	Among the Clinical Studies listed in Section 14.7 of the Keytruda Label is KEYNOTE-016. 14.7 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 65: MSI-H Trials <table><tr><th>Study</th><th>Design and Patient Population</th><th>Number of Patients</th><th>MSI-H/dMMR Testing</th><th>Dosage</th><th>Prior Therapy</th></tr><tr><td>KEYNOTE-016 NCT01876511</td><td> - prospective, investigator-initiated 6 sites - patients with CRC and other tumors </td><td>28 CRC 30 non-CRC</td><td>local PCR or IHC</td><td>10 mg/kg every 2 weeks</td><td> - CRC: ≥ 2 prior regimens - Non-CRC: ≥1 prior regimen </td></tr></table> Label at 89 (highlighting added). KEYNOTE-016 (NCT01876511, titled “Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C) (“MSI Clinical Trial”) compared the efficacy of KEYTRUDA in patients with a tumor that does not exhibit MSI-high or a MMR deficient status 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. (Ex. B at 5.) KEYNOTE-016, as reported in the New England Journal of Medicine article “PD-1 Blockade in Tumors with Mismatch-Repair Deficiency” (“NEJM Article”), 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. (Ex. 6 (NEJM Article).) A physician reading the Keytruda Label and the Clinical Studies cited therein would understand that patients with tumors that are MSI-high or MMR deficient will exhibit an improved	Study	Design and Patient Population	Number of Patients	MSI-H/dMMR Testing	Dosage	Prior Therapy	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
Study	Design and Patient Population	Number of Patients	MSI-H/dMMR Testing	Dosage	Prior Therapy								
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Claim 1 [b]	Merck's Keytruda (Pembrolizumab)
	outcome compared to reference patients with a tumor that does not exhibit a MSI-high or a MMR deficiency status.

Claim 1 [c]	Merck's Keytruda (Pembrolizumab)
[c] wherein the patient has received a prior cancer therapy drug.	The Keytruda Label instructs physicians to administer Keytruda to patients with a tumor that is MSI-high or MMR deficient and who have already received a prior cancer therapy drug. The Keytruda Label indicates that Keytruda is approved for the treatment of patients with solid tumors and endometrial tumors that are MSI-H or MMR deficient as determined by an FDA-approved test wherein the patients had received a prior cancer therapy drug: 1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer 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)]. 1.15 Endometrial Carcinoma KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, 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)]. 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)]. Label at 5-6 (highlighting added).