Protocol Number:	PHS IRB: 15-166
Title:	Phase IB Study of a Galectin Inhibitor (GR-MD-02) and Pembrolizumab in Patients with Metastatic Melanoma, Non-Small Cell Lung Cancer and Head and Neck Squamous Cell Carcinoma
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PROTOCOL SIGNATURE PAGE

Protocol Number: **PHS IRB 15-166**

Protocol Title: **Phase IB Study of a Galectin Inhibitor (GR-MD-02) and Pembrolizumab in Patients with Metastatic Melanoma, Non-Small Cell Lung Cancer (NSCLC) and Head and Neck Squamous Cell Carcinoma (HNSCC)**

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

Brendan Curti, MD		
Investigator Name (print)	Investigator Signature	Date

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1. BACKGROUND AND RATIONALE

1.0 Clinical Overview of Pembrolizumab in Selected Metastatic Cancers

The American Cancer Society estimates that there were over 76,000 new diagnoses and 9,100 deaths from melanoma in the United States in 2012.(1) Metastatic melanoma has a poor prognosis with less than 5% of patients surviving five years from the manifestation of visceral organ involvement, although this may be changing with new immunotherapies and targeted therapies. Disease-specific survival curves in all stages of melanoma have a negative slope, implying that metastatic disease can originate from thin primary lesions and that metastatic melanoma can develop many years after the initial diagnosis. For instance, in survival data compiled by Balch, et al., up to 10% of patients presenting with stage I melanoma (primary site less than 1 mm in depth and no nodal involvement) will die as a consequence of metastatic disease within 10 years.(2) Disease recurrence can manifest years or even decades after the initial diagnosis. The potential lethality of early stage melanoma distinguishes it from other solid tumors.

Immunotherapy has been studied for decades to treat melanoma and the only FDA-approved immunotherapeutic agent for metastatic melanoma was interleukin-2 until 2011. There have been recent significant advances in the treatment of melanoma. Two randomized phase III studies have shown improved survival for patients with advanced melanoma treated with ipilimumab. (3), (4) The FDA approved the use of ipilimumab for first or second-line treatment of metastatic melanoma in March 2011. Pembrolizumab (anti-PD-1) was approved by the FDA in September 2014 to treat patients whose melanoma had progressed after ipilimumab or targeted therapy in melanomas that have a BRAF mutation. Combinations of T-cell check point inhibitors are also showing significant clinical promise. Nivolumab (anti-PD-1) and ipilimumab showed an objective response rate of 40% in patients with metastatic melanoma. (5) Targeted therapy in melanoma has also shown promise. Vemurafenib, which targets the BRAFV600E mutation, has an objective response rate of approximately 50%.(6) A phase III study comparing vemurafenib to dacarbazine showed a significant increase in survival for patients receiving vemurafenib. The median progression-free survival was 5.3 months in the vemurafenib group, leading to FDA approval in August 2011.(7) Similar findings have been observed with another BRAF inhibitor, dabrafenib used in conjunction with trametinib, which has recently garnered FDA approval.(8)

Even with the recent FDA approvals of ipilimumab showing a 4 month improvement in median survival,(3), pembrolizumab with an objective response of 26% after ipilimumab progression (9) and targeted agents such as vemurafenib having a high initial response rate, (10),(6) there is still a substantial unmet need for new successful therapies in patients with widespread melanoma. There has been a similar experience with the systemic therapy of other solid tumors such as non-small cell lung carcinoma (NSCLCA) and head and neck squamous cell carcinoma (HNSCC). Existing treatments can improve survival by several months, but are rarely curative or induce durable remissions in the setting of stage IV disease.

1.1 Anti-PD-1 Biology and Clinical Results

A pathway that significantly influences the behavior of T cells in the periphery (e.g. at sites of chronic infection or tumors) is programmed death-1 (PD-1). PD-1 and the ligands for this pathway (PD-L1 (B7-H1) and PD-L2 (B7-DC)) are up-regulated at the time of T-cell activation. PD-1 and PD-L1 expression are associated with anergy and exhaustion of T cells, especially in the setting of chronic antigen exposure that occurs during unresolved infection or malignancy.(11) Triggering PD-1 via PD-L1 or PD-L2 limits T cell activity at sites of chronic infection and may decrease autoimmunity during immune responses to pathogens. Regulatory T cells (Treg) have high expression of PD-1 at tumor sites and may exert other inhibitory influences on anti-tumor responses.(12) Antigen-specific CD8+ T cells that infiltrate tumors also have high levels of PD-1 expression.(13) At these sites, the cytotoxic CD8+ T cells exhibited decreased cytokine production, while PD-1+ Treg also expressed the proliferation marker Ki-67. Proliferation of Treg in the tumor would be expected to further abrogate anti-tumor responses. Peripheral blood T cells in the same patients from whom the TIL were

studied did not show increased PD-1 expression. It is also known that many tumor histologies including melanoma, ovarian cancer, colon cancer and non-small cell lung cancer secrete PD-L1.(14) Thus, immune modulation by the tumor within the tumor microenvironment may promote survival of the malignancy and decrease the ability of cytotoxic T cells to eradicate the tumor. Blockade of PD1 or PD-L1 using antagonistic antibodies has been shown to enhance tumor responses in many murine tumor models and in combination with anti-CTLA-4.(15) These findings provided a strong rationale for the clinical translation of blocking PD-1 in patients with melanoma and other malignancies.

The first anti-PD-1 antibody tested in patients with melanoma was MDX-1106, a fully human IgG4, now referred to as nivolumab.(16) A total of 39 patients participated in the study and included other cancer types (advanced prostate cancer, colon cancer, renal cancer and non-small cell lung (NSCLCA)). The antibody was administered at doses from 0.3 to 10 mg/kg and was well tolerated with a lower incidence of immune mediated toxicities compared to ipilimumab. Partial responses were observed in melanoma, renal cancer and one complete response was documented in colon cancer. Similar to preclinical studies, biopsy specimens from this clinical trial showed expression of PD-L1 in the tumor, which the authors suggested correlated with response.

A larger phase I study investigated nivolumab at doses from 0.1 to 10 mg/kg and enrolled 239 patients with advanced melanoma, renal cancer and NSCLCA.(17) Twenty-six of the 94 melanoma patients (28%) had objective tumor regression and the progression-free survival was 41 weeks. In addition, 6 patients had stability of melanoma for more than 24 weeks. The expression of PD-L1 was also assessed in tumor biopsies of 42 patients. Objective response was observed in 9 of 25 patients whose tumors expressed PD-L1 and 0 of 17 patients whose tumors were PD-L1 negative. Subsequent studies have shown that response to anti-PD-L1 is higher in patients whose tumor expresses PD-L1, but responses have also been described in patients whose tumors are PD-L1 negative.

Another antagonistic antibody targeted to compete with the interaction between PD-1 and PD-L1 and PD-L2 known as pembrolizumab has been studied in melanoma.(18) The antibody is also a fully human IgG4. 173 patients with unresectable or metastatic melanoma who had disease progression after having received at least 2 doses of ipilimumab received pembrolizumab at 2 mg/kg (N = 89) or 10 mg/kg (N = 84). The objective response was 26% at both dose levels with a median time to response of 12 weeks. The median duration of response was not reached at the time of the publication. Immune mediated toxicities were also observed, but with a lower severity and incidence compared to anti-CTLA-4. Fatigue (33%), pruritis and rash were the most common toxicities and did not differ in severity or incidence comparing the 2 and 10 mg/kg dose levels.

The FDA approved Pembrolizumab in September 2014 for the treatment of patients with advanced melanoma progressive after ipilimumab or BRAF-targeted therapy in patients whose melanomas express a BRAF mutation.

In the Keynote-012 phase 1b study, 192 patients with recurrent or metastatic HNSCC were treated with pembrolizumab, either 10mg/kg every 2 weeks (n=60) or 200mg IV every 3 weeks (n=130) until progression. The objective response was 18% at both doses. The median duration of response was not reached after 30 months. Adverse reactions were similar to those observed for patients with melanoma or NSCLC, aside from hypothyroidism due to prior neck irradiation. (19)

The FDA approved Pembrolizumab on August 5, 2016 for the treatment of patient with recurrent or metastatic HNSCC with disease progression during or after platinum-containing chemotherapy.
[http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125514s009lbl.pdf]
[http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm515627.htm]

The FDA has also approved pembrolizumab for selected patients with NSCLCA. The criteria for pembrolizumab administration includes tumors that express PD-L1 on an FDA-approved assay and who have disease progression on or after platinum-containing chemotherapy. For patients with tumors that express

EGFR or ALK genomic aberrations, progression should be documented after treatment with an FDA-approved agent for the genomic alteration expressed by the tumor. In these selected patients, the overall objective response in NSCLCA was 45% (all partial responses) and 44% of responding patients had disease control for 6 months or longer. (20)

1.2 **Galectins and Tumor Biology**

Galectins are a family of proteins that bind to β-galactoside sugars that have numerous functions in normal mammalian biology including the facilitation of cell-cell interactions, regulation of apoptosis, regulation of immune responses via the T-cell receptor and transmembrane signaling. (22) Galectin-3, one of the most prominent galectins expressed in cancer cells, has a carbohydrate recognition domain (CRD) which is shared among galectin proteins (23), but in contrast to other galectin proteins, it has an N-terminal domain that is involved in forming multimers. (24) Although galectins are defined by their ability to bind to model carbohydrates containing galactose, such as lactosamine, the individual galectins appear to bind to different sets of glycans on glycoproteins, thus providing specificity between galectins. (25) For example, galectin-1 and galectin-3 bind to distinct cell surface receptors on T-cells. (26) There are many potential ligands for the lectin properties of galectin-3 including laminin, integrins, collagens, fibronectin, elastin, mucins, CD4+, CD8+, TGFBR, neural cell adhesion molecules, and many others (27). Binding of galectin-3 to N-glycans has been connected to multiple cellular processes including cell adhesion and migration, immune cell function, inflammation, and neoplasia (23, 28-32). It is likely that inhibition of galectin-3 modulates multiple protein interactions in the extracellular space thereby altering cellular function. In addition to glycan interactions, there are protein-protein interactions that occur with un-glycosylated proteins, mainly in the nucleus and cytoplasm (33). It appears, therefore, that the extracellular effects of galectins are related to their lectin properties to bind to glycoproteins whereas their intracellular effects are more related to protein-protein interactions.

Intracellular galectins are important in tumorigenesis resulting in activation of oncogenes, enhancement of angiogenesis, and regulation of growth-promoting pathways including c-myc and cyclin E. Cancer cells secrete galectins (especially galectin-3), which can promote cell matrix interactions that facilitate metastasis, suppress T-cell responses by cross-linking T cell receptors, and inhibit cytokine secretion resulting in T cell and dendritic cell anergy (34),(35),(36) Galectin-3 is elevated in the peripheral blood of patients with many cancer types including melanoma and is associated with poor prognosis and early onset of metastatic disease.(37), (38) These examples illustrate the central importance of galectins in tumor biology. Antagonists of galectin have significant potential as cancer therapeutics.

1.3 **Preclinical Models of Galectin Antagonists and T-cell Checkpoint Antibodies**

We tested whether Gal-3 was expressed by tumor cell lines including B16/F10 (melanoma), 4T1 (HER-2^{neg} mammary carcinoma), TRAMP-C1 (prostate cancer), MCA-205 (sarcoma), NOP-17 (HER-2^{+} mammary carcinoma), and SCN (negative control; rat suprachiasmatic nucleus). High levels of Gal-3 were secreted by B16/F10, 4T1, and TRAMP-C1 tumors, while NOP-17 cells secreted low levels of Gal-3 (Fig. 1A). These data are consistent with published studies demonstrating that Gal-3 is highly expressed in numerous tumor types, including B16 melanoma. We also examined the extent of intracellular Gal-3 expression and as seen in Fig. 1B, detected high levels of Gal-3 among the tumors with the highest levels of Gal-3 secretion (Fig. 1A). Next, we determined the extent to which checkpoint inhibitor blockade with anti-CTLA-4, anti-PD-1, anti-PD-L1 mAb, plus Gal-3 inhibition with GR-MD-02 reduced tumor growth in TRAMP-C1, 4T1, MCA-205, and B16/F10 tumor-bearing mice. Tumor-bearing mice were treated with IgG (ctrl), anti-CTLA-4, anti-PD-1, anti-PD-L1, and/or GR-MD-02. These data revealed that checkpoint inhibitor blockade with anti-CTLA-4, anti-PD-1, anti-PD-L1, plus GR-MD-02 significantly reduced tumor growth as compared to controls (Fig. 2A-D).

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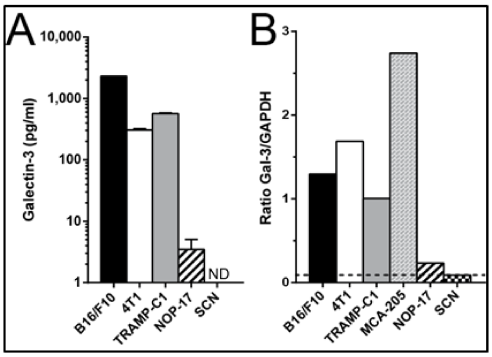

Figure 1. A) Gal-3 secretion (24 hrs) was determined by ELISA (graph depicts the mean+/-SEM; ND=not detected). B) The ratio of intracellular Gal-3:GAPDH in whole cell lysates was determined by Western blot (Odyssey infrared imaging, Li-Cor Biosciences). The dotted line represents the level of background staining.

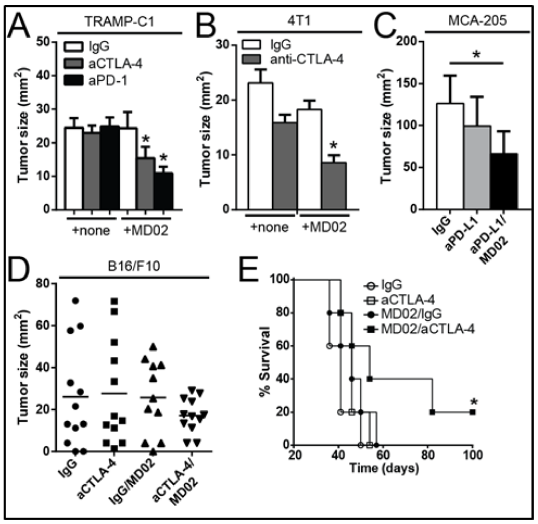

Figure 2. Tumor-bearing mice were treated with IgG (ctrl), anti-CTLA-4, anti-PD-1, anti-PD-L1 mAb (200 mcg; day 4,6,8), and/or GR-MD-02 (120 mg/kg; day 4,6,8,11,13,15). Tumor size (A,B,D=d11; C=d25) and E) survival (TRAMP-C1) were determined. Graphs depict the mean+/-SD from A, B, E) n=5, C) n=7, or D) n=12/group. *P<0.05.

As reviewed above, galectins influence many aspects of tumor biology and the immune response to cancer. Galectin-3 appears to be the most important of the galectin proteins in tumor biology and thus an antagonist for galectin-3 was selected for study in a variety of tumor immunology models.

The animal models employed a variety of different dose schedules, but in general, GR-MD-02 was administered concurrent with the T-cell checkpoint antibody. There was no toxicity observed in the tumor-bearing mice that received the combination of GR-MD-02 and anti-PD-1 or other T-cell directed antibodies. These preclinical experiments illustrate the potential of galectin antagonism when given with immunomodulatory agents and provide a strong rationale for testing the clinical and immunological activity of GR-MD-02 with pembrolizumab in humans with advanced melanoma. The augmentation of antigen-specific responses, T-cell proliferation, cytolytic function and T-cell memory from the combination galectin antagonism and PD-1 blockade is remarkable. In addition, the non-overlapping mechanism of action is not expected to exacerbate the toxicity of pembrolizumab.

1.4 **Clinical Trials with Galectin Antagonists**

There are currently three galectin antagonists in development for the treatment of human diseases, two from Galectin Therapeutics and one from La Jolla Pharmaceuticals. All three of these drugs are based on similar technology that is using complex carbohydrate compounds to inhibit the lectin binding of galectin-3.

GM-CT-01 is a Galectin Therapeutics compound derived from galactomannan, which is administered as an intravenous dose, has an open IND with the FDA, and has been investigated as a combination with chemotherapy in cancer. GM-CT-01 was evaluated in colorectal cancer based on pre-clinical studies that demonstrated efficacy when combined with 5-FU against cancer and seemed to additionally mitigate 5-FU toxicity. Four clinical trials were performed by Pro-Pharmaceuticals (now Galectin Therapeutics), as found on ClinicalTrials.gov:

1. http://clinicaltrials.gov/ct2/show/NCT00054977?term=GM-CT-01&rank=3
2. http://clinicaltrials.gov/ct2/show/NCT00110721?term=GM-CT-01&rank=2

3. http://clinicaltrials.gov/ct2/show/NCT00388700?term=GM-CT-01&rank=4
4. http://clinicaltrials.gov/ct2/show/NCT00386516?term=GM-CT-01&rank=1

A Phase I dose-escalating safety clinical trial enrolled patients with different types of solid tumors and had failed standard, approved treatments. This study evaluated the tolerability of dose escalation of GM-CT-01 alone ranging from 30 to 280 mg/m2 and in combination with 5-FU (500 mg/m2) over 2 cycles of therapy. Treatment of a total of 40 patients enrolled in the study demonstrated that GM-CT-01 was well tolerated without dose limiting toxicity identified.

Three phase 2, open label clinical trials were partially completed, two in patients with metastatic colorectal cancer, and one in patients with cholangiocarcinoma. While the three trials were not completed, there was evidence of efficacy in metastatic colorectal cancer and a reduction in 5-FU related side effects. Trial number 2 listed above, which enrolled 20 patients, had 1 patient with a partial response and 6 patients with stable disease. The reduction in side effects occurred despite the fact that 5-FU serum levels were not reduced. Adverse events related to 5-FU were evaluated by combining the 57 patients from all four clinical trials and comparing them to the results of adverse events reported in the literature. There was a markedly lower incidence of grade 3-4 adverse events associated with 5-FU when GM-CT-01 was combined with 5-FU. Additionally, there were no consistent adverse events related to GM-CT-01, although all the patients in these three studies received other therapies in addition to GM-CT-01.

GM-CT-01 is now being tested in patients with advanced metastatic melanoma in conjunction with a peptide vaccine (MAGE-3A1 and/or NA17.A2) in Brussels, Belgium under an investigator IND. The peptide vaccine is administered every 3 weeks and GM-CT-01 is administered at 3, 6, 9 12, 15 and 18 days after the 3rd, 5th and 6th peptide vaccinations. GM-CT-01 is administered at 280 mg/m^2 via intravenous infusion over one hour for each dose. This proof-of-principle study is configured to assess toxicity and measure immunogenicity of the study treatments. Of the 6 patients enrolled thus far, there have been no toxicities and no other adverse event, although in two patients there was a transient reduction in mononuclear cells that lasted less than 24 hours after infusion.

The other galectin-3 inhibitor under development at Galectin Therapeutics is known as GR-MD-02 (the galectin antagonist to be tested in this trial), and is derived from apple pectin. GR-MD-02 is a compound that inhibits lectin interactions with galectin-3 and to a lesser extent other galectin proteins such as galectin-1. GR-MD-02 is a galactoarabino-rhamnogalacturonan polysaccharide, molecular weight of approximately 50 KDa, with a backbone comprised predominantly of 1,4-linked galacturonic acid (GalA) moieties, with a lesser backbone composition of alternating 1,4-linked GalA and 1,2-linked rhamnose, which in-turn is linked to any number of side chains that include both 1,4-β-D-galactose (Gal) and 1,5-α-L-arabinose (Ara). GR-MD-02 binds to the galectin-3 CRD through a defined set of amino acid residues with an affinity of 2.9 μM. This compares to galectin-1 binding affinities for GR-MD-02 of 8 μM. The high molecular weight of GR-MD-02 and the lectin binding properties suggest that they likely act predominantly on extracellular galectins.

Pharmaceutical grade material prepared following GMP guidelines has been manufactured and an IND has been filed with the FDA for the treatment of non-alcoholic steatohepatitis (NASH) with advanced fibrosis based on pre-clinical work showing reversal of hepatic fibrosis in rats with this agent. It is also administered as an intravenous infusion. The first clinical trial with GR-MD-02 has been completed in patients with non-alcoholic hepatic NASH. The clinical trial (A Multi-Center, Partially Blinded, Maximum Tolerated Dose Escalation, Phase 1 Clinical Trial to Evaluate the Safety of GR-MD-02 in Subjects with Non-Alcoholic Steatohepatitis (NASH) With Advanced Hepatic Fibrosis) enrolled 38 patients and a total of 132 doses of GR-MD-02 were administered. Doses of GR-MD-02 up to 8 mg/kg IV were safe and well tolerated. The maximum proposed dose of GR-MD-02 in this protocol is 8 mg/kg, thus we also anticipate that it will be well tolerated. Since GR-MD-02 administration is ongoing on other studies, this clinical protocol may be modified in the future to incorporate any new data regarding toxicity, drug interactions, pharmacokinetics or clinically appropriate monitoring learned as a result.

The third galectin inhibitor in development is GCS-100, a modified citrus pectin compound, was evaluated in three clinical trials performed by GlycoGenesys/Prospect Therapeutics and now under development by La Jolla Pharmaceuticals; each of these studies were suspended for lack of funding, as found on ClinicalTrials.gov:

1. http://clinicaltrials.gov/ct2/show/NCT00776802?term=gcs-100&rank=1
2. http://clinicaltrials.gov/ct2/show/NCT00514696?term=gcs-100&rank=2
3. http://clinicaltrials.gov/ct2/show/NCT00609817?term=gcs-100&rank=3

Preliminary data from two of these trials was reported in abstract form. In a phase 1 dose escalating trial, GCS-100 was administered to patients with refractory solid tumors to determine dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and pharmacokinetics (PK) and efficacy. The DLT was a Grade 3 erythematous, maculopapular rash, resolving with systemic steroid treatment. Skin biopsy revealed a vasculitis similar to findings seen in dog models. Other adverse events included nausea, vomiting, diarrhea, fatigue, fever and hyperglycemia. Sustained periods of stable disease were achieved in a number of patients with previously treated advanced solid tumors. (39) A phase 2 clinical trial was conducted in elderly patients with CLL, in which it was reported that 6 of 24 patients had partial responses and two patients had to discontinue treatment because of rash. (40) There is also a study of GR-MD-02 plus ipilimumab that we are conducting in patients with metastatic melanoma with objectives and immunological monitoring that parallel this study. There have been no dose-limiting or unanticipated toxicities thus far and the immune monitoring strategy has revealed changes in peripheral blood T cells that we believe may be relevant to melanoma anti-tumor responses.

1.5 Rationale for Combining GR-MD-02 and Pembrolizumab in Patients with Advanced Malignancy

As summarized above, the combination of GR-MD-02 and anti-PD1 (pembrolizumab) enhances T-cell activation, memory and effector function, and promotes better antitumor responses in multiple murine models. Pembrolizumab appears to enhance survival and can induce tumor regression in a minority of patients with an objective response probability of approximately 18% in treatment refractory HNSCC [http://www.ncbi.nlm.nih.gov/pubmed/27247226] and 26% in patients who have melanoma progression after ipilimumab.(9) Our hypothesis is that galectin-3 antagonism using GR-MD-02 will enhance the probability of response to pembrolizumab by inducing proliferation, activation and memory function of CD8+ T cells that recognize tumor antigens. We will also explore the possibility that GR-MD-02 can enhance objective tumor response in patients who have radiographic progression on pembrolizumab monotherapy, who are also eligible for this study.

We have experience with GR-MD-02 combined with ipilimumab in patients with advanced melanoma in whom ipilimumab would be considered the standard of care. As of June 2015, six patients have completed therapy with three patients each receiving GR-MD-02 at 1 and 2 mg/kg. No toxicities have been observed related to GR-MD-02 and thus we plan to dose GR-MD-02 starting at 2 mg/kg in this study. Immunological effects have been observed with one patient showing a marked increase in gamma delta T cells, and another showing expansion of CD8 effector T cells. Although preliminary, the findings of the GR-MD-02 + ipilimumab study lend further support to the investigation of galectin inhibitors with other T-cell checkpoints.

This study will employ a 3+3 phase I design with dose escalation of GR-MD-02 in conjunction with the standard therapeutic dose of pembrolizumab. In addition to monitoring for toxicity and clinical response, blood and tumor samples will be obtained to assess immunologic measures relevant to galectin biology and pembrolizumab T-cell checkpoint inhibition (see section 8.4 for more details about immune monitoring).

1.6 Preliminary Clinical Results and Activity of GR-MD-02 + Pembrolizumab

As of September 2018, there were 14 melanoma patients who were assessed for response; and 6 with OHN cancer. No patients with lung cancer were enrolled to this trial, although they were one of the target groups for enrollment. There were 6 patients treated in cohort 1 with a GRMD-02 dose of 2 mg/kg, 3 patients in cohort 2

at a dose of 4 mg/kg and 11 patients in cohort 3 with a dose of 8 mg/kg. All patients received pembrolizumab at a fixed dose of 200 mg per cycle. Table 1 summarizes the clinical characteristics of these patients.

	Median Age	Range	Prior Immuno-Therapy	Prior RT	Prior Surgery (biopsy excluded)	Prior Targeted Therapy	Median Immunotx Pre Protocol	Median Total Regimens Pre Protocol
Melanoma n = 14	66	38 - 85	10	7	12	2	2	4
OHNSCC n = 6	61	41 - 69	2	5	0	0	0	3

The combination of GRMD-02 + pembrolizumab was well tolerated. There were no toxicities deemed related or probably related to GR-MD-02. All of the toxicities were deemed related to pembrolizumab and almost all were grade 1 or 2 (see Table 2 for more details). The only grade 3 toxicity was tumor pain and no grade 4 toxicities were observed with the combination. No patient required steroids or other immunosuppressive agents for the management of immune-mediated toxicities. There was no clear association between cohort assignment and the frequency or severity of toxicity. No dose-limiting toxicities were observed and the overall level of toxicity was less than we anticipated for pembrolizumab monotherapy.

Table 2: Most common toxicities associated with pembrolizumab by grade, all cohorts.

Toxicity	Grade 1	Grade 2	Grade 3
Rash	9		
Fatigue	7	3	
Flu-like symptoms	3		
Pruritis	9	2	
Diarrhea	3	2	
Joint pain	3		
Hyperglycemia	5		
Increased alkaline phosphatase	4		
Increased AST	4		
Increased ALT	4		
Transient lymphopenia	3		

Objective responses were seen at each dose level of GR-MD-02 and in both melanoma and OHN cancer. The objective response assessed at day 85 (after 5 cycles of GR-MD-02 + pembrolizumab) is depicted in Figure 3:

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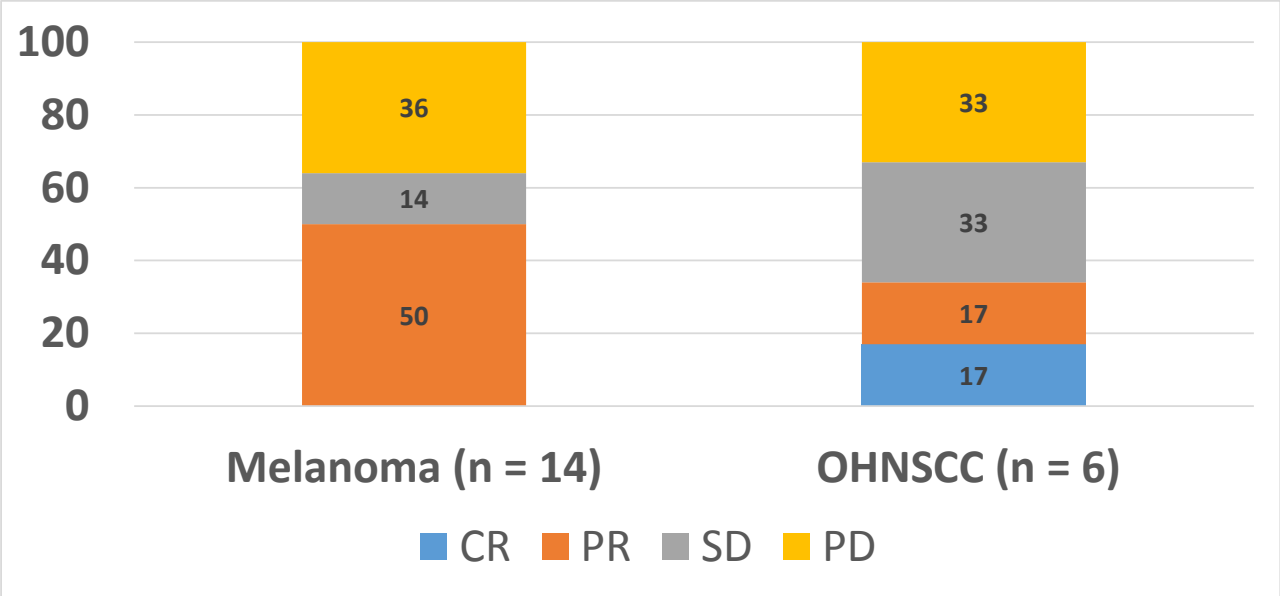
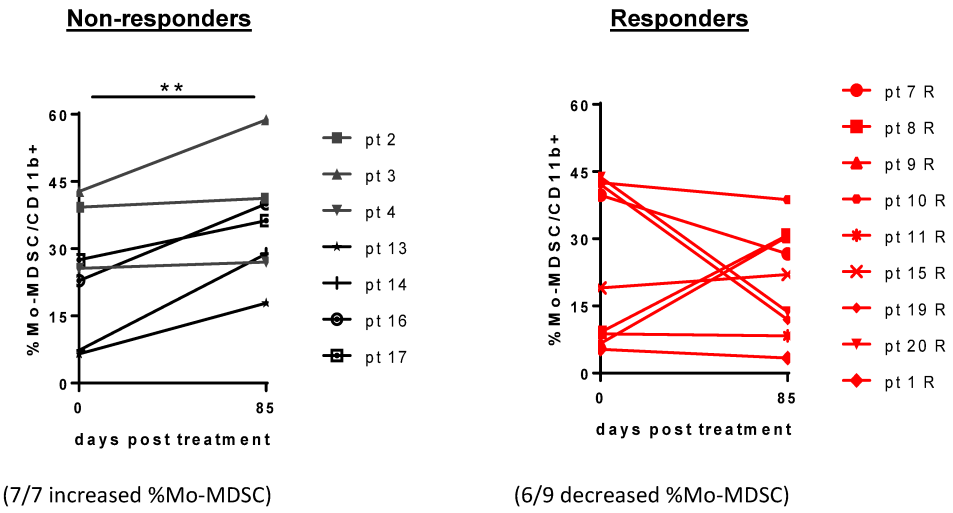
Figure 3: Tumor response using RECIST 1.1 criteria at day 85 after GR-MD-02 + pembrolizumab in patient with melanoma and OHN cancer. CR = Complete Response, PR = Partial Response, SD = Stable Disease and PD = Progressive Disease.



As summarized above, the range of objective response probabilities to pembrolizumab in randomized studies using pembrolizumab in patients with advanced melanoma ranges from 21% in patients who have had prior therapy to 39.1% in patients who had not received prior systemic therapy. Similarly, the objective response of pembrolizumab in OHN cancer is 18%. (19) Our results showing a 50% objective response in melanoma and 34% response in OHN cancer are within the confidence intervals for the response probability of pembrolizumab monotherapy, yet were better than we anticipated and warrant further investigation.

In addition to the clinically relevant tumor responses, the immune monitoring revealed a difference in myeloid-derived suppressor cells (MDSC) in the peripheral blood of patients with tumor regression (Responding) versus tumor progression (Non-responding) patients. Six out of 9 patients who achieved an objective response showed decreases in the percent MDSC at day 85 compared to baseline while 7 out of 7 patients with disease progression showed increased percent MDSC (Figure 4). This observation suggests a possible biomarker for response and provides insight into the potential mechanism of effect for the combination of GR-MD-02 + pembrolizumab. To the best of our knowledge, this relationship between percent MDSC and response has not been observed before in patients who received anti-PD-1.

Figure 4: Percent MDSC in responding and non-responding patients after GR-MD-02 + pembrolizumab.



(7/7 increased %Mo-MDSC) (6/9 decreased %Mo-MDSC)

Based on these clinical and immune monitoring findings, the original study will be enlarged to enroll an additional 10 melanoma patients and 5 OHN patients to cohort 4. The 4 mg/kg GR-MD-02 dose level was chosen for expansion as it was well-tolerated and anti-tumor responses were observed. Other studies with GR-MD-02 in patients with liver disease showed no enhanced biological effect at higher dose levels of GR-MD-02. In addition, patients assigned to cohort 4 will have continued GR-MD-02 dosing as long as pembrolizumab is administered. Immune monitoring and pharmacokinetic data will also be gathered in the expansion as detailed below. In addition, the frequency and severity of immune-mediated toxicity was less than we anticipated and provides further rationale to expand the investigation of the combination.

OBJECTIVES

Primary objective:

1) Determine a safe dose of GR-MD-02 used in combination with pembrolizumab 200mg IV every 3 weeks.

Secondary objectives:

1.1.1 Measure the response rate to combined therapy with GR-MD-02 and pembrolizumab in patients with metastatic melanoma who have had melanoma progression after ipilimumab and/or BRAF targeted therapy in melanomas with a BRAF mutation.

1.1.2 Measure the response rate to combined therapy with GR-MD-02 and pembrolizumab in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression during or after platinum-containing chemotherapy are eligible. PD-L1 testing is not required for HNSCC.

1.1.3 Measure the response rate of combined therapy with GR-MD-02 and pembrolizumab in patients with metastatic melanoma, NSCLC or HNSCC with tumor progression after pembrolizumab monotherapy.

1.1.4 Assess the biological activity of GR-MD-02 in combination with pembrolizumab by measuring:

a. $CD4^+$T cells with a memory phenotype ($CD3^+CD4^+Ki67^+CD25^+FoxP3^-CCR7^-CD45RA^-$

$CD27^{+}CD28^{+/-}$).

b. $CD8^{+}$ T cells with effector phenotype ($CD3^{+}CD8^{+}CD28^{-}CD95^{+}$)

c. Tumor-specific T cells using autologous and/or HLA-matched tumor when available.

d. Examine the composition of the tumor immune infiltrate from tumor biopsies (when feasible).

1.1.5 Assess quality of life during therapy using the FACT-M questionnaire.

1.1.6 Assess pharmacokinetics of GR-MD-02 at the 4 mg/kg dose level in the expansion cohort.

2. PATIENT SELECTION

2.1 Inclusion Criteria

2.1.1 Patients with unresectable or metastatic melanoma. Histological confirmation of melanoma will be required by previous biopsy or cytology. Patients with metastatic non-small cell lung cancer whose tumor expresses PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. In addition to tumor PD-L1 expression, NSCLCA patients with EGFR or ALK genomic tumor mutations must have disease progression after targeted therapy to be eligible for this study. **Patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression during or after platinum-containing chemotherapy are eligible. PD-L1 testing is not needed for OHN cancers. Only patients with melanoma and OHN cancer are eligible for cohort 4.**

2.1.2 Patients who have radiographic progression using RECIST criteria currently on pembrolizumab or who have recently discontinued pembrolizumab treatment and meet all other eligibility criteria are also eligible.

2.1.3 Patients must be ≥ 18 years of age.

2.1.4 ECOG performance status of 0-2.

2.1.5 Women of childbearing potential must have a serum or urine pregnancy test performed within 72 hours prior to the start of protocol treatment. The results of this test must be negative in order for the patient to be eligible. In addition, women of childbearing potential as well as male patients must agree to take appropriate precautions to avoid pregnancy.

2.1.6 No active bleeding.

2.1.7 Anticipated lifespan greater than 12 weeks.

2.1.8 Patients must sign a study-specific consent document.

2.2 Exclusion Criteria

2.2.1 Patients who have previously received a galectin antagonist

2.2.2 Patients with active autoimmune disease except for autoimmune thyroiditis or vitiligo (see Appendix C).

2.2.3 Patients with history of autoimmune colitis

2.2.4 Patients with untreated brain metastases. Patients with treated brain metastases who demonstrate control of brain metastases with follow-up imaging 4 or more weeks after initial therapy are eligible.

2.2.5 Patients requiring other systemic oncologic therapy, including experimental therapies

2.2.6 Patients with active infection requiring antibiotics.

2.2.7 Pregnant or lactating women, as treatment involves unforeseeable risks to the embryo or fetus.

2.2.8 Need for steroids at greater than physiologic replacement doses. Inhaled corticosteroids are acceptable.

2.2.9 Laboratory exclusions (to be performed within 28 days of enrollment):

- WBC < 3.0 x 10^{9}/L
- Hgb < 9.0 g/dL
- AST or ALT > 1.5 times ULN
- Total bilirubin > 1.9 g/dL, unless due to Gilbert's Syndrome. If Gilbert's Syndrome is present by clinical history, then direct bilirubin must by < 3.0 g/dl.
- Known history of HIV
- Known history of Hepatitis B
- Known history of Hepatitis C
- INR > 1.5x ULN

2.2.10 Inability to give informed consent and comply with the protocol. Patients with a history of psychiatric illness must be judged able to understand fully the investigational nature of the study and the risks associated with the therapy.

2.2.11 Any medical condition that in the opinion of the Principal Investigator would compromise the safety or conduct of the study procedures.

2.2.12 Unresolved immune-mediated pneumonitis, diarrhea, elevation of hepatocellular enzymes or other toxicities requiring greater than physiological replacement doses of steroids.

2.3 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial. Given the reduced incidence of melanoma in the non-white population, we expect that few of the patients enrolled will be non-white. The expected distribution of men and women enrolled is based on our experience with

other clinical trials at our Cancer Center. The anticipated study population is illustrated in the table below. For patients with NSCLCA or HNSCC, we anticipate that the distribution of gender and race/ethnicity will reflect the general population of Oregon, which is the main referral area for the patient treated at our cancer center.

Table 2.

	Race/Ethnicity					
Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male	18	0	0	0	0	18
Female	17	0	0	0	0	17
Total	35	0	0	0	0	35

3. REGISTRATION PROCEDURES

Patients must meet all of the eligibility requirements and undergo all pre-study procedures.

If a patient enrolls in the study, but does not receive study therapy, the patient's enrollment may be canceled. Reasons for cancellation will be documented in writing. Any patient whose enrollment was canceled before receiving study therapy will be replaced.

Assignment of Study Numbers

Study Numbers will be assigned at enrollment based on order of enrollment by the Immune Monitoring Laboratory. Patient initials, birthday, social security numbers or other traceable personal identifiers are not used.

All case report forms, study reports, and laboratory samples for research tests, including immune parameters or pharmacokinetics, will be labeled with the full patient Study Number.

4. TREATMENT AND STUDY DESIGN

Eligible patients will be registered and consecutively assigned to a cohort comprised of 3 – 6 patients in the dose escalation portion of the study. A total of 10 patients will be treated at the maximum tolerated dose to obtain more information on the immunomodulatory and clinical effects of the combination. In the study expansion conducted after completion of the dose escalation completed in September 2018, a total of 10 melanoma patients and 5 OHN patients will accrue to cohort 4. The study treatment is given in 21-day periods called a cycle. Pembrolizumab will be administered at a fixed dose of 200 mg every 3 weeks until progression or intolerable toxicity, which is the standard dose, indication and schedule for this agent. Individuals who have had melanoma progression on pembrolizumab and who meet all other eligibility criteria can also participate in the study. The dose and schedule of pembrolizumab and GR-MD-02 will be the same for this subgroup of patients. GR-MD-02 will be given 2 hours before each pembrolizumab dose and the pembrolizumab shall be administered assuming no toxicities are observed after a one-hour observation period following administration of GR-MD-02. Patients may receive up to 5 doses of GR-MD-02 over 85 days in cohorts 1, 2 and 3 and after Day 85, pembrolizumab monotherapy may continue every three weeks until disease progression and/or patients has achieved maximum benefit as determined by the Investigator. Patients in Cohort 4 will have GR-MD-02 dosing with each pembrolizumab dose up to a maximum of 17 cycles, which is the standard duration of pembrolizumab therapy in individuals who are deriving a benefit from therapy. For patients who progressed on

pembrolizumab monotherapy before participation in this study, but have stability or regression on the combination of pembrolizumab and GR-MD-02, those individuals shall continue GR-MD-02 and pembrolizumab until progression.

Cohort	GR-MD-02 dose (mg/kg lean body mass)
1	2*
2	4
3	8
4	4

* The dose levels of GR-MD-02 proposed in this study may be modified as more toxicity and pharmacokinetic information becomes available from other GR-MD-02 clinical trials.

Toxicities will be assessed using CTCAE v. 4.0. DLT is defined as any grade ≥ 3 toxicities, with the following exceptions:

- Hypothyroidism, hypopituitarism, adrenal insufficiency that is adequately controlled with medical management, hypokalemia, hyponatremia, hypomagnesemia.
- Asymptomatic alteration of amylase or lipase.
- Vitiligo

Lymphopenia will not be considered a DLT. If DLT is observed in 2 or more patients at any dose level, then the previous dose level of GR-MD-02 will be the maximum tolerated dose (MTD). If no DLTs are encountered, then the highest planned GR-MD-02 dose level will be considered the MTD. When the MTD is determined, patients will be treated at the MTD until accrual is completed.

Number of Patients with DLT in a Given Cohort	**Escalation Decision Rule**
0 out of 3	Enter 3 patients in the next cohort
$\geq$ 2	Dose escalation will stop. The dose level of the current cohort will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, proceed to the next dose level. If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended maximum tolerated Phase II dose. At least 6 patients must be entered at the recommended Phase II dose.

GR-MD-02 administration will stop for any individual patient experiencing DLT from this agent. There will be no GR-MD-02 dose modifications for individual patients unless there is greater than 10% change in body weight. If there is a +/- 10% change in body weight, the GR-MD-02 dose will be adjusted accordingly. If GR-MD-02 dosing is stopped in an individual patient, any remaining planned pembrolizumab doses can be administered if clinically indicated. For patients experiencing pembrolizumab toxicity, these toxicities will be managed per established guidelines. The general strategy to abrogate immune-mediated toxicities is to

administer high-dose steroids (e.g.: prednisone) until the toxicity resolves, followed by a taper of the steroid dose. If the toxicity does not recur during the taper and no other adverse events ensue, then pembrolizumab dosing can continue. If the toxicity resolves and pembrolizumab is resumed, then GR-MD-02 can also resume per protocol.

The rules for dose escalation of GR-MD-02 are given in the Table 3 above.

The DLT observation period will be the first cycle of treatment.

Dose escalations in individual patients will not be permitted. Standard supportive medications including anti-emetics, and pain medications will be offered during treatment. Steroids will not be used for the treatment of nausea, but can be used to ameliorate pembrolizumab-induced immune related toxicity as detailed above and in Appendix B.

For patients with clinical evidence of progression prior to receiving all 5 planned doses of GR-MD-02, patients may continue to receive GR-MD-02 provided that there:

a. Are no signs or symptoms indicating disease progression (including worsening of laboratory values)
b. Is no decline in ECOG performance status
c. Is no rapid progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) that requires urgent alternative medical intervention

Infusion Reaction Monitoring Plan

In toxicology studies, single and multiple (four) intravenous infusions of GR-MD-02 in multiple animal species up to concentrations of 30 mg/mL did not cause local reactions in the vessels or surrounding tissues and histology showed only mild inflammation in several cynomolgus monkeys. Additionally, in cardiovascular safety pharmacology studies in cynomolgus monkeys there was no evidence of systemic reactions following single intravenous infusions. In the human Phase 1 Clinical Trial (GT-020), as of January 25, 2014 six patients have received infusions of GR-MD-02 (2 mg/kg) and four of them received a total of four infusions at the same dose. There were no local or systemic infusion reactions.

Because GR-MD-02 infusion reactions are not anticipated, no premedication should be given to patients. Symptoms and vital signs (heart rate, blood pressure, temperature, and respiratory rate) will be monitored within 30 min prior to start of infusion , at the end of infusion, and prior to the start of pembrolizumab. Infusion reactions will be graded using CTCAE v. 4.0.

Instructions for treating infusion reactions:

Stop infusion if:	Stop infusion if infusion reaction is >= Grade 2. Have another nurse notify MD.
Check vital signs	Check vital signs q5 minutes until back to baseline, then q15 minutes until the resolution of symptoms.
Start oxygen	Start oxygen at 6-8 LPM for O2 <= 90%.
Diphenhydramine (Benadryl) injection 25 mg	25 mg intravenous every 15 min PRN.
Methylprednisolone sodium succinate (solu-medrol) 62.5 mg/ml injection 125 mg	125 mg intravenous once PRN
Dexamethasone (Decadron) 20 mg in sodium chloride 0.9% 50 mL IVPB	20 mg intravenous for 15 min once PRN

Instructions for anaphylactic reactions:

Stop infusion and call code blue	Stop infusion and call code blue (follow notification process specific to your facility). Have another nurse notify MD.
Nursing communication	Place patient in a supine position and maintain airway, STAT
Epinephrine 1 mg/ml injection 0.3 mg	0.3 mg intramuscular every 5 min PRN. Administer in the anterior lateral thigh using 1-1.5 inch needle.
Sodium chloride 0.9% (NS) infusion 500 mL	Intravenous, continuous. Run wide open to gravity.
Start oxygen	Start O2 at 6-8 LPM by nasal cannula
Albuterol (Ventolin HFA) 90 mcg/puff inhaler 2 puff	2 puff, inhalation, once. May repeat 1 time
Diphenhydramine (Benadryl) injection 50 mg	50 mg intravenous, once
Methylprednisone sodium succinate (solu-medrol) 62.5 mg/mL injection 125 mg	125 mg intravenous, once PRN. Choose only one steroid.
Dexamethasone (Decadron) 20 mg in sodium chloride 0.9% 50 mL IVPB	20 mg intravenous for 15 min, once. Choose only one steroid.
Famotidine (Pepcid) 2mg/mL IV syringe 20 mg	20 mg intravenous for 1 min, once PRN. Keep in refrigerator.
Check vital signs	Monitor vital signs every 5 minutes

Infusions will not be stopped for grade 1 reactions. For grade 2 infusion reactions, infusions will be interrupted until resolution of symptoms with appropriate medical management and prophylactic medications will be administered during subsequent infusions. For grade 3 or 4 infusion reactions, GR-MD-02 will be discontinued for that individual patient. For pembrolizumab, we will use the same guidelines for administration and toxicity management as defined in the pembrolizumab (Keytruda®) Package Insert (Appendix B), which are in accordance with the FDA labeling for this medication.

PHS IRB 15-166
Version 09/26/2018

STUDY CALENDARS

Cohorts 1, 2, and 3

Study Days	Scrn ± 3 days	Day 1 ± 3 days	Day 4 ± 3 days	Day 22 ± 3 days	Day 43 ± 3 days	Day 64 ± 3 days	Day 68 ± 3 days	Day 85 ± 3 days	Monotherapy every 3 weeks ± 3 days	Survival F/U [7]
Medical history	X	X		X	X	X		X	X	
Physical exam	X	X		X	X	X		X	X	
Research RN toxicity check[8]		X	X	X	X	X	X	X	X	
Vital Signs, weight	X	X	X	X	X	X		X	X	
GR-MD-02[1]		X		X	X	X		X		
Pembrolizumab[2]		X		X	X	X		X	X	
CBC, Diff, plt	X		X	X	X	X		X	X	
Chemistry panel[12]	X		X	X	X	X		X	X	
TSH/T4	X			X	X	X		X	X	
PT/PTT	X			X				X	X	
Testosterone[3]	X			X		X			X	
FSH/LH[6]	X			X		X			X	
ACTH/Cortisol	X			X	X	X			X	
Hepatitis Serology	X									
HIV	X									
Immunologic monitoring		X		X	X	X		X	X[14]	
ECG	X									
CT(chest/abd/pelvis)[4]	X[9]							X	X[13]	
QOL assessment	X[11]	X		X	X	X		X	X	
PET scan [4]	X							X		
Brain MRI[5]	X									
Pregnancy test[6]	X	X		X	X	X				
Tumor biopsy[10]	X						X			
Survival										X

1. GR-MD-02 dose per cohort assignment (see Section 4). The dose is administered IV over 60 (+/- 10) minutes.
2. Pembrolizumab will be administered at 200 mg IV to be given one hour after completion of GR-MD-02 infusions.
3. Male patients only.
4. Melanoma or lung cancer patients only. Other imaging studies as clinically appropriate as determined by the treating physician.
5. Repeat brain MRI as clinically indicated. (Brain MRI not required for OHN patients)
6. Female patients only. Pregnancy test only required for WOCBP.
7. Survival F/U will occur every 12 weeks (or at the discretion of the Investigator) after treatment discontinuation.
8. Research nurse will meet with the patient as indicated during office visits or contact the patient by phone weekly during the treatment through day 85 to assess and grade toxicities.
9. Other imaging to assess tumor response at the discretion of the investigator.
10. Tumor biopsy of lesions greater than 1 cm if patient consents and specimen can be obtained using physical exam or ultrasound to identify lesions. Tumor tissue from archived samples will also be sent for galectin expression as part of study enrollment.
11. QOL assessment using the FACT-M, Fact-L, or Fact-H&N questionnaire to be filled out by the patient and data gathered by the research nurse at the time points indicated.

12. Chemistry panel to include alanine amino transferase (ALT), alkaline phosphatase, albumin, aspartate amino transferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, carbon dioxide, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphorous, potassium, total protein, and sodium
13. During follow-up, CT (chest/abdomen/pelvis) to occur every 12 weeks
14. During follow-up, immune monitoring will occur every 12 weeks

Cohort 4

Study Days	**Scrn**	**Day 1**	**Day 2**	**Day 22 ± 3 days**	**Day 43 ± 3 days**	**Day 64 ± 3 days**	**Day 68 ± 3 days**	**Day 85 ± 3 days**	**Subsequent Cycles every 3 weeks ± 3 days**	**Survival F/U [7]**
Medical history	X	X		X	X	X		X	X	
Physical exam, AE's and Con Meds	X	X		X	X	X		X	X[17]	
Vital Signs, weight	X	X[14]		X[14]	X[14]	X[14]		X[14]	X	
GR-MD-02[1]		X		X	X	X		X	X	
Pembrolizumab[2]		X		X	X	X		X	X	
CBC, Diff, plt	X			X	X	X		X	X	
Chemistry panel[10]	X			X	X	X		X	X	
TSH with reflex to Free T4 if abnormal	X			X	X	X		X	X[16]	
PT/PTT	X			X				X	X[16]	
Testosterone Total[3]	X			X		X			X[16]	
FSH/LH[6]	X			X		X			X[16]	
ACTH/Cortisol	X			X	X	X			X[16]	
Immunologic monitoring		X		X	X	X		X	X[12]	
ECG	X									
CT Imaging[4]	X							X[15]	X[11]	
QOL assessment[9]		X		X	X	X		X	X	
Brain MRI[5]	X									
Pregnancy test[6]	X	X		X	X	X				
Tumor biopsy[8]	X						X			
Pharmacokinetics[13]		X	X							
Survival										X

1. GR-MD-02 4 mg/kg. The dose is administered IV over 60 (+/- 10) minutes before pembrolizumab.
2. Pembrolizumab will be administered at 200 mg IV to be given one hour after completion of GR-MD-02 infusions.
3. Male patients only.
4. Imaging studies as clinically appropriate as determined by the treating physician.
5. Repeat brain MRI as clinically indicated. (Brain MRI not required for OHN patients)
6. Female patients only. Pregnancy test only required for WOCBP.
7. Survival F/U will occur every 12 weeks (or at the discretion of the Investigator) after treatment discontinuation.
8. Tumor biopsy of lesions greater than 1 cm if patient consents and specimen can be obtained using physical exam or ultrasound to identify lesions. Tumor tissue from archived samples will also be sent to Redmond Lab for galectin expression

at completion of study cohort.
9. QOL assessment using the FACT-M, or Fact-H&N questionnaire to be filled out by the patient and data gathered by the research nurse at the time points indicated.
10. Chemistry panel to include alanine amino transferase (ALT), alkaline phosphatase, albumin, aspartate amino transferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, carbon dioxide, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphorous, potassium, total protein, and sodium
11. Imaging studies as clinically appropriate as determined by the treating physician to occur every 12 weeks +/- 1 week.
12. Immune monitoring and noted lab tests will occur every 12 weeks
13. PK will be obtained for the first GR-MD-02 dose only using an EDTA plasma tube (3 ml purple top). Samples will be obtained before GR-MD-02 administration, 2 and 24 hours after the start of GR-MD-02 administration. For the 2- and 24-hour time points, there is a window of up to 4 hours and 26 hours, respectively. The exact time of the pre-dose sample, start and end times for the GR-MD-02 infusion and the exact time of the subsequent specimens will be recorded.
14. Vitals to occur within 30 min prior to start of infusion, at the end of infusion and prior to starting pembrolizimab.
15. +/- 1 week allowable window
16. Labs to occur every 6 weeks.
17. Once off tx, follow any grade 3 toxicities until reach grade 1.

5. ADMINISTRATION OF STUDY TREATMENTS

5.1 **GR-MD-02**

GR-MD-02 is prepared from USP apple pectin through a process of controlled hydrolysis and purification. The molecular structure is a complex carbohydrate that contains terminal galactose molecules. It binds to both galectin-1 and galectin-3 proteins, with a greater affinity for the latter. Pharmacokinetics have been studied in rodent and primate models. The elimination half-life for a single IV dose in the range of 60-120 μg/kg is in the range of 20-48 hours and the half-life in one human subject in the phase 1 trial was found to be 20 hours after a 2 mg/kg dose. There are limited data on GR-MD-02 elimination, but very little is excreted in the urine in bile. It is hypothesized that the main pathway of elimination is through lysosomal degradation in macrophages.

PRE-CLINICAL TOXICITY: Weekly doses of up to 600 mg/kg/dose in rats and 300 mg/kg/dose in cynomolgus monkeys have been administered. No deaths in test animals were observed. There was no change in body weight, food consumption, or electrocardiography or clinical pathology in the monkeys at any dose level. There were no changes in clinical laboratories; however, at doses greater than 120 mg/kg, vacuolated macrophages were observed in the spleen and mesenteric lymph nodes, medullary casts were noted in the kidneys and hypertrophy of hepatic sinusoids was also present on histopathology. These findings are similar to foreign body type granulomatous inflammation promulgated by macrophages and improved during a 28-day washout period. There were no adverse events at doses $\leq$ 60 mg/kg/dose in monkeys and 120 mg/kg in rats, which is approximately 15 times greater than the dose levels planned in this study.

HOW SUPPLIED: Single-use vials containing GR-MD-02 at a concentration of 27 mg/ml in sterile aqueous solution of phosphate buffered saline for a total amount of 270 mg GR-MD-02 per vial. Galectin Therapeutics will supply study medication.

STORAGE: Must be stored under refrigerated conditions between 2° C and 8° C. It must be administered within 24 hours of preparation and refrigerated until one hour prior to patient administration at which time it will be removed from the refrigerator and warmed to room temperature.

The temperature monitor log is reviewed by the Clinical Research staff and the research pharmacist at Providence Portland Medical Center.

PREPARATION/ADMINISTRATION: The appropriate dose of GR-MD-02 will be diluted to a total volume of 100 ml NS warmed to room temperature for one hour and administered by intravenous infusion using a 0.2 micron filter over 60 (+/-10) minutes at each planned dose.

5.2 Pembrolizumab

Please see the full package insert in Appendix B. Pembrolizumab (Keytruda™) is a recombinant, human monoclonal antibody that binds to programmed death-1 (PD-1) expressed on T cells. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

TOXICITY: Side effects of pembrolizumab are immune-mediated and include fatigue, diarrhea, pyrexia, pneumonitis, enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and ocular manifestations.

HOW SUPPLIED: Pembrolizumab is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial will be reconstituted and diluted to a total volume of 100 ml for intravenous infusion. Each 2 ml of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate-80 (0.4 mg) and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5. The study and cancer center will not cover the costs for pembrolizumab.

STORAGE: Store reconstituted pembrolizumab under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours or room temperature for no more than 4 hours. Do not freeze.

PREPARATION/ADMINISTRATION: Pembrolizumab will be administered at the recommended dose of 200 mg IV over 30 (+/- 10) minutes every 3 weeks until progression, unacceptable toxicity or maximum benefit has been achieved as determined by the Investigator. Administer infusion solution through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line 0.2 – 5 micron in-line filter. Do not co-administer other drugs through the same infusion line.

5.3 5.3 Study Treatment Discontinuation

Participants MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by the sponsor
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration
- Disease progression in the absence of clinical benefit as determined by the Investigator.
- Noncompliance of the participant with protocol-mandated procedures based on the judgment of the Investigator
- Symptomatic disease progression after GR-MD-02 and pembrolizumab or the follow up period; the patient should be re-staged and sites of recurrence and/or progression documented.
- Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow up.

- Up to two doses of GR-MD-02 and pembrolizumab can be missed. If a third consecutive dose needs to be held, the patient is off study and can receive whatever standard care deemed appropriate by their physician.

All reasons for discontinuation of treatment must be documented. All patients will be followed for survival or until death post-treatment.

6. MEASUREMENT OF EFFECT

It is expected that clinically significant tumor regressions may be delayed, or occur after a period of progression in patients who receive T-cell checkpoint-based immunotherapy.(40) Response and progression will be evaluated in this study using the immune-related response criteria in solid tumors as described by Hoos et al. (44),(45)

6.1.1 Definitions

Measurable disease: Measurability is defined as 5 × 5 mm or more on helical computer tomography scans. The sum of the perpendicular diameters (SPD) of index lesions at baseline is added to that of new lesions to calculate total tumor burden according to the following formula:

$$\text{Tumor Burden} = SPD_{\text{index lesions}} + SPD_{\text{new measurable lesions}}$$

Decrease in total measurable tumor burden is assessed relative to the baseline tumor burden, that is, SPD of all index lesions at baseline. The response category irPD should be confirmed at two consecutive time points as already done for irPR or irCR. Overall, immune-related response based on two or more tumor assessments is derived as shown in this table:

Derivation of overall immune-related response for all assessed time points

Measurable response	Nonmeasurable response		Overall response
Index and new measurable lesions (total measurable tumor burden)†	**Non-index lesions**	**New nonmeasurable lesions**	**Using irRC**
100% decrease	Absent	Absent	irCR‡
≥50% decrease	Any	Any	irPR‡
<50% decrease to <25% increase	Any	Any	irSD
≥25% increase	Any	Any	irPD‡

* After Wolchok et al. (43). irCR = immune-related compete response—complete disappearance of all index and new measurable lesions; irPR = immune-related partial response—decrease in tumor volume ≥50% relative to baseline; irSD = immune-related stable disease—not meeting criteria for irCR or irPR, in absence of irPD; irPD = immune-related progressive disease—increase in tumor volume ≥25% relative to nadir.

† Index and non-index lesions are selected at baseline. Index lesions are measurable (>5 × 5 mm), and non-index lesions are not measurable (<5 × 5 mm, ascites, bone lesions, etc.). Changes are assessed relative to baseline and include measurable lesions only (>5 × 5 mm).

‡ Assuming response and progression are confirmed by a second assessment at least 4 weeks apart.

Using irCR, the appearance of new lesions alone does not constitute irPD if they do no7.5 for partial response (≥50% decrease) or qualifying for stable disease (<50% decrease to >25% increase) are considered to have irPR or irSD, respectively (same percentage changes including new lesions).

7. REGULATORY AND REPORTING REQUIREMENTS

7.1 **Adverse Event Reporting**

7.1.1 **Definitions**

Serious adverse event:

A serious adverse drug experience is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected adverse event:
Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Associated with the use of the drug / intervention:
There is a reasonable possibility that the experience may have been caused by the drug.

Disability:
A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse event:
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Unanticipated Problem
An unanticipated problem is an adverse event that is (i) unexpected; (ii) serious; and (iii) felt by the investigator to be possibly, probably, or definitely related to the research intervention. Only adverse events that meet this definition need be reported to the IRB.

For more information on the definition of an unanticipated problem and reporting requirement, consult the current PH&S AE Guidelines published on the IRB website (http://phsnet.phsor.org/institutional_review_board).

7.1.2 **Reporting**

PHS IRB:
An unanticipated event that is serious and definitely, probably, or possiblycaused by the study treatment (drugs or device) will be reported to the IRB in accordance with their guidelines and within their timelines.

FDA Reporting

An unanticipated event that is serious and definitely or probably caused by the study treatment will be reported to the FDA within 10 days using a MedWatch report.

7.2 Continuing Review and Final Reports

An annual progress report (continuing review) will be submitted to the IRB for the duration of the study. A final report to the IRB will be submitted at the summation of the study.

7.3 Protocol Modifications and Amendments

All modifications or amendments to the protocol or informed consent document must be approved by the Principal Investigator and submitted to the Providence Health & Services Regional Institutional Review Board (IRB) for review and approval. All modifications and amendments will be documented with a new version number and date. All changes to the informed consent document will include the date of the revision on the form.

No changes will be implemented until IRB approval is obtained except when a potential threat to patient safety exists.

The IRB will be notified of any significant deviations from the approved protocol. Documentation of all IRB correspondence will be maintained in the central regulatory file according to section 10.5.

7.4 Record Retention

According to 21 CFR 312.62(c), the investigator shall retain required records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the investigator shall retain these records until 2 years after the investigation is discontinued or the IND is withdrawn and the FDA is notified.

The investigator must retain protocols, amendments, IRB/IBC approvals, completed, signed, dated consent forms, patient source documents, case report forms, quality monitoring reports, drug accountability records and all documents of any nature regarding the study or patients enrolled. All records will be maintained under restricted access by the Clinical Trials Department at Providence Portland Medical Center while the study remains active. Records may be placed in long-term storage after the study is completed. The location of long-term storage will be secure and easily accessed for regulatory purposes.

7.5 Quality Assurance Plan

The Providence Health & Services Quality Assurance (QA) plan for cancer clinical trials comprises Standard Operating Procedures (SOPs) that require ongoing review of activities associated with all investigator-initiated trials including protocol compliance, accuracy of data and safety of participants.

7.5.1 Study Monitoring

Study monitoring activities (Quality Control Reviews) are performed by clinical research staff members who have completed specialized training in study monitoring procedures and human subjects protections. Individuals who perform study monitoring activities do not report to Principal Investigators or research scientists and may not monitor studies for which they have direct responsibility.

Study monitoring activities are conducted regularly and include (but are not limited to) review and verification of the following:

- Eligibility
- Informed Consent process
- Adherence to protocol treatment plan
- Case Report Forms (CRFs)
- Source Documentation
- Adverse Events
- Regulatory Reporting

Results of study monitoring activities will be reported to applicable study personnel, the Clinical Trials Manager and Quality Assurance.

7.5.2 Quality Assurance

Quality Assurance (QA) personnel review study monitoring reports and if necessary, determine follow-up actions to resolve significant findings. QA has the authority to request immediate corrective action if significant patient safety issues are identified.

QA will track and trend results from study monitoring reports as well as associated corrective and preventive actions. A QA summary report will be provided to the IRB at the time of continuing review.

QA personnel do not have a direct reporting relationship to the Principal Investigator and are not responsible for enrollment or coordination of care for study participants.

7.5.3 Plans For Assuring Accuracy Of Data

Case report forms will undergo quality assurance review and periodic audits per iinstitutional standard operating procedures. All quality assurance reviews will include verification of the accuracy and integrity of data entered to case report forms. Incorrect data will be identified and corrected. The existence of adequate source documents for all data will be verified. All annual reports (continuing reviews) or publications will be reviewed by a staff person not associated with patient care coordination, data completion and submission, or writing such reports.

A committee of outside clinical researchers who are skilled in the administration of immunotherapy and who are not actively involved in the care of patients on the trial will be formed to review all serious adverse events that occur during the study. They will also review summaries of the adverse events at the completion of each accrued cohort and participate in decisions to open the next cohort for enrollment. Records of all committee reviews and input will be kept in the study binder.

8 STATISTICAL CONSIDERATIONS

8.1 Study Endpoints

The primary study endpoint is to determine the maximum tolerated dose of GR-MD-02 when given in conjunction with pembrolizumab given at the standard dose and schedule. The main secondary objective is to estimate the response of GR-MD-02 and pembrolizumab in patients with metastatic melanoma, HNSCC or NSCLC. Other secondary objectives are not germane to the calculation of sample size.

8.2 Sample Size

A standard 3+3 phase I design will be used to determine the maximum tolerated dose of GR-MD-02. After determining the maximum tolerated dose of GR-MD-02 in the dose-escalation portion of the study, a total of 10 patients will enroll in the trial at the MTD. A maximum of 22 patients and a minimum of 16 patients will accrue to the study assuming that the MTD is found to be the highest planned dose level. After the initial 20 patients were enrolled and assessed, we have chosen to amend the protocol to accrue an additional 10 patients with melanoma and 5 patients with OHN cancer to cohort 4 (see Sections 1.7 and 4.0 for further details).

8.3 Patient Accrual

It is anticipated that three patients every 2 months can accrue to this trial, assuming no dose-limiting toxicities. A 28-day observation period shall occur after the last patient at a dose level has completed all 5 planned doses of GR-MD-02 to assure that there are no late toxicities related to study medication. Accrual to the next dose level will commence only after the 28-day observation period is complete. A late toxicity that meets the criteria described in Section 4 will be considered a dose-limiting toxicity. If a dose-limiting toxicity for the combination of GR-MD-02 and pembrolizumab is observed in one of the first 3 patients at a dose level, then patient accrual will be decreased to one per 4-week interval until 6 patients are accrued at that dose level. Assuming that one DLT is observed at each dose level, then accrual to the dose-escalation portion of the study would take a maximum of 18 months. Accrual to the Cohort 4 expansion is anticipated to take 10 months.

8.4 Immunological Monitoring

As detailed in the schedule of events, samples for immunological monitoring will include blood, melanoma tumor biopsies and collecting peripheral blood mononuclear cells. The main objectives of the monitoring will be to characterize circulating T-cell subsets and antibody responses to representative tumor antigens.

The immunological monitoring lab will perform flow cytometry with a panel of markers including CD3, CD4, CD8, CD27, CD28, CD95, CD25, CD127, CCR-7, FoxP3, ICOS and CD45RA. T cell sub-populations of interest include T_{reg}, central memory and effector cells. Other immunological measures may be evaluated including but not limited to serum galectin-3 levels, immunoscore of biopsy samples, assessment of tumor-specific tumor responses using overlapping peptide libraries and ELISPOT, and measurement of serum cytokine levels using Luminex beads to generate hypotheses for future studies and to gain preliminary information on possible biomarkers.

T-cell response to cancer cell lines and antigens identified by protein array may also be analyzed using autologous tumor if available from biopsy or using a bank of tumor specimens that were triple enzyme digested and cryopreserved at the EACRI in Dr. Fox's lab in selected patients. We will start by evaluating whether post treatment samples recognize HLA-matched melanoma, HNSCC or NSCLC cells. If we identify patients with detectable interferon gamma responses against matched cell lines we will then evaluate whether the same response exists in the limited number of pretreatment cryopreserved PBMC.

8.5 Quality of Life Assessment

A commonly used quality of life (QOL) questionnaire known as FACT-M (Functional Assessment of Cancer - Melanoma), FACT H&N (Functional Assessment of Cancer – Head & Neck), and FACT – L (Functional Assessment of Cancer – Lung) shall be used before and during the planned study treatment (Appendix D). This survey tool was designed for patients with melanoma, head and neck cancer, and lung cancer specifically and will be administered at the times indicated in the study

calendar (Section 5). The gathering of QOL data is hypothesis generating and shall not influence dosing decisions, monitoring or other clinical interventions.

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APPENDIX A
ECOG PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

5 Death (Karnofsky 0)

PHS IRB 15-166
Version 09/26/2018

APPENDIX B

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KEYTRUDA safely and effectively. See full prescribing information for KEYTRUDA.

KEYTRUDA® (pembrolizumab) for injection, for intravenous use
KEYTRUDA® (pembrolizumab) injection, for intravenous use
Initial U.S. Approval: 2014

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1.1) 12/2015
Indications and Usage (1.2) 10/2015 Indications and Usage (1.3) 08/2016 Dosage and Administration (2.1, 2.3) 10/2015
Dosage and Administration (2.2) 08/2016
Warnings and Precautions (5.1, 5.2, 5.3, 5.5, 5.6, 5.7) 12/2015
Warnings and Precautions (5.4) 08/2016

----------INDICATIONS AND USAGE ----------

--KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of:

- patients with unresectable or metastatic melanoma. (1.1)
- patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.2)
- patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.3)

---------- DOSAGE AND ADMINISTRATION ----------

- Melanoma and NSCLC: 2 mg/kg every 3 weeks. (2.2)
- HNSCC: 200 mg every 3 weeks. (2.2)

Administer KEYTRUDA as an intravenous infusion over 30 minutes.

---------- DOSAGE FORMS AND STRENGTHS ----------

- For injection: 50 mg lyophilized powder in single-use vial for reconstitution (3)
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Immune-mediated Pneumonitis: Withhold for moderate, and permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)
- Immune-mediated Colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.2)
- Immune-mediated Hepatitis: Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue. (5.3)
- Immune-mediated Endocrinopathies (5.4):
  - Hypophysitis: Withhold for moderate and withhold or permanently discontinue for severe or life-threatening hypophysitis.
  - Thyroid disorders: Monitor for changes in thyroid function. Withhold or permanently discontinue for severe or lifethreatening hyperthyroidism.
  - Type 1 diabetes mellitus: Monitor for hyperglycemia. Withhold KEYTRUDA in cases of severe hyperglycemia.
- Immune-mediated nephritis: Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or
  life-threatening nephritis. (5.5)
- Infusion-related reactions: Stop infusion and permanently discontinue KEYTRUDA for severe or life-threatening infusion reactions. (5.7)
- Embryofetal toxicity: KEYTRUDA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.8)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (reported in ≥20% of patients) were fatigue, decreased appetite, and dyspnea (6.1). Other common adverse reactions in patients with:

- melanoma included pruritus, rash, constipation, diarrhea, and nausea. (6.1)
- NSCLC included cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

--Lactation: Discontinue nursing or discontinue KEYTRUDA. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

1.1. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*.

1.2 Non-Small Cell Lung Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA *[see Clinical Studies (14.2)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.3 Head and Neck Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy *[see Clinical Studies (14.3)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for second line or greater treatment of metastatic NSCLC with KEYTRUDA based on the presence of positive PD-L1 expression *[see Clinical Studies (14.2)]*. Information on FDA-approved tests for the detection of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CcompanionDiagnostics.

2.2 Recommended Dosing

Melanoma and Non-Small Cell Lung Cancer

The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

Head and Neck Cancer

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.3)]*.

2.3 Dose Modifications

Withhold KEYTRUDA for any of the following:

- Grade 2 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 2 or 3 colitis *[see Warnings and Precautions (5.2)]*
- Grade 3 or 4 endocrinopathies *[see Warnings and precautions (5.4)]*
- Grade 2 nephritis *[see Warnings and Precautions (5.5)]*
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction *[see Warnings and Precautions (5.6)]*

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue KEYTRUDA for any of the following:

- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy)
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity *[see Warnings and Precautions (5.1)]*
- Grade 3 or 4 nephritis *[see Warnings and Precautions (5.5)]*
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN ○ For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions *[see Warnings and Precautions (5.7)]*
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of
  KEYTRUDA
- Any severe or Grade 3 treatment-related adverse reaction that recurs *[see Warnings and Precautions (5.6)]*

2.4 Preparation and Administration

Reconstitution of KEYTRUDA for Injection (Lyophilized Powder)

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder 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. 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.

Storage of Reconstituted and Diluted Solutions The product does not contain a preservative. Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

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 infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

Administration

- Administer infusion 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.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 50 mg lyophilized powder in a single-use vial for reconstitution
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis, including fatal cases, occurred in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Pneumonitis occurred in 32 (2.0%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3, including Grade 1 (0.8%), Grade 2 (0.8%), and Grade 3 (0.4%) pneumonitis. The median time to development of pneumonitis was 4.3 months (range: 2 days to 19.3 months). The median duration was 2.6 months (range: 2 days to 15.1 months). Twelve (38%) of the 32 patients received corticosteroids, with 9 of the 12 receiving high-dose systemic corticosteroids for a median duration of 8 days (range: 1 day to 1.1 months) followed by a corticosteroid taper. Pneumonitis led to discontinuation of KEYTRUDA in 9 (0.6%) patients. Pneumonitis completely resolved in 21 (66%) of the 32 patients.

NSCLC

Pneumonitis occurred in 19 (3.5%) of 550 patients with NSCLC, including Grade 2 (1.1%), Grade 3 (1.3%), Grade 4 (0.4%), or Grade 5 (0.2%) pneumonitis in patients receiving KEYTRUDA in Trial 3. The median time to development of pneumonitis was 1.7 months (range: 4 days to 12.9 months). In patients receiving KEYTRUDA 10 mg/kg every 14 days, the median time to development of pneumonitis was shorter (1.5 months) compared with patients receiving 10 mg/kg every 21 days (3.5 months). Sixteen of the 19 patients (84%) received corticosteroids, with 14 of the 19 (74%) requiring high-dose systemic corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day). The median starting dose of high-dose corticosteroid treatment for these fourteen patients was 60 mg/day with a median duration of treatment of 8 days (range: 1 day to 4.2 months). The median duration of pneumonitis was 1.2 months (range: 5 days to 12.4 months). Pneumonitis occurred more frequently in patients with a history of asthma/chronic obstructive pulmonary disease (5.4%) than in patients without a history of these diseases (3.1%). Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.0%) than in patients who did not receive prior thoracic radiation (2.6%). Pneumonitis led to discontinuation of KEYTRUDA in 12 (2.2%) patients. Pneumonitis completely resolved in 9 patients.
Pneumonitis was reported as ongoing in 9 patients and one patient with ongoing pneumonitis died within 30 days of the last dose of KEYTRUDA.

5.2 Immune-Mediated Colitis

Immune-mediated colitis occurred in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Colitis occurred in 31 (2.0%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3, including Grade 2 (0.5%), Grade 3 (1.1%), and Grade 4 (0.1%) colitis. The median time to onset of colitis was 3.4 months (range: 10 days to 9.7 months). The median duration of colitis was 1.4 months (range: 1 day to 7.2 months). Twenty-one (68%) of the 31 patients received corticosteroids, all of whom required highdose systemic corticosteroids for a median duration of 6 days (range: 1 day to 5.3 months) followed by a corticosteroid taper. Colitis led to discontinuation of KEYTRUDA in 14 (0.9%) patients. Colitis resolved in 27 (87%) of the 31 patients.

NSCLC

Colitis occurred in 4 (0.7%) of 550 patients, including Grade 2 (0.2%) or Grade 3 (0.4%) colitis in patients receiving KEYTRUDA in Trial 3. The median time to onset of colitis was 1.6 months (range: 28 days to 2.2 months) and the median duration was 16 days (range: 7 days to 1.3 months). Two patients were started on high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) and two patients were started on low dose corticosteroids. One patient (0.2%) discontinued KEYTRUDA due to colitis. Three patients with colitis experienced complete resolution of the event.

5.3 Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in patients receiving KEYTRUDA. Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Hepatitis occurred in 16 (1.0%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3, including Grade 2 (0.1%), Grade 3 (0.7%), and Grade 4 (0.1%) hepatitis. The time to onset was 26 days (range: 8 days to 21.4 months). The median duration was 1.2 months (range: 8 days to 4.7 months). Eleven (69%) of the 16 patients received corticosteroids, with 10 of the 11 receiving high-dose systemic corticosteroids for a median duration of 5 days (range: 1 to 14 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of KEYTRUDA in 6 (0.4%) patients. Hepatitis resolved in 14 (88%) of the 16 patients.

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

Hypophysitis occurred in patients receiving KEYTRUDA. Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis and withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Hypophysitis occurred in 13 (0.8%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3 including Grade 2 (0.3%), Grade 3 (0.3%), and Grade 4 (0.1%) hypophysitis. The time to onset was 3.3 months (range: 1 day to 7.2 months). The median duration was 2.7 months (range: 12 days to 12.7 months). Twelve (92%) of the 13 patients received corticosteroids, with 4 of the 12 patients receiving high-dose systemic corticosteroids. Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.3%) patients. Hypophysitis resolved in 7 (54%) of the 13 patients.

NSCLC

In Trial 3, hypophysitis occurred in 1 (0.2%) of 550 patients, which was Grade 3 in severity. The time to onset was 3.7 months. The patient was treated with systemic corticosteroids and physiologic hormone replacement therapy. The patient did not discontinue KEYTRUDA due to hypophysitis.

Thyroid Disorders
Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma
Hyperthyroidism occurred in 51 (3.3%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, or 3, including Grade 2 (0.6%) and Grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months). The median duration was 1.7 months (range: 1 day to 12.8 months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (0.1%) patients. Hyperthyroidism resolved in 36 (71%) of the 51 patients.

Hypothyroidism occurred in 127 (8.1%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3 including Grade 3 (0.1%) hypothyroidism. The median time to onset of hypothyroidism was 3.3 months (range: 5 days to 18.9 months). The median duration was 5.4 months (range: 6 days to 24.3 months). No patients discontinued KEYTRUDA due to hypothyroidism. Hypothyroidism resolved in 24 (19%) of the 127 patients.

NSCLC
Hyperthyroidism occurred in 10 (1.8%) of 550 patients receiving KEYTRUDA in Trial 3, including Grade 2 (0.7%) or Grade 3 (0.3%) hyperthyroidism. The median time to onset was 1.8 months (range: 2 days to 3.4 months), and the median duration was 4.5 months (range: 4 weeks to 7.5 months). No patients discontinued KEYTRUDA due to hyperthyroidism.

Hypothyroidism occurred in 38 (6.9%) of 550 patients receiving KEYTRUDA in Trial 3, including Grade 2 (5.5%) or Grade 3 (0.2%) hypothyroidism. The median time to onset was 4.2 months (range: 20 days to 11.2 months), and the median duration was 5.8 months (range: 11 days to 22.8 months). No patients discontinued KEYTRUDA due to hypothyroidism.

HNSCC
New or worsening hypothyroidism occurred in 28 (14.6%) of 192 patients receiving KEYTRUDA in Trial 4, including Grade 3 (0.5%) hypothyroidism. Of these 28 patients, 15 had no prior history of hypothyroidism.

Type 1 Diabetes mellitus
Type 1 diabetes mellitus, including diabetic ketoacidosis, occurred in 3 (0.1%) of 2117 patients with melanoma or NSCLC receiving KEYTRUDA in Trials 1, 2, and 3. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer anti-hyperglycemics in patients with severe hyperglycemia *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

5.5 Immune-Mediated Nephritis and Renal Dysfunction
Immune-mediated nephritis occurred in patients receiving KEYTRUDA. Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma
Nephritis occurred in 7 (0.4%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3, including Grade 2 (0.2%), Grade 3 (0.2%), and Grade 4 (0.1%) nephritis. The median time to onset of nephritis was 5.1 months (range: 12 days to 12.8 months). The median duration was 1.1 months (range: 3 days to 3.3 months). Six (86%) of the 7 patients received corticosteroids, with 5 of the 6 receiving high-dose systemic corticosteroids for a median duration of 15 days (range: 3 days to 1.6 months) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 2 (0.1%) patients. Nephritis resolved in 4 (57%) of the 7 patients.

5.6 Other Immune-Mediated Adverse Reactions
Other clinically important immune-mediated adverse reactions can occur.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma
The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 1567 patients with melanoma treated with KEYTRUDA in Trials 1, 2, and 3: arthritis (1.6%), exfoliative dermatitis, bullous pemphigoid, uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma.

NSCLC
The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of 550 patients with NSCLC treated with KEYTRUDA in Trial 3: rash, vasculitis, hemolytic anemia, serum sickness, and myasthenia gravis.

5.7 Infusion-Related Reactions
Severe and life-threatening infusion-related reactions have been reported in 3 (0.1%) of 2117 patients receiving KEYTRUDA in Trials 1, 2, and 3. Monitor patients for signs and symptoms of

infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.3)]*.

5.8 Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for 4 months after the last dose of KEYTRUDA *[see Use in Specific Populations (8.1, 8.3)].*

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-mediated pneumonitis *[see Warnings and Precautions (5.1)].*
- Immune-mediated colitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated hepatitis *[see Warnings and Precautions (5.3)]*.
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.4)]*.
- Immune-mediated nephritis and renal dysfunction *[see Warnings and Precautions (5.5)]*.
- Other immune-mediated adverse reactions *[see Warnings and Precautions (5.6)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.7)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to KEYTRUDA in 2117 patients in two randomized, open-label, active-controlled clinical trials, which enrolled 912 patients with unresectable or metastatic melanoma and one single-arm trial which enrolled 655 patients with metastatic melanoma and 550 patients with NSCLC. In addition, these data reflect exposure to KEYTRUDA in a non-randomized, open-label, multi-cohort trial which enrolled 192 patients with HNSCC. Across all studies, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among these 2117, 43% of the patients were exposed for 6 months or more and 10% of the patients were exposed for 12 months or more.

The data described below were obtained in two randomized, open-label, active-controlled clinical trials which enrolled 912 patients with unresectable or metastatic melanoma and two non-randomized, openlabel, multi-cohort trials which enrolled 550 patients with NSCLC and 192 patients with HNSCC. In these trials, KEYTRUDA was administered at 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks.

Melanoma

Ipilimumab-Naive Melanoma (Trial 1)

The safety of KEYTRUDA for the treatment of patients with unresectable or metastatic melanoma who had not received prior ipilimumab and who had received no more than one prior systemic therapy was investigated in Trial 1. Trial 1 was a multicenter, open-label, active-controlled trial where patients were randomized (1:1:1) and received KEYTRUDA 10 mg/kg every 2 weeks (n=278) or KEYTRUDA 10 mg/kg every 3 weeks (n=277) until disease progression or unacceptable toxicity or ipilimumab 3 mg/kg every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity (n=256) *[see Clinical Studies (14.1)]*. Patients with autoimmune disease, a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for KEYTRUDA and similar in both treatment arms. Fifty-one and 46% of patients received KEYTRUDA 10 mg/kg every 2 or 3 weeks, respectively, for ≥6 months. No patients in either arm received treatment for more than one year.

The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 32% had an elevated lactate dehydrogenase (LDH) value at baseline, 65% had M1c stage disease, 9% with history of brain metastasis, and approximately 36% had been previously treated with one or more lines of systemic therapy which included a BRAF inhibitor (15%), chemotherapy (13%), and immunotherapy (6%).

In Trial 1, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both KEYTRUDA arms. Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 9% of patients. Adverse reactions leading to discontinuation of KEYTRUDA in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions (reported in at least 20% of patients) were fatigue and diarrhea. Table 1 and Table 2 summarize the incidence of selected adverse reactions and laboratory abnormalities, respectively, that occurred in at least 10% of patients receiving KEYTRUDA.

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Table 1: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA (Trial 1)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
Adverse Reaction	**All Grades† (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Fatigue	28	0.9	28	3.1
Skin and Subcutaneous Tissue Disorders				
Rash‡	24	0.2	23	1.2
Vitiligo§	13	0	2	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	0.4	10	1.2
Back pain	12	0.9	7	0.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	7	0.4
Dyspnea	11	0.9	7	0.8
Metabolism and Nutrition Disorders				
Decreased appetite	16	0.5	14	0.8
Nervous System Disorders				
Headache	14	0.2	14	0.8

* Adverse reactions occurring at same or higher incidence than in the ipilimumab arm
† Graded per NCI CTCAE v4.0
‡ Includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, and exfoliative rash.
§ Includes skin hypopigmentation

Other clinically important adverse reactions occurring in ≥10% of patients receiving KEYTRUDA were diarrhea (26%), nausea (21%), and pruritus (17%).

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Table 2: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA (Trial 1)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks		Ipilimumab	
Laboratory Test†	**All Grades‡ %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	45	4.2	45	3.8
Hypertriglyceridemia	43	2.6	31	1.1
Hyponatremia	28	4.6	26	7
Increased AST	27	2.6	25	2.5
Hypercholesterolemia	20	1.2	13	0
Hematology				
Anemia	35	3.8	33	4.0
Lymphopenia	33	7	25	6

* Laboratory abnormalities occurring at same or higher incidence than in ipilimumab arm
† Each test incidence is based on the number of patients who had both baseline and at least one onstudy laboratory measurement available: KEYTRUDA (520 to 546 patients) and ipilimumab (237 to 247 patients); hypertriglyceridemia: KEYTRUDA n=429 and ipilimumab n=183; hypercholesterolemia: KEYTRUDA n=484 and ipilimumab n=205).
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were increased hypoalbuminemia (27% all Grades; 2.4% Grades 3-4), increased ALT (23% all Grades; 3.1% Grades 34), and increased alkaline phosphatase (21% all Grades, 2.0% Grades 3-4).

Ipilimumab-Refractory Melanoma (Trial 2)

The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Trial 2. Trial 2 was a multicenter, partially blinded (KEYTRUDA dose), randomized (1:1:1), active-controlled trial in which 528 patients received KEYTRUDA 2 mg/kg (n=178) or 10 mg/kg (n=179) every 3 weeks or investigator's choice of chemotherapy (n=171), consisting of dacarbazine (26%), temozolomide (25%), paclitaxel and carboplatin (25%), paclitaxel (16%), or carboplatin (8%) *[see Clinical Studies (14.1)]*. The trial excluded patients with autoimmune disease, severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or an active infection requiring therapy, including HIV or hepatitis B or C.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.7 months (range: 1 day to 16.6 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 16.8 months). The data described below reflect exposure to KEYTRUDA 2 mg/kg in 36% of patients exposed to KEYTRUDA for ≥6 months and in 4% of patients exposed for ≥12 months. In the KEYTRUDA 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA for ≥6 months and 6% of patients were exposed to KEYTRUDA for ≥12 months.

The study population characteristics were: median age of 62 years (range: 15 to 89 years), 61% male, 98% White, 41% with an elevated LDH value at baseline, 83% with M1c stage disease, 73% received two or more prior therapies for advanced or metastatic disease (100% received ipilimumab and 25% a BRAF inhibitor), and 15% with history of brain metastasis.

In Trial 2, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both KEYTRUDA arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving KEYTRUDA; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculopapular rash (1%). The most common adverse reactions (reported in at least 20% of patients) of KEYTRUDA were fatigue, pruritus, rash, constipation, nausea, diarrhea, and decreased appetite.

Table 3 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 3: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA (Trial 2)

	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks n=357		Chemotherapy† n=171	
Adverse Reaction	**All Grades‡ (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Pyrexia	14	0.3	9	0.6
Asthenia	10	2.0	9	1.8
Skin and Subcutaneous Tissue Disorders				
Pruritus	28	0	8	0
Rash§	24	0.6	8	0
Gastrointestinal Disorders				
Constipation	22	0.3	20	2.3
Diarrhea	20	0.8	20	2.3
Abdominal pain	13	1.7	8	1.2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	18	0	16	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	14	0.6	10	1.2

* Adverse reactions occurring at same or higher incidence than in chemotherapy arm

† Chemotherapy : dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel, or carboplatin

‡ Graded per NCI CTCAE v4.0

§ Includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (43%), nausea (22%), decreased appetite (20%), vomiting (13%), and peripheral neuropathy (1.7%).

Table 4: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA (Trial 2)

	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks		Chemotherapy	
Laboratory Test†	**All Grades‡ %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	49	6	44	6
Hypoalbuminemia	37	1.9	33	0.6
Hyponatremia	37	7	24	3.8
Hypertriglyceridemia	33	0	32	0.9
Increased Alkaline Phosphatase	26	3.1	18	1.9
Increased AST	24	2.2	16	0.6
Bicarbonate Decreased	22	0.4	13	0
Hypocalcemia	21	0.3	18	1.9
Increased ALT	21	1.8	16	0.6

* Laboratory abnormalities occurring at same or higher incidence than in chemotherapy arm.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 320 to 325 patients) and chemotherapy (range: 154 to 161 patients); hypertriglyceridemia: KEYTRUDA n=247 and chemotherapy n=116; bicarbonate decreased: KEYTRUDA n=263 and chemotherapy n=123).
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were anemia (44% all Grades; 10% Grades 3-4) and lymphopenia (40% all Grades; 9% Grades 3-4).

NSCLC

Among the 550 patients with metastatic NSCLC enrolled in Trial 3, the median duration of exposure to KEYTRUDA was 2.8 months (range: 1 day to 25.6 months). Patients with NSCLC and autoimmune disease, a medical condition that required immunosuppression, or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible for Trial 3. The median age of patients was 64 years (range: 28 to 93), 47% were age 65 years or older, 53% were male, 83% were White, and 67% received two or more prior systemic treatments. Disease characteristics were Stage III (4%), Stage IV (96%), and brain metastases (11%). Baseline ECOG performance status (PS) was 0 (35%) or 1 (65%).

KEYTRUDA was discontinued due to adverse reactions in 14% of patients. Serious adverse reactions occurred in 38% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pleural effusion, pneumonia, dyspnea, pulmonary embolism, and pneumonitis. The incidence of adverse reactions, including serious adverse reactions, was similar between the two 10 mg/kg dosing schedules; therefore, these data were pooled. The majority of patients treated with KEYTRUDA 2 mg/kg every three weeks

had shorter follow-up compared with patients treated with the 10 mg/kg schedules; therefore, comparisons of adverse reactions between doses were not appropriate.

Table 5 summarizes adverse reactions that occurred in at least 10% of patients. The most common adverse reactions (reported in at least 20% of patients) were fatigue, decreased appetite, dyspnea, and cough.

Table 5: Adverse Reactions in ≥10% of Patients with NSCLC (Trial 3)

	KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=550	
Adverse Reaction	All Grades (%)	Grade 3* (%)
General Disorders and Administration Site Conditions		
Fatigue†	44	4
Pyrexia	12	1
Peripheral Edema	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	25	1
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	23	4
Cough‡	29	<1
Gastrointestinal Disorders		
Nausea	18	1
Diarrhea	15	1
Constipation	15	<1
Vomiting	12	1
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	15	1
Back pain	10	2
Blood and Lymphatic System Disorders		
Anemia	12	2
Skin and Subcutaneous Tissue Disorders		
Pruritus	12	0
Rash§	18	<1

* Of the ≥10% adverse reactions, none was reported as Grade 4 or 5.
† Includes the terms fatigue and asthenia
‡ Includes the terms cough, productive cough and hemoptysis
§ Includes the terms dermatitis, dermatitis acneiform, erythema multiforme, drug eruption, rash, rash generalized, rash pruritic, rash macular/maculopapular, papular

Table 6: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with NSCLC (Trial 3)

	KEYTRUDA n=550	
Laboratory Test	**All Grades %**	**Grades 3-4 %**
Chemistry		
Hyperglycemia	48	3*
Hyponatremia	38	6
Hypoalbuminemia	32	1
Increased alkaline phosphatase	26	1
Hypertriglyceridemia	23	0
Increased aspartate aminotransferase	20	1
Hypercholesterolemia	20	1*
Hematology		
Anemia	36	2*

* Grade 4 abnormalities in this table limited to hyperglycemia (n=4), hypercholesterolemia (n=3), and anemia (n=1).

HNSCC

Among the 192 patients with HNSCC enrolled in Trial 4, the median duration of exposure to KEYTRUDA was 3.3 months (range: 1 day to 27.9 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for Trial 4. The median age of patients was 60 years (range: 20 to 84), 35% were age 65 years or older, 83% were male, 77% were White, 15% were Asian, and 5% were Black. Sixty-one percent of patients had two or more lines of therapy in the recurrent or metastatic setting, and 95% had prior radiation therapy. Baseline ECOG PS was 0 (30%) or 1 (70%) and 86% had M1 disease.

KEYTRUDA was discontinued due to adverse reactions in 17% of patients. Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks); these data were pooled. The most common adverse reactions (occurring in ≥20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3-4) and new or worsening hypothyroidism *[see Warnings and Precautions (5.4)]*.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with

pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every two or three weeks, 20 (1.7%) of 1149 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies. Among the 20 patients who tested positive for treatment emergent anti-pembrolizumab antibodies, only 4 patients were tested for neutralizing antibodies and one was positive. There was no evidence of an altered pharmacokinetic profile or increased infusion reactions with anti-pembrolizumab binding antibody development.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to KEYTRUDA with the incidences of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue *[see Data]*. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. There are no available human data informing the risk of embryo-fetal toxicity. Apprise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with KEYTRUDA to evaluate its effect on reproduction and fetal development, but an assessment of the effects on reproduction was provided. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering KEYTRUDA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immunemediated disorders or of altering the normal immune response.

8.2 Lactation

Risk Summary

It is not known whether KEYTRUDA is excreted in human milk. No studies have been conducted to assess the impact of KEYTRUDA on milk production or its presence in breast milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for at least 4 months following the final dose.

8.4 Pediatric Use

Safety and effectiveness of KEYTRUDA have not been established in pediatric patients.

8.5 Geriatric Use

Of 2309 patients treated with KEYTRUDA in clinical studies, 43% were 65 years and over. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

10 OVERDOSAGE

There is no information on overdosage with KEYTRUDA.

11 DESCRIPTION

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

KEYTRUDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.3 Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 2195 patients with various cancers who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on

population pharmacokinetic analyses in patients with solid tumors, the geometric mean [% coefficient of variation (CV%)] for clearance (CL), steady-state volume of distribution, and terminal half-life were 202 mL/day (38%), 7.38 L (19%) and 27 days (38%), respectively.

Steady-state concentrations of pembrolizumab were reached by 19 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Specific Populations: The following factors had no clinically important effect on the CL of pembrolizumab: age (range: 15 to 94 years), sex, race (94% White), renal impairment (eGFR greater than or equal to 15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1 and 1.5 times ULN and any AST), or tumor burden. There is insufficient information to determine whether there are clinically important differences in the CL of pembrolizumab in patients with moderate or severe hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

14 CLINICAL STUDIES

14.1 Melanoma

Ipilimumab-Naive Melanoma (Trial 1)

The safety and efficacy of KEYTRUDA were evaluated in Trial 1, a randomized (1:1:1), open-label, multicenter, active-controlled trial. Patients were randomized to receive KEYTRUDA at a dose of 10 mg/kg every 2 weeks or 10mg/kg every 3 weeks as an intravenous infusion until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg every 3 weeks as an intravenous infusion for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Randomization was stratified by line of therapy (0 vs. 1), ECOG

PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma with progression of disease; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors [RECIST v1.1]). Additional efficacy outcome measures were overall response rate (ORR) and response duration.

A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease , 69% ECOG PS of 0, 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay, 65% had M1c stage disease, 68% with normal LDH, 36% with reported BRAF mutation-positive melanoma, and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor.

The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab (Table 7 and Figure 1).

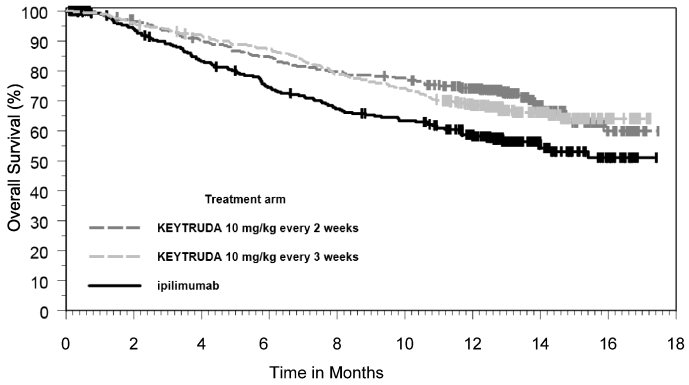
Table 7: Efficacy Results in Trial 1

	KEYTRUDA 10 mg/kg every 3 weeks n=277	**KEYTRUDA 10 mg/kg every 2 weeks n=279**	**Ipilimumab 3 mg/kg every 3 weeks n=278**
OS			
Deaths (%)	92 (33%)	85 (30%)	112 (40%)
Hazard ratio* (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value (stratified log-rank)	0.004	<0.001	---
PFS by BICR			
Events (%)	157 (57%)	157 (56%)	188 (68%)
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Hazard ratio* (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Best overall response by BICR			
ORR % (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response %	6%	5%	1%
Partial response %	27%	29%	10%

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

Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to KEYTRUDA 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months.

Figure 1: Kaplan-Meier Curve for Overall Survival in Trial 1



Number at Risk										
KEYTRUDA 10 mg/kg every 2 weeks:	279	266	248	233	219	212	177	67	19	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	266	251	238	215	202	158	71	18	0
ipilimumab:	278	242	212	188	169	157	117	51	17	0

Ipilimumab-Refractory Melanoma (Trial 2)

The safety and efficacy of KEYTRUDA were evaluated in Trial 2, a multicenter, randomized (1:1:1), active-controlled trial. Patients were randomized to receive one of two doses of KEYTRUDA in a blinded fashion or investigator's choice chemotherapy. The treatment arms consisted of KEYTRUDA 2 mg/kg or 10 mg/kg intravenously every 3 weeks or investigator's choice of any of the following chemotherapy regimens: dacarbazine 1000 mg/m^2 intravenously every 3 weeks (26%), temozolomide 200 mg/m^2 orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 intravenously plus paclitaxel 225 mg/m^2 intravenously every 3 weeks for four cycles then carboplatin AUC of 5 plus paclitaxel 175 mg/m^2 every 3 weeks (25%), paclitaxel 175 mg/m^2 intravenously every 3 weeks (16%), or carboplatin AUC 5 or 6 intravenously every 3 weeks (8%). Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutationpositive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with uveal melanoma and active brain metastasis. Patients received KEYTRUDA until unacceptable toxicity; disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging; withdrawal of consent; or physician's decision to stop therapy for the patient. Assessment of tumor status was performed at 12 weeks after randomization, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced progression of disease were offered KEYTRUDA. The major efficacy outcomes were progression-free survival (PFS) as assessed by BICR per

RECIST v1.1 and overall survival (OS). Additional efficacy outcome measures were confirmed overall response rate (ORR) as assessed by BICR per RECIST v1.1 and duration of response.

The treatment arms consisted of KEYTRUDA 2 mg/kg (n=180) or 10 mg/kg (n=181) every 3 weeks or investigator's choice chemotherapy (n=179). Among the 540 randomized patients, the median age was 62 years (range: 15 to 89 years), with 43% age 65 or older; 61% male; 98% White; and ECOG performance score was 0 (55%) and 1 (45%). Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease.

The study demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared to control arm (Table 8). There was no statistically significant difference between KEYTRUDA 2 mg/kg and chemotherapy or between KEYTRUDA 10 mg/kg and chemotherapy in the interim OS analysis with 220 deaths (59% of required events for the final analysis).

Table 8: Efficacy Results in Trial 2

	KEYTRUDA 2 mg/kg every 3 weeks n=180	**KEYTRUDA 10 mg/kg every 3 weeks n=181**	**Chemotherapy n=179**
Progression-Free Survival			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
P Value (stratified log-rank)	<0.001	<0.001	---
Hazard ratio* (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
Objective Response Rate			
ORR, n% (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response %	2%	3%	0%
Partial response %	19%	23%	4%

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

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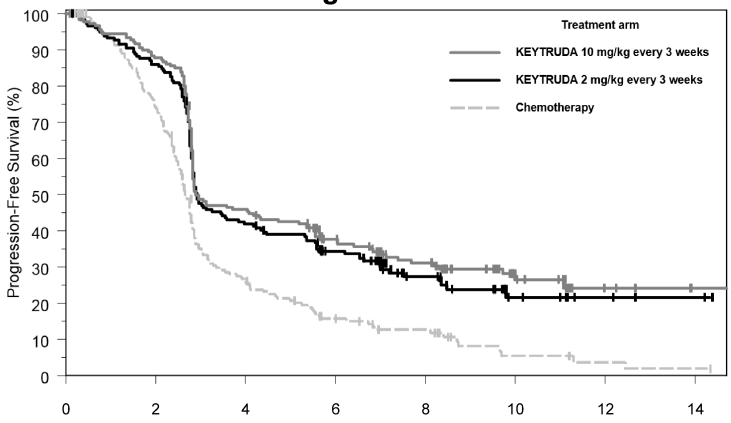
Figure 2: Kaplan-Meier Curve for Progression-Free Survival in Trial 2



Time in Months

Number at Risk

KEYTRUDA 10 mg/kg:	181	158	82	55	39	15	5	1
KEYTRUDA 2 mg/kg:	180	153	74	53	26	9	4	2
Chemotherapy:	179	128	43	22	15	4	2	1

Among the 38 patients randomized to KEYTRUDA 2 mg/kg with an objective response, response durations ranged from 1.3+ to 11.5+ months. Among the 46 patients randomized to KEYTRUDA 10 mg/kg with an objective response, response durations ranged from 1.1+ to 11.1+ months.

14.2 Non-Small Cell Lung Cancer

The efficacy of KEYTRUDA was investigated in a sub-group of a cohort of 280 patients enrolled in a multicenter, open-label multi-cohort, activity-estimating study (Trial 3). The cohort consisted of patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations and any evidence of PD-L1 expression by a clinical trial immunohistochemistry assay. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

A prospectively defined sub-group was retrospectively analyzed using an analytically validated test for PD-L1 expression tumor proportion score (TPS). This retrospectively identified sub-group of 61 patients accounts for 22% of the 280 patients in the cohort. Patients included in this sub-group had a PD-L1 expression TPS of greater than or equal to 50% tumor cells as determined by the PD-L1 IHC 22C3 pharmDx Kit. Patients received KEYTRUDA 10 mg/kg every 2 (n=27) or 3 (n=34) weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1 as assessed by BICR and duration of response.

Among the 61 patients with a TPS greater than or equal to 50%, the baseline characteristics were: median age 60 years (34% age 65 or older); 61% male; 79% White; and 34% and 64% with an ECOG PS 0 and 1, respectively. Disease characteristics were squamous (21%) and non-squamous (75%); M1 (98%); brain metastases (11%); one (26%), two (30%), or three or more (44%) prior therapies; and the incidence of genomic aberrations was EGFR (10%) or ALK (0%).

Efficacy results are summarized in Table 9. The ORR and duration of response were similar regardless of schedule (every 2 weeks or every 3 weeks) and thus the data below are pooled.

Table 9: Efficacy Results

Endpoint	n=61
Overall Response Rate	
ORR %, (95% CI)	41% (29, 54)
Complete Response	0%
Partial Response	41%

Among the 25 responding patients, 21 (84%) patients had ongoing responses at the final analysis of ORR; 11 (44%) patients had ongoing responses of 6 months or longer.

In a separate subgroup of 25 patients with limited follow-up with PD-L1 expression TPS greater than or equal to 50% receiving KEYTRUDA at a dose of 2 mg/kg every 3 weeks in Trial 3, activity was also observed.

14.3 Head and Neck Cancer

The efficacy of KEYTRUDA was investigated in Trial 4, a multicenter, nonrandomized, open-label, multicohort study that enrolled 174 patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy. Patients with active autoimmune disease, a medical condition that required immunosuppression, evidence of interstitial lung disease, or ECOG PS ≥ 2 were ineligible.

Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=53) or 200 mg every 3 weeks (n=121) until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

Among the 174 patients, the baseline characteristics were median age 60 years (32% age 65 or older); 82% male; 75% White, 16% Asian, and 6% Black; 87% had M1 disease; 33% had HPV positive tumors; 63% had prior cetuximab; 29% had an ECOG PS of 0 and 71% had an ECOG PS of 1; and the median number of prior lines of therapy administered for the treatment of HNSCC was 2.

The ORR was 16% (95% CI: 11, 22) with a complete response rate of 5%. The median follow-up time was 8.9 months. Among the 28 responding patients, the median duration of response had not been reached (range 2.4+ to 27.7+ months), with 23 patients having responses of 6 months or longer. The ORR and duration of response were similar irrespective of dosage regimen (10 mg/kg every 2 weeks or 200 mg every 3 weeks) or HPV status.

16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA for injection (lyophilized powder): carton containing one 50 mg single-use vial (NDC 00063029-02).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

KEYTRUDA injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-use vial (NDC 0006-3026-02)

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA, including:
- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
- Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes *[see Warnings and Precautions (5.4)]*.
- Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.4)]*.
- Type 1 Diabetes Mellitus: Advise patients to contact their healthcare provider immediately for signs or symptoms of type 1 diabetes *[see Warnings and Precautions (5.4)]*.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.5)]*. ☐ Advise patients to contact their healthcare provider immediately for signs or symptoms of infusionrelated reactions *[see Warnings and Precautions (5.7)]*.
- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (5.3, 5.4, 5.5)]*.
- Advise women that KEYTRUDA can cause fetal harm. Instruct women of reproductive potential to use highly effective contraception during and for 4 months after the last dose

of KEYTRUDA *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.3)]*.

- Advise nursing mothers not to breastfeed while taking KEYTRUDA and for 4 months after the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
U.S. License No. 0002

For KEYTRUDA for injection, at:
Schering-Plough (Brinny) Co.,
County Cork, Ireland

For KEYTRUDA injection, at:
MSD Ireland (Carlow)
County Carlow, Ireland

For patent information: www.merck.com/product/patent/home.html

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MEDICATION GUIDE

KEYTRUDA® (key-true-duh) (pembrolizumab) for injection	**KEYTRUDA® (key-true-duh) (pembrolizumab) injection**

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What is the most important information I should know about KEYTRUDA?

KEYTRUDA is a medicine that may treat your melanoma, lung cancer, or head and neck cancer by working with your immune system. KEYTRUDA can cause your immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

Call or see your doctor right away if you develop any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Symptoms of pneumonitis may include:

- shortness of breath
- chest pain
- new or worse cough

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:

- diarrhea or more bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems (hepatitis). Signs and symptoms of hepatitis may include: □

- yellowing of your skin or the whites of your eyes
- nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine
- feeling less hungry than usual
- bleeding or bruising more easily than normal

Hormone gland problems (especially the thyroid, pituitary, adrenal glands, and pancreas). Signs and symptoms that your hormone glands are not working properly may include:

- rapid heart beat
- weight loss or weight gain
- increased sweating
- feeling more hungry or thirsty
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- muscle aches
- dizziness or fainting
- headaches that will not go away or unusual headache

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:

- change in the amount or color of your urine.

Problems in other organs. Signs of these problems may include:

- rash
- changes in eyesight
- severe or persistent muscle or joint pains

- severe muscle weakness
- low red blood cells (anemia)

Infusion (IV) reactions, that can sometimes be severe and life-threatening. Signs and symptoms of infusion reactions may include:

- chills or shaking
- shortness of breath or wheezing
- itching or rash
- flushing
- dizziness
- fever
- feeling like passing out

Getting medical treatment right away may help keep these problems from becoming more serious. Your doctor will check you for these problems during treatment with KEYTRUDA. Your doctor may treat you with corticosteroid or hormone replacement medicines. Your doctor may also need to delay or completely stop treatment with KEYTRUDA, if you have severe side effects

What is KEYTRUDA?

KEYTRUDA is a prescription medicine used to treat:

- a kind of skin cancer called melanoma. KEYTRUDA may be used when your melanoma has spread or cannot be removed by surgery (advanced melanoma).
- a kind of lung cancer called non-small cell lung cancer (NSCLC). KEYTRUDA may be used when your lung cancer:
  - has spread **and,**
  - tests positive for “PD-L1” **and,**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working **and,**
  - if your tumor has an abnormal “EGFR” or “ALK” gene, and you have also tried an EGFR or ALK inhibitor medicine.
- a kind of cancer called head and neck squamous cell cancer (HNSCC). KEYTRUDA may be used when your HNSCC:
  - has returned or spread **and**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.

It is not known if KEYTRUDA is safe and effective in children less than 18 years of age.

What should I tell my doctor before receiving KEYTRUDA?

Before you receive KEYTRUDA, tell your doctor if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have any other medical problems
- are pregnant or plan to become pregnant
  - KEYTRUDA can harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control during and for at least 4 months after the final dose of KEYTRUDA. Talk to your doctor about birth control methods that you can use during this time.
  - Tell your doctor right away if you become pregnant during treatment with KEYTRUDA.
- are breastfeeding or plan to breastfeed.
  - It is not known if KEYTRUDA passes into your breast milk.
  - Do not breastfeed during treatment with KEYTRUDA and for 4 months after your final dose of KEYTRUDA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive KEYTRUDA?

- Your doctor will give you KEYTRUDA into your vein through an intravenous (IV) line over 30 minutes.
- KEYTRUDA is usually given every 3 weeks.
- Your doctor will decide how many treatments you need.
- Your doctor will do blood tests to check you for side effects.
- If you miss any appointments, call your doctor as soon as possible to reschedule your appointment.

What are the possible side effects of KEYTRUDA?

KEYTRUDA can cause serious side effects. See "What is the most important information I should know about KEYTRUDA?"

Common side effects of KEYTRUDA include:

- in people who receive KEYTRUDA: feeling tired, decreased appetite, and shortness of breath
- in people with melanoma:
  - itching
  - rash
  - diarrhea
  - constipation
  - nausea
- in people with NSCLC:
  - cough

These are not all the possible side effects of KEYTRUDA. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of KEYTRUDA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about KEYTRUDA, talk with your doctor. You can ask your doctor or nurse for information about KEYTRUDA that is written for healthcare professionals. For more information, go to www.keytruda.com.

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What are the ingredients in KEYTRUDA? Active ingredient:
pembrolizumab **Inactive ingredients:**
KEYTRUDA for injection: L-histidine, polysorbate 80, and sucrose. May contain hydrochloric acid/sodium hydroxide. KEYTRUDA injection: L-histidine, polysorbate 80, sucrose, and Water for Injection, USP.

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For KEYTRUDA for injection, at:
Schering-Plough (Brinny) Co., County Cork, Ireland
For KEYTRUDA injection, at:
MSD Ireland (Carlow), County Carlow, Ireland
U.S. License No. 0002
For patent information: www.merck.com/product/patent/home.html

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: August 2016

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Appendix C
Listing of Autoimmune Diseases

Subjects should be carefully questioned about any history of acquired immune deficiencies or autoimmune disease. Subjects are not eligible for the study if there is any history of immune deficiencies or autoimmune disease. Possible exceptions could be subjects with a medical history of atopic disease or childhood arthralgias where the clinical suspicion of an autoimmune process is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Vitiligo or immune-mediated hypothyroidism from prior melanoma immunotherapy are not excluded. Diseases that may be autoimmune-related include but are not limited to the following:

Acute disseminated encephalomyelitis
Alopecia universalis
Antiphospholipid antibody syndrome
Asthma
Autoimmune hepatitis
Autoimmune hypophysitis
Autoimmune oophoritis
Autoimmune thrombocytopenic purpura
Bullous pemphigold
Chronic fatigue syndrome
Churg-Strauss syndrome
Dermatomyositis
Eczema
Gestational pemphigoid
Goodpasture's syndrome
Guillain-Barré syndrome
IgA nephropathy
Interstitial cystitis
Lambert-Eaton myasthenia syndrome
Lyme disease – chronic
Mooren's ulcer
Multiple sclerosis
Neuromyotonia
Opsoclonus myoclonus syndrome
Pemphigus
Polyarteritis nodusa
Polygrandular autoimmune syndrome
Psoriasis
Rheumatoid arthritis
Scleroderma
Stiff-Person syndrome
Ulcerative colitis
Addison's disease
Ankylosing spondylitis
Aplastic anemia
Autoimmune hemolytic anemia
Autoimmune hypoparathyroidism
Autoimmune myocarditis
Autoimmune orchitis
Behcet's disease
Celiac disease
Chronic inflammatory demyelinating polyneuropathy
Crohn's disease
Dysautonomia
Epidermolysis bullosa acquista
Giant cell arteritis
Graves' disease
Hashimoto's disease
Inflammatory bowel disease
Kawasaki's disease
Lupus erythematosus
Meniere's syndrome
Morphea
Myasthenia gravis
Optic neuritis
Ord's thyroiditis
Pernicious anemia
Polyarthritis
Primary biliary cirrhosis
Reiter's syndrome
Sarcoidosis
Sjögren's syndrome

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Appendix D
FACT-M

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4

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GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4

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GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
M1	I have pain at my melanoma site or surgical site	0	1	2	3	4
M2	I have noticed new changes in my skin (lumps, bumps, color(colour))	0	1	2	3	4
M3	I worry about the appearance of surgical scars	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
ITU4	I have to limit my physical activity because of my condition	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
Hep3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
M5	I have aches and pains in my bones	0	1	2	3	4
M6	I have noticed blood in my stool	0	1	2	3	4
ITU3	I have to limit my social activity because of my condition	0	1	2	3	4

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MS8	I feel overwhelmed by my condition	0	1	2	3	4
M8	I isolate myself from others because of my condition	0	1	2	3	4
M9	I have difficulty thinking clearly (remembering, concentrating)	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	At the site of my melanoma surgery:	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
M10	I have swelling at my melanoma site	0	1	2	3	4
M11	I have swelling as a result of surgery	0	1	2	3	4
M12	I am bothered by the amount of swelling	0	1	2	3	4
M13	Movement of my swollen area is painful	0	1	2	3	4
M14	Swelling keeps me from doing the things I want to do	0	1	2	3	4
M15	Swelling keeps me from wearing clothes or shoes I want to wear	0	1	2	3	4
M16	I feel numbness at my surgical site	0	1	2	3	4
M17	I have good range of movement in my arm or leg	0	1	2	3	4

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FACT – H&N

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4

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GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4

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GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

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FACT – L

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4

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GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4

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GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking	0	1	2	3	4