Official Protocol Title:	A Prospective, Open-label, Phase 4 Study to Evaluate the Safety of Pembrolizumab (KEYTRUDA®) in Subjects with Unresectable or Metastatic Melanoma or PD-L1 positive Non-small Cell Lung Cancer (NSCLC) in India (Keynote-593)
NCT number:	NCT03715205
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Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Prospective, Open-label, Phase 4 Study to Evaluate the Safety of Pembrolizumab (KEYTRUDA®) in Subjects with Unresectable or Metastatic Melanoma or PD-L1 positive Non-small Cell Lung Cancer (NSCLC) in India (Keynote-593)

EudraCT NUMBER: Not Applicable

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	28-JUN-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 04	03-JUN-2021	Text added or edited for clarity
Amendment 03	14-DEC-2018	Text added or edited for clarity
Amendment 02	17-MAY-2018	Text added for clarity
Amendment 01	27-NOV-2017	Text added for clarity
Original Protocol	22-DEC-2016	N/A

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
Title Page Section 12.1 Throughout	Title page Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	A Prospective, Open-label, Phase 4 Study to Evaluate the Safety of Pembrolizumab (KEYTRUDA®) in Subjects with Unresectable or Metastatic Melanoma or PD-L1 positive Non-small Cell Lung Cancer (NSCLC) in India (Keynote-593)
Sponsor Product Identifiers	MK-3475 Pembrolizumab (Keytruda®)
Trial Phase	4
Clinical Indication	Unresectable or metastatic melanoma, and non-small cell lung cancer (NSCLC) subjects who are either untreated (PD-L1 ≥50%) or have experienced disease progression after a platinum-containing systemic therapy (PD-L1 ≥1%)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab (Keytruda®)
Number of trial subjects	Approximately 150 subjects will be enrolled, with a minimum of 25 unresectable or metastatic melanoma subjects.
Estimated duration of trial	The Sponsor estimates the trial will end approximately 2 years from the time the last subject provides documented informed consent.
Duration of Participation	Each subject will participate in the trial from the time the subject provides documented informed consent through the final protocol-specified contact. After a screening phase of 30 days, each subject will be assigned to receive trial treatment with pembrolizumab monotherapy until disease progression is confirmed by the site per Response Evaluation Criteria in Solid Tumors (RECIST 1.1), unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, Investigator's decision to withdraw the subject, non-compliance with trial treatment or procedures requirements or administrative reasons requiring cessation of treatment, or until the subject has received 35 cycles of pembrolizumab (approximately 2 years), whichever occurs first. Each cycle is defined as 21 days. After the end of treatment, each subject will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 7.2 of the protocol. Subjects who discontinue for reasons such as radiologic or clinical disease progression, safety events, or investigator or subject decision to stop treatment will have an end of treatment (EOT) visit and a 30-day safety follow-up visit per Section 7.1.4.1.

A list of abbreviations used in this document can be found in Section 12.6.

2.0 TRIAL DESIGN

2.1 Trial Design

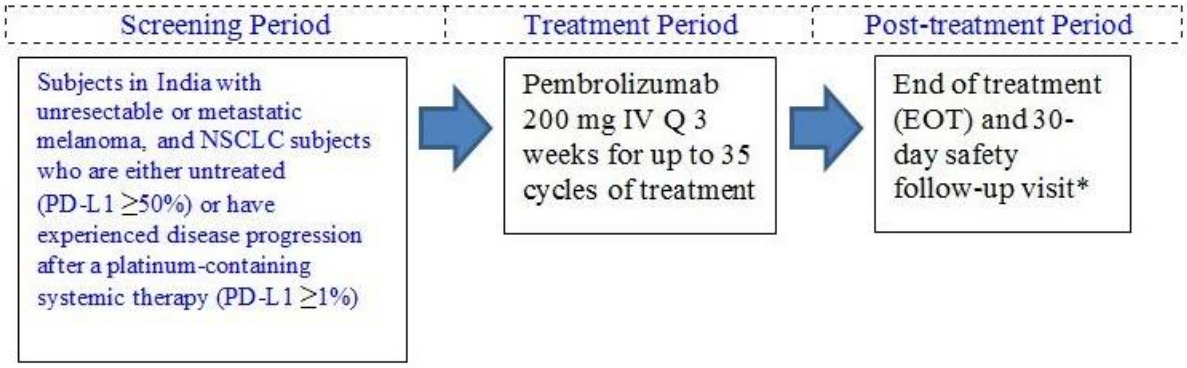
This is a nonrandomized, open-label Phase 4 trial to evaluate the safety of pembrolizumab in India in subjects with unresectable or metastatic melanoma, and non-small cell lung cancer (NSCLC) subjects who are either untreated (programmed cell death ligand 1 [PD-L1] ≥50%) or have experienced disease progression after a platinum-containing systemic therapy (PD-L1 ≥1%). The trial will be conducted in conformance with Good Clinical Practices (GCP). Approximately 150 subjects are planned to be enrolled in this study in India, with a minimum of 25 unresectable or metastatic melanoma subjects. Subjects who are eligible per this protocol to receive a fixed dose of 200 mg intravenous (IV) pembrolizumab every 3 weeks for up to 35 cycles will be enrolled after obtaining documented informed consent and audiovisual recording of the consenting process, as per local regulatory requirements. Subjects will have a follow-up visit 30 days after the last dose of pembrolizumab or before the start of a new antineoplastic therapy, whichever is earlier. The objective of this study is to assess the safety of pembrolizumab in India in subjects with unresectable or metastatic melanoma, and metastatic and advanced NSCLC subjects who are either untreated (PD-L1 ≥50%) or have experienced disease progression after a platinum-containing systemic therapy (PD-L1 ≥1%). This is not a hypothesis-driven study.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

Figure 1 Clinical Trial Design



* Follow-up visit 30 days after the last dose of pembrolizumab or before the start of a new antineoplastic therapy, whichever is earlier.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

This study has been designed to evaluate the safety of pembrolizumab in India in subjects with unresectable or metastatic melanoma, and NSCLC subjects who are either untreated (PD-L1 ≥50%) or have experienced disease progression after a platinum-containing systemic therapy (PD-L1 ≥1%) (KEYNOTE-593). There will be no formal hypothesis testing performed in this study.

3.1 Primary Objective(s) & Hypothesis(es)

(1) Objective: To assess the safety of pembrolizumab in India in subjects with unresectable or metastatic melanoma, and NSCLC subjects who are either untreated (PD-L1 ≥50%) or have experienced disease progression after a platinum-containing systemic therapy (PD-L1 ≥1%).

3.2 Secondary Objective(s) & Hypothesis(es)

There are no secondary objectives for this trial.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Programmed Cell Death 1 as a Target in Cancer Treatment:

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma [2] [3].

The PD-1 receptor-ligand interaction is a major immune checkpoint pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or

excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [4] [5].

The structure of murine PD-1 has been resolved [6]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [4] [7] [8] [9]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [10] [11]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in melanoma and NSCLC.

4.1.1.2 Melanoma Background

Malignant melanoma is the most lethal form of skin cancer. In the United States of America, the reported incidence of melanoma in 2017 is 87,110, with 9,730 deaths attributed to melanoma [12]. In the U.S., this approximates 1.6% of all cancer-related deaths. The main risk factors for melanoma are white ethnicity and exposure to ultraviolet (UV) radiation. The prognosis of melanoma worsens with the disease stage at diagnosis [13]. Patients with metastatic disease have a poor prognosis, with a 5-year survival rate of <20% [14]. In Asian populations and dark skin types, incidence rates are lower but disease specific survival is also lower due to the tendency for atypical locations and unclear etiology. Less than 1% of patients at a surgical oncology unit at a regional cancer center in North India were treated for melanoma between 1995 and 2002 as reported by Deo et al. [15]. Therefore, although melanoma has a low incidence in India, it does carry higher morbidity due to its often late presentation [16].

4.1.1.3 Therapies in Melanoma

In India, approved therapies for advanced melanoma include interferon and dacarbazine. In line with other global markets, there is a need for more efficacious therapies to be available in India. Treatment options for unresectable and metastatic melanoma are rapidly expanding.

Surgery is the definitive treatment for early-stage melanoma, and medical management is reserved for both adjuvant therapy for early-stage melanoma and for treatment of advanced melanoma [17]. Prior to 2011, dacarbazine was the most active single agent for metastatic melanoma, with an overall response rate of 15% to 21% [18] [19]. There have been no randomized controlled studies demonstrating improvement in survival with dacarbazine relative to best supportive care or any other control agent. A review of 9 of the largest randomized controlled trials published between 1999 and 2014 using single-agent dacarbazine as the control arm is presented in Table 1 and indicates the limited activity of this agent in melanoma. Collectively, in nearly 1700 subjects randomized to single-agent

dacarbazine, the overall response rates (ORRs) ranged from 6% to 12%, with the median duration of response ranging from 7 to 11 months (response duration is not reliable in most studies due to the small fraction of subjects who respond to treatment). In addition, no other conventional cytotoxic chemotherapies (as either single agents or combinations) have demonstrated superiority to single-agent dacarbazine in the treatment of melanoma in randomized controlled trials. A historical benchmark for effect size in terms of progression-free survival (PFS) and overall survival (OS) was suggested in a retrospective analysis of 2100 metastatic melanoma subjects treated in 42 different clinical trials (70 treatment arms) from 1997 to 2005. Korn et al. reported median PFS of 1.7 months (95% confidence interval [CI]: 1.6 months, 1.8 months) with a 14.5% 6-month PFS rate (95% CI: 12.9%, 16.1%) [20]. Median OS was 6.2 months (95% CI: 5.9 months, 6.5 months) with a reported 1-year survival rate of 25.5% (95% CI: 23.6%. 27.4%). The experience with dacarbazine and the Korn et al. meta-analysis underscore the limitations of chemotherapies and the challenges of developing effective agents to treat metastatic melanoma [21] [22] [23] [20] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33].

Table 1 Data From Randomized Controlled Trials With Dacarbazine in Advanced Melanoma 1999-2014

Reference (Author, Year)	Agents	N	ORR % (CR+PR)	Median Response Duration (months)	Median PFS (months)	Median OS (months)
Haushchild, 2014	Dacarbazine	63	6.0	NR	2.7	15.6
	Dabrafenib	187	50.0	5.5	6.9	20.0
Flaherty, 2012	Dacarbazine or paclitaxel	108	8.0	NR	1.5	NR
	Trametinib	214	22.0	NR	4.8	NR
Patel, 2011	Dacarbazine	388	9.8	11.2	2.2	9.4
	Temozolomide	401	14.5	4.6	2.3	9.1
Robert, 2011	Dacarbazine	252	10.3	8.1	2.2	9.1
	Ipilimumab-Dacarbazine	250	15.2	19.3	2.2	11.2
Chapman 2012, NICE 2012	Dacarbazine	337	8.6	NR	1.6	10.3
	Vemurafenib	338	57.0	NR	6.9	13.6
Bediken, 2006	Dacarbazine	385	7.5	NR	1.6	7.8
	Oblimersen-Dacarbazine	386	13.5	NR	2.6	9.0
Avril, 2004	Dacarbazine	117	7.2	6.9	NR	5.6
	Fotemustine	112	15.5	5.8	NR	7.3
Middleton, 2000	Dacarbazine	149	12.1	NR	1.5	6.4
	Temozolomide	156	13.5	NR	1.9	7.7
Chapman, 1999	Dacarbazine	118	10.2	NR	NR	6.3
	Dartmouth[a]	108	18.5	NR	NR	7.7
All 1999-2014	Dacarbazine	1917	8.9 (avg) 6.0-12.1	6.9-11.2	1.5-2.7	5.6-15.6

[a] Dartmouth regimen = dacarbazine, cisplatin, carmustine, tamoxifen
Avg = average; CR = complete response; N = sample size; NR= not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response

[25], [21], [27], [23], [28], [29], [30], [31], [32], [24]

Since 2011, 3 new agents were approved in the United States for the treatment of BRAF mutant melanoma: vemurafenib, dabrafenib, and trametinib, which produce response rates of

22-57% and have demonstrated a survival advantage relative to chemotherapy [27] [24] [22]. Of note, vemurafenib demonstrated statistically significant superiority in OS to dacarbazine (median 13.6 months versus 10.3 months; hazard ratio [HR] 0.76; $p<0.01$) [23] [24]. The median response duration of approximately 7 months observed with these agents is similar to the durability observed with conventional chemotherapies. In the United States, a combination of dabrafenib and trametinib was approved for treatment of patients with BRAF mutant melanoma based on the demonstration of durable response rate. Based on independent review committee (IRC) assessment using RECIST 1.1, ORR was 57% (95% CI; 43, 71) and 46% (95% CI; 33, 60) for the combination arm and the dabrafenib alone arm, respectively. The median duration of response was 7.6 months for both arms [34]. In a randomized Phase 3 trial recently reported, dabrafenib plus trametinib demonstrated improved OS compared with vemurafenib monotherapy (HR 0.69; 95% CI: 0.53, 0.89; $p=0.005$). It is important to note these agents are not indicated for up to 60% of melanoma subjects whose tumors do not contain a BRAF mutation [24] [27] [32] [35]. In addition, a major limitation with kinase inhibitors in the treatment of BRAF mutant melanoma is a nearly universal development of resistance to these agents leading to the lack of response durability. Although high response rates (RRs) offer benefits to the majority of subjects with BRAF mutant melanoma, most subjects develop resistance rather quickly and experience progressive disease Moreover, published literature indicates that subjects who experience progressive disease after the above-mentioned kinase inhibitors tend to experience rapid progressive disease that cannot be easily salvaged with other available therapies [36].

Ipilimumab (IPI), an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody (mAb), demonstrated that immune modulation could be effective in the treatment of metastatic melanoma. In a Phase 3 study, IPI administered with or without a gp100 peptide vaccine was compared with gp100 alone in subjects with previously treated metastatic melanoma. An ORR of 10.9% (Investigator assessment per RECIST 1.1), a median PFS of 2.9 months, an OS rate at 12 months of 45.6%, and a median OS of 10.1 months were observed in the IPI monotherapy arm. In addition, a relative reduction of 34% ($p=0.003$) in the risk of death was demonstrated for IPI compared with the vaccine alone. A reduction of the risk of death (28%; $p<0.001$) was also demonstrated for IPI in the first-line setting when combined with dacarbazine in comparison with dacarbazine alone, and the ORRs were 15% and 10% (investigator assessment per RECIST 1.1) in the IPI/dacarbazine arm and dacarbazine alone arm, respectively. Notably, inspection of the Kaplan-Meier PFS curves in this study indicated that comparison of median was less informative than inspection of curves, as the median PFS was reached before the first tumor assessment time point followed by a significant separation of the curve. The IPI/dacarbazine arm did show a statistically significant PFS improvement (HR 0.76; $p=0.006$) over the dacarbazine alone arm. Median OS in the IPI/dacarbazine and dacarbazine arms was 11.2 months and 9.1 months, respectively. The 1-year OS rate for the IPI/dacarbazine arm was 47.3%; the rate for the dacarbazine arm was 36.3%. In 2011, the Food and Drug Administration (FDA) approved IPI for treatment of subjects with unresectable or metastatic melanoma in the United States. The European Medicines Agency (EMA) subsequently approved IPI for treatment of subjects with advanced melanoma in the European Union (EU).

Although the IPI results support the concept that responses to immunotherapy are long lasting (first demonstrated by high-dose interleukin-2 [IL-2]), given the 10% response rate

observed with IPI, a majority of subjects may not experience a significant clinical benefit. Furthermore, treatment with IPI is associated with an approximate 23% incidence of severe or life-threatening (Grade 3 or 4) drug-related adverse reactions and a 3% incidence of fatal drug-related adverse reactions [37] [38]. High-dose IL-2, another available immunotherapy, achieves durable complete responses (CRs) in a small percentage (~5%) of subjects, although OS benefit has never been established in a randomized controlled study. In addition, high-dose IL-2 should be used only in a hospital setting with an intensive care facility due to its unfavorable toxicity profile [39]. Thus, there is a great need for an immunotherapy with an improved therapeutic index.

4.1.1.4 Pembrolizumab in Treatment of Metastatic Melanoma

Pembrolizumab has shown in a randomized Phase 3 study (KEYNOTE-006) a significant benefit in OS, PFS and response rate in patients with unresectable or metastatic melanoma compared to ipilimumab [40]. Additionally, pembrolizumab demonstrated a favorable safety profile compared to ipilimumab. Furthermore, in a randomized Phase 2 study (KEYNOTE-002), pembrolizumab has demonstrated improved PFS over standard of care chemotherapy in ipilimumab-refractory subjects with advanced melanoma [41]. Refer to the IB for comprehensive non-clinical and clinical information about pembrolizumab.

On 04-SEP-2014, the U.S. FDA granted accelerated approval for pembrolizumab 2 mg/kg every 3 weeks (Q3W) to be used in advanced melanoma patients with progressive disease following IPI and, if BRAF V600 mutation was positive, a BRAF inhibitor [42]. The approval was based on a strong efficacy and safety profile demonstrated in 4 melanoma expansion parts of the Phase 1 trial; the B2 IPI-refractory population was the subject population for the approval. On 18-DEC-2015, the U.S. FDA granted full approval of pembrolizumab for the treatment of patients with unresectable or metastatic melanoma. This indication included first-line treatment of patients with unresectable or metastatic melanoma with pembrolizumab.

Pembrolizumab was approved in India for unresectable or metastatic melanoma on 16-JUN-2016.

4.1.1.5 Lung Cancer Background

Lung cancer is the most common malignancy and contributor to cancer-related deaths in the world [43]. Lung cancer is a significant burden in India as well, with an estimate incidence according to GLOBOCAN 2012 of 70,275 in all ages and from both sexes [44] [45] [46]. Lung cancer, therefore, ranks fourth among the various types of cancer (excluding nonmelanoma skin cancer) in India. However, it is suspected that incidence calculations in India are likely gross under-estimations. While epidemiological studies link smoking to the cause of lung cancer among men in India, such is not the case for women, suggesting other contributing risk factors likely exist. Furthermore, studies have shown that 90% of the lung cancer cases present in inoperable or advanced stages [45].

Non-small cell lung cancer represents approximately 80% to 85% of all lung cancer [47]. At the time of diagnosis, approximately 70% of subjects with NSCLC have advanced disease which is not amenable to surgical resection. Of those patients diagnosed with early stage NSCLC and treated with surgery, a significant percentage subsequently develop distant

recurrence [48]. These factors contribute to the dismal 5-year relative survival rates of 17.7% in patients diagnosed with NSCLC, and a mere 4.3% in those with metastatic disease [49].

4.1.1.6 Therapies in Non-Small Cell Lung Cancer

In India, the standard of care for advanced NSCLC includes molecular classification for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutation status. However, accessibility of such testing to a majority of patients may be limited at this time [50]. Recommended and approved therapies for patients with driver mutations include EGFR tyrosine kinase inhibitors (TKIs). Platinum-based doublet chemotherapy is standard of care for patients without driver mutations or patients that have progressed on TKIs in India [51]. Thus, while combination chemotherapy and TKIs are available, current therapeutic options in India for NSCLC are not sufficient.

Platinum-based combination chemotherapy with or without maintenance therapy was the standard first-line therapy for patients with metastatic NSCLC whose tumors do not harbor oncogenic drivers, such as epidermal EGFR mutations or ALK translocations, until studies of pembrolizumab first-line therapy [52]. Regimens used in NSCLC include cisplatin or carboplatin in combination with paclitaxel, gemcitabine, pemetrexed, or docetaxel [53]. Multiple Phase 3 studies have demonstrated similar efficacy for most platinum doublets in NSCLC patients [54].

The use of targeted therapies for patients with nonsquamous NSCLC whose tumors are known to harbor specific molecular alterations has resulted in higher RRs and improved outcomes. Approved agents for treatment-naïve, metastatic, EGFR-mutant lung cancers include erlotinib, gefitinib, and afatinib. Crizotinib and ceritinib are approved TKIs in the first-line treatment of patients whose tumors harbor ALK- or ROS1-translocations. For patients with NSCLC containing a V600E BRAF mutation, the combination of trametinib and drabrafenib is approved. Despite advances in the ability to molecularly characterize tumors and in targeted therapy development, the majority of patients with metastatic NSCLC do not harbor tumors with an actionable target, and those who do become resistant to these inhibitors.

However, for the majority of patients with no targetable oncogenic driver mutation receiving first-line platinum-based doublets with or without maintenance chemotherapy, the options primarily include single-agent docetaxel or pemetrexed (for nonsquamous NSCLC). Response rates are modest at less than 10%, with median PFS of approximately 2.4 to 2.9 months and median OS ranging from 5.5 to 8.3 months. With increasing use of pemetrexed in the first-line and maintenance settings, docetaxel is the most widely accepted second-line therapy for the majority of patients with metastatic NSCLC with progressive disease (PD) after first-line therapy.

Resistance to targeted therapies in patients with adenocarcinoma of the lung who harbor sensitizing mutations is inevitable, and relapse occurs in almost all individuals, resulting in PD after approximately 9 to 13 months. As mentioned previously, based on improvement in RR and PFS compared to conventional chemotherapy, EGFR TKIs (including gefitinib, erlotinib, and afatinib) are well accepted first-line treatments in this subset of patients. The only third generation EGFR TKI to overcome acquired resistance in the presence of a T790M mutation is osimertinib. In a Phase 3 study that randomized patients with T790M positive

NSCLC who had progressed on an EGFR TKI in a 2:1 fashion to receive osimertinib or pemetrexed-platinum doublet, osimertinib demonstrated an improvement in median PFS (10.1 months vs 4.4 months; HR 0.30 [95% CI: 0.23, 0.41], $p<0.001$) and an ORR of 71% versus (vs) 31% (odds ratio, 5.39; [95% CI: 3.47, 8.48], $p<0.001$) when compared to chemotherapy [55]. These results led to approval of osimertinib in patients with T790M positive EGFR TKI acquired resistance. For the remainder of patients with an EGFR sensitizing mutation who develop resistance to TKIs and whose tumors do not harbor a T790M mutation, treatment includes a platinum-based doublet at the time of progression with RRs of 20% to 30% and a median PFS of 4 to 5 months [56].

For 3% to 7% of patients with lung adenocarcinoma with echinoderm microtubule protein-like 4 (EML4)/ALK translocation, crizotinib, and ceritinib are now approved agents in the first-line setting. Recently, alectinib, a potent and selective ALK inhibitor with central nervous system (CNS) penetration, was approved as second-line therapy in patients with crizotinib-refractory ALK-rearranged NSCLC. In a Phase 2 study, alectinib yielded an ORR of 50% (95% CI: 41, 59) and a PFS of 8.9 months (95% CI: 5.6 to 11.3 months) [57].

4.1.1.7 Pembrolizumab in Treatment of Non-Small Cell Lung Cancer

The standard of care in NSCLC was revolutionized by regulatory approval of pembrolizumab as monotherapy and in combination with chemotherapy [58]. Pembrolizumab was approved as monotherapy in subjects with metastatic NSCLC whose tumor expressed programmed cell death 1 ligand 1 (PD-L1) with a tumor proportion score (TPS) ≥50% without targetable EGFR or ALK genetic aberrations based on the primary analysis of KEYNOTE (KN)-024 (see [Section 7.4] for details) [59]. The TPS is the percentage of tumor cells that express PD-L1, identified using immunohistochemical (IHC) analysis.

Pembrolizumab in combination with pemetrexed and carboplatin for patients with treatment-naïve metastatic nonsquamous NSCLC without targetable EGFR or ALK genetic aberrations, irrespective of PD-L1 tumor expression, was approved in the U.S. based on an interim analysis of KN021 [60], a randomized, open-label trial comparing pembrolizumab plus carboplatin and pemetrexed Q3W followed by pembrolizumab Q3W for 24 months and indefinite pemetrexed maintenance therapy to carboplatin and pemetrexed alone followed by indefinite pemetrexed maintenance therapy. In the pembrolizumab plus chemotherapy group, 33 of 60 subjects (55%; 95% confidence interval [CI]: 42, 68) achieved an objective response compared with 18 of 63 subjects (29%; 95% CI: 18, 41) in the chemotherapy alone group (estimated treatment difference 26% [95% CI: 9, 42]; $p=0{\cdot}0016$) [60]. PFS was significantly longer with pembrolizumab plus chemotherapy compared with chemotherapy alone (hazard ratio [HR]: 0.53 [95% CI: 0.31, 0.91], $p=0{\cdot}010$). No difference in OS was noted over the median follow-up of 10.6 months. Yet, in a recent update with an extended median follow-up of 18.7 months (range, 0.8 – 29.0 months) the median OS was not reached (NR) (95% CI: 22.8, NR) with pembrolizumab plus chemotherapy compared to 20.9 months (95% CI: 14.9, NR) with chemotherapy alone (HR: 0.59 [95% CI: 0.34, 1.05], $p=0.03$) [61]. Notably, patients in the chemotherapy alone group were able to crossover to the pembrolizumab group upon central verification of progression. These findings are being further explored in an ongoing international, randomized, double-blind, Phase 3 trial, KN189.

NSCLC remains a challenge for patients in India. Upon approval of pembrolizumab for NSCLC in India, pembrolizumab will offer a more effective treatment option with a good benefit/risk ratio.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The purpose of this Phase 4 study is to fulfill the Indian regulatory post-approval requirement for an interventional Phase 4 study for pembrolizumab while granting permission to market the product in India. The safety data collected in this study will help to inform the safety profile of pembrolizumab in subjects treated in India with unresectable or metastatic melanoma and NSCLC subjects who are either untreated (PD-L1 ≥50%) or have received a minimum of 2 cycles of a platinum-containing systemic therapy (PD-L1 ≥1%). Due to the low incidence rate of melanoma in India, the number of melanoma subjects is anticipated to be lower than the number of NSCLC subjects.

Pembrolizumab monotherapy is the current standard of care for the treatment of patients with good Eastern Cooperative Oncology Group (ECOG) performance status (ECOG 0 or 1) and previously untreated, advanced, or metastatic NSCLC with a programmed cell death ligand 1 (PD-L1) TPS ≥50% with no EGFR or ALK genomic tumor aberrations. Approximately 30% of patients with newly diagnosed, advanced NSCLC highly express PD-L1 to a TPS ≥50% [59].

4.2.2 Rationale for Dose Selection/Regimen/Modification

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W) for up to 35 cycles, disease progression, unacceptable toxicity, death due to any cause, investigator decision, or patient decision or withdrawal of consent, whichever occurs first. The initial dose approved by the U.S. Food and Drug Administration (FDA) for treatment of melanoma subjects was 2 mg/kg Q3W. Currently, clinical trials evaluating pembrolizumab are using a fixed dose of 200 mg Q3W and the current U.S. FDA-approved dose for both melanoma and NSCLC is 200 mg Q3W. The use of a fixed dose is based on PK findings summarized below.

The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other subject covariates on exposure using available data from 1139 subjects (from Keynote-001 and Keynote-002) has been performed. The majority of these subjects (1077; 94.6%) had advanced melanoma. The distribution of exposures from the 200 mg fixed dose were predicted to considerably overlap those obtained with the 2 mg/kg dose, and importantly, maintained individual subject exposures within the exposure range established in melanoma as associated with maximal clinical response. This comparison also demonstrated that the 200 mg Q3W regimen provided no substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the antitumor effect of pembrolizumab is driven through immune system activation rather than

through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types.

A fixed-dose regimen is expected to simplify the dosing regimen (potentially reducing dosing errors), as well as be more convenient for physicians. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities, as well as reducing waste.

4.2.2.1 Rationale for the Use of Comparator/Placebo

This is a single-arm, open-label, study using pembrolizumab. There is no comparator or placebo.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Efficacy endpoints are not being assessed in this study, but are collected during this trial for patient management as therapy will need to be discontinued for disease progression either by clinical signs or symptoms or radiographic progression.

4.2.3.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anti-cancer treatments are included as safety endpoints for the study including, but not limited to, the incidence of, causality, severity, and outcome of adverse events/serious adverse events; changes in vital signs and laboratory values. Adverse events will be assessed as defined by Common Terminology for Adverse Events (CTCAE), Version 4.0.

4.2.3.3 Planned Exploratory Biomarker Research

Not applicable for this study.

4.2.3.4 Future Biomedical Research

Not applicable for this study.

4.3 Benefit/Risk

The study is designed to provide information about the safety of pembrolizumab for patients being treated in India for advanced melanoma and NSCLC.

It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation.

Pembrolizumab is safe and well tolerated, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related adverse events (13.8%), discontinuations due to adverse events (11.9%), and deaths due to drug-related adverse events (3.9%). Furthermore, the frequency of immune-mediated adverse reactions is low, and these events are readily managed in the clinical setting. The safety and efficacy data generated to date provided a favorable benefit-risk assessment for the use of pembrolizumab as a treatment for subjects with a number of

carcinomas including advanced/metastatic melanoma, NSCLC and head and neck nonsquamous cell carcinoma.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and informed consent documents.

The protocol-specified clinical procedures for this study do not impart any additional risk beyond that found in standard clinical practice.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/female subjects in India who are of at least 18 years of age with a histologically confirmed diagnosis of unresectable or metastatic melanoma, and NSCLC subjects who are either untreated (PD-L1 ≥50%) or have experienced disease progression after a platinum-containing systemic therapy (PD-L1 ≥1%) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide documented informed consent and agrees to audiovisual recording of the documented informed consent process, per local regulations for the study.
2. Be at least 18 years of age on the day of providing documented informed consent.
3. Have one of the below diagnoses:

   MELANOMA SUBJECTS

   a. Have a histologically confirmed diagnosis of unresectable Stage III or metastatic melanoma (Stage IV) not amenable to local therapy.

   b. Have received no more than 1 line of prior systemic therapy for unresectable Stage III or Stage IV melanoma (including mitogen activated protein kinase inhibitors).

   c. Have a Lactate Dehydrogenase (LDH) ≤1.5 × upper limit of normal (ULN) by local lab.

   NSCLC SUBJECTS

   a. Have a life expectancy of at least 3 months

   b. **2nd Line Treatment and Beyond Subjects:**

      Have a histologically or cytologically confirmed diagnosis of stage IIIB//IIIC/IV (including any future updates to AJCC guideline or recurrent NSCLC.

      i) Have tumor that expresses PD-L1 (PD-L1 ≥1%).

ii) Have received prior treatment with at least two cycles of a platinum-containing doublet for Stage IIIB/IV or recurrent disease. A platinum-containing doublet is defined as a platinum-based cytotoxic systemic agent administered in the same cycle as another cytotoxic systemic chemotherapeutic agent. Completion of treatment with a platinum-containing doublet as neoadjuvant/adjuvant therapy within 6 months of providing documented informed consent will satisfy the prior treatment requirement.

iii) Have received an EGFR tyrosine kinase inhibitor (either erlotinib, gefitinib, or afatinib) in a similar manner to that above for the platinum-containing doublet if they have an EGFR sensitizing mutation.

iv) Have received crizotinib in a similar manner to that above for the platinum-containing doublet if they have an ALK translocation.

Note: In subjects treated previously with a tyrosine kinase inhibitor separately from a platinum-containing doublet; the order of treatment does not matter.

c. **1st Line Treatment Subjects:**

Have a histologically or cytologically confirmed diagnosis of Stage IV NSCLC:

i) Have tumors demonstrate PD-L1 strong expression (PD-L1 ≥50%)

ii) Do not have an EGFR sensitizing mutation AND be ALK translocation negative,

iii) Have received no systemic anti-cancer therapy for their metastatic NSCLC.

Note: Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant/definitive therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.

All NSCLC subjects must also meet the following requirements:

a. Have provided a formalin fixed tumor tissue sample for PD-L1 biomarker analysis from a recent biopsy of a tumor lesion not previously irradiated; For 1st line subjects, biopsies obtained PRIOR to the administration of any systemic therapy administered for the treatment of a subject's tumor (such as neoadjuvant/adjuvant/definitive therapy) will not be permitted for analysis. For 2nd line treatment and beyond subjects, no systemic antineoplastic therapy may be administered between the PD-L1 biopsy and initiating study medication. Although 2nd line treatment and beyond subjects using tyrosine kinase inhibitors prior to treatment on this protocol may continue using these until it is time to begin the appropriate wash out period for these medications. For subjects in whom obtaining a new tumor biopsy will be medically inappropriate, the investigator may consult with the Sponsor's study clinical director, and if there is agreement, the investigator may submit an archival formalin fixed, paraffin-embedded tumor specimen for PD-L1 analysis. Fine needle aspirates Endobronchial Ultrasound (EBUS) or cellblocks are not acceptable. Needle or

excisional biopsies, or resected tissue is required. The tissue sample must be received and evaluated by the laboratory prior to randomization.

b. Investigators must be able to produce the source documentation of the EGFR mutation status or ALK translocation status. If unable to test for these molecular changes, formalin fixed paraffin-embedded tumor tissue of any age should be submitted to a central laboratory designated by the Sponsor for such testing. Subjects will not be randomized until EGFR mutation and ALK translocation status is available in source documentation at the site.

   NOTE: If a subject is known to have one molecular alteration (either sensitizing EGFR mutation or ALK translocation), then testing for the other alteration is not required.

   NOTE: If a subject is known to have a mutation in KRAS, then testing for an EGFR mutation or for an ALK translocation will not be required given that all of these molecular alterations are mutually exclusive in subjects with nonsquamous NSCLC.

   NOTE: For subjects enrolled who are known to have a tumor of predominantly squamous histology, molecular testing for EGFR mutation and ALK translocation will not be required as this is not standard of care and is not part of current diagnostic guidelines.

4. Have adequate organ function as defined in Table 2. Specimens must be collected within 10 days prior to the start of trial treatment.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin [a]	≥9.0 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated [b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥30 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN OR ≤5 × ULN for subjects with liver metastases
Coagulation	
International normalized ratio (INR) **OR** prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR = glomerular filtration rate; ULN = upper limit of normal.

5. Have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiologist. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Cutaneous lesions not visible on scans are not considered measurable.
6. Have an ECOG performance status of 0 to 1.
7. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of trial treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

8. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of trial treatment.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

9. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. **NSCLC Subjects only (1st Line, 2nd Line, and Beyond Subjects):** Has a tumor specimen that is not evaluable for PD-L1 expression by the laboratory.
2. Is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment.

   Note: Subjects who have entered the follow-up phase of an investigational trial may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

3. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another T-cell receptor (ie, CTLA-4, OX-40, CD137) or has previously participated in a pembrolizumab (MK-3475) clinical trial.
4. Has received prior anti-cancer therapy including investigational agent or device within 4 weeks, or completed palliative radiotherapy within 7 days, prior to allocation Exception to this rule would be use of denosumab, which is not excluded.

   a. Note: Subjects must have recovered from all AEs due to previously therapies to ≤ Grade 1 or baseline. Subjects with ≤ Grade 2 neuropathy may be eligible.

   b. Note: If subjects had major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting trial treatment.

5. Is expected to require any other form of antineoplastic therapy while participating in the trial.
6. Is on systemic corticosteroid therapy within 7 days before the planned date for first dose of treatment or any other form of immunosuppressive medication.
7. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (exceeding 10 mg daily dose of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of trial treatment.

8. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

9. Has a known additional malignancy that is progressing or requires active treatment.

   Note: Subjects with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, cervical cancer in situ, breast carcinoma) that have undergone potentially curative therapy are not excluded.

10. Has had an allogeneic tissue/solid organ transplant.

11. Has a history of or current radiographically detectable (even if asymptomatic and/or previously treated) central nervous system metastases and/or carcinomatous meningitis as assessed by local site investigator. Baseline brain magnetic resonance imaging (MRI) is required at screening.

12. Has a severe hypersensitivity (≥ Grade 3) to any excipients in pembrolizumab (excipients are listed in the pembrolizumab IB).

13. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease.

14. Has an active infection requiring systemic therapy including known history of active TB (*Bacillus tuberculosis*).

15. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

16. Has a known history of or is positive for hepatitis B (HbsAg reactive) or hepatitis C (HCV RNA [qualitative] is detected). Note: Without known history, testing needs to be performed to determine eligibility.

17. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.

18. If subject received prior radiation therapy to a symptomatic metastatic lesion (excluding brain or other central nervous system metastases), the subject must have recovered to CTCAE Grade 1 or Grade 0 from the AEs due to radiation therapy.

19. Is at the time of providing documented informed consent a regular user (including 'recreational use') of any illicit drug or has a recent history (within the last 3 months) of substance abuse (including alcohol).

20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

21. Has received a live vaccine within 30 days before the first dose of trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

5.2 Trial Treatment(s)

Pembrolizumab is to be used in this trial as outlined below in Table 3.

Table 3 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each cycle	Experimental

All trial treatments will be administered in an out-patient clinic setting.

All supplies indicated in Table 3 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study etc.). The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

5.2.1.2.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion-Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK 3475) with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, vacation, and/or holidays). Subjects should be placed back on trial treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with and approved by the Sponsor. The reason for interruption should be documented in the subject's study record.

5.2.2 Timing of Dose Administration

200 mg pembrolizumab will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min). The reason for any delay in infusion outside of the protocol-specified window should be documented in the subject's chart and recorded on the electronic Case Report Forms (eCRFs).

Every effort should be made to begin the first dose of trial treatment on the day of treatment allocation/randomization, but if this is not achieved, trial treatment should be initiated no later than 3 days from the date of treatment allocation/randomization. All subsequent cycles of trial treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle, up to and including Cycle 9, due to administrative reasons per the investigator's judgment. From Cycle 10 onwards, trial treatment may be administered up to 5 days before or 5 days after the scheduled Day 1 of each cycle. All trial treatments will begin on Day 1 of each cycle after all pre-dose study procedures and assessments have been completed as detailed on the Trial Flow Chart – Section 6.0.

The Pharmacy Manual contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

5.2.3 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the

investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the eCRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery for tumor control or symptom management is not permitted during the study. Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician. Trial therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of trial therapy. The specifics of the radiation treatment, including the location, will be recorded.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for serious AEs and ECIs as defined in Section 7.2.3.2.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
- Note: Radiation therapy to a symptomatic solitary lesion, in the absence of disease progression and excluding the brain and CNS, may be allowed at the investigator's discretion and approval by the Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse experience. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (eg, for chronic obstructive pulmonary disease [COPD] exacerbation). Please note that inhaled or topical steroids are allowed, and systemic steroids at doses ≤10 mg/day prednisone or equivalent are allowed, as described in Section 5.6.

Subjects who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2, Table 4. Where appropriate, these guidelines include the use of oral or intravenous corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the Investigator does not need to follow the treatment guidance (as outlined below). Refer to Table 4 in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to AEs such as diarrhea, nausea, or vomiting.

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving trial treatment and for 120 days after the last dose of trial treatment by complying with 1 of the following:

(1) practice abstinence[a] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[b]:

- Single method (1 of the following is acceptable):
  - intrauterine device (IUD)
  - vasectomy of a female subject's male partner
  - contraceptive rod implanted into the skin
- Combination method (requires use of 2 of the following):
  - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - cervical cap with spermicide (nulliparous women only)
  - contraceptive sponge (nulliparous women only)
  - male condom or female condom (cannot be used together)
  - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

[a] Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and internal review boards/ethical review committees (IRBs/ERCs). Periodic abstinence (e.g., calendar,

ovulation, symptothermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

[b] If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the trial treatment may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirements (described above) from the day of trial treatment initiation (or 14 days prior to the initiation of trial treatment for oral contraception) throughout the study period up to 120 days after the last dose of trial treatment. If there is any question that both female and male subjects of childbearing potential will not reliably comply with the requirements for contraception, those subjects should not be enrolled into the study.

5.7.3 Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will be immediately discontinued from treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 7.2.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of pembrolizumab does not represent withdrawal from the trial.

As certain data on clinical events beyond trial treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued trial treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 – Trial Flow Chart and Section 7.1.5.3 – Discontinued Subjects Continuing to be Monitored in the Trial.

Subjects may discontinue trial treatment at any time for any reason or be dropped from trial treatment at the discretion of the investigator should any untoward effect occur. In addition,

a subject may be discontinued from trial treatment by the investigator or the Sponsor if trial treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at trial treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from trial treatment but continue to be monitored in the trial for any of the following reasons:

1. The subject or subject's legally acceptable representative requests to discontinue trial treatment.
    - Confirmed radiographic disease progression by RECIST 1.1 outlined in Section 7.1.5
    - Unacceptable adverse experiences as described in Section 7.2
    - Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
    - Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
    - Recurrent Grade 2 pneumonitis
    - A confirmed positive serum pregnancy test
    - Non-compliance with trial treatment or procedure requirements
    - Investigator's decision to discontinue treatment
    - Completion of 35 cycles with pembrolizumab
    - Note: 35 cycles (approximately. 2 years) are calculated from the first dose (Cycle 1 Day 1)
    - Discontinuation of study treatment after a complete response. Discontinuation of trial treatment may be considered for subjects who have attained an investigator-determined confirmed CR per RECIST 1.1 and have been treated for at least 8 cycles (at least 24 weeks) and had at least 2 doses of pembrolizumab beyond the date when the initial CR was declared. These subjects will not continue to be assessed by imaging thereafter.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the trial, they will no longer receive trial treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues or withdraws from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject (or their legally acceptable representative) provides documented informed consent. The overall trial ends when the last subject completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

	Screening	Week/Cycle (21-day Cycle)									Visit 10 and Beyond (21-day Cycle)	End of Treatment (EOT)[17] Treatment Discontinuation	Safety Follow-up[17]
												At time of treatment discontinuation	(30 days after EOT or prior to start of new antineoplastic therapy)
Treatment Cycle	-30 to -1	1	2	3	4	5	6	7	8	9	10-35		
Week (approximate)		0	3	6	9	12	15	18	21	24			
Scheduling Window: Days			±3	±3	±3	±3	±3	±3	±3	±3	±5	+7	+7
Administrative Procedures													
Informed Consent [1]	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X (dispense)											X (collect)	
Demographics/Medical History and Prior Medications[2]	X												
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments													
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X[3]
ECOG Performance Status	X[4]	X[4]	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[6]	X				X				X		X[6]	X	X
Administration of Pembrolizumab (30-min Infusion)		X	X	X	X	X	X	X	X	X	X		

	Screening	Week/Cycle (21-day Cycle)									Visit 10 and Beyond (21-day Cycle)	End of Treatment (EOT)[17] Treatment Discontinuation	Safety Follow-up[17]
												At time of treatment discontinuation	(30 days after EOT or prior to start of new antineoplastic therapy)
Treatment Cycle	-30 to -1	1	2	3	4	5	6	7	8	9	10-35		
Week (approximate)		0	3	6	9	12	15	18	21	24			
Scheduling Window: Days			±3	±3	±3	±3	±3	±3	±3	±3	±5	+7	+7
Laboratory Procedures/Assessments[7]													
Hepatitis B and C[8]	X												
Pregnancy Test- Urine or Serum β-HCG[9]	X	X	X	X	X	X	X	X	X	X	X	X	
PT/INR and aPTT[10]	X												X
CBC With Differential[11]	X		X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[11]	X		X	X	X	X	X	X	X	X	X	X	X
Urinalysis[12]	X		X				X				X	X	X
T3, FreeT4 (FT4), and TSH[13]	X		X		X		X		X		X	X	X
ALK Translocation Testing, NSCLC subjects only[15]	X												
EGFR Mutation Testing, NSCLC subjects only[15]	X												
Disease Assessments													
Tumor Imaging[14]	X					X			X		X[14]	X[14]	
Brain Imaging[14]	X					X					X[14]	X[14]	
Tumor Biopsies/Archival Tissue Collection													
Tumor Tissue Collection, NSCLC subjects only[16]	X												

	Screening	Week/Cycle (21-day Cycle)									Visit 10 and Beyond (21-day Cycle)	End of Treatment (EOT)[17] Treatment Discontinuation	Safety Follow-up[17]
												At time of treatment discontinuation	(30 days after EOT or prior to start of new antineoplastic therapy)
Treatment Cycle	-30 to -1	1	2	3	4	5	6	7	8	9	10-35		
Week (approximate)		0	3	6	9	12	15	18	21	24			
Scheduling Window: Days			±3	±3	±3	±3	±3	±3	±3	±3	±5	+7	+7

1. Documented informed consent and audiovisual recording of the documented informed consent process must be obtained prior to performing any protocol-specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within 30 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is documented.
2. Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments within the previous 10 years. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history taken within 30 days prior to the screening visit (Visit 1).
3. All AEs should be reported for at least 30 days following treatment cessation. Serious adverse events and ECIs should be reported for 90 days following treatment cessation. A serious adverse event considered drug-related by the investigator should be reported regardless of how long has elapsed since treatment cessation. Pregnancies and lactation events should be reported for 120 days following treatment cessation or for 30 days if the subject initiates new anticancer therapy.
4. ECOG of 0 or 1 is required at screening and at C1D1.
5. Vital signs to include temperature, pulse, respiratory rate, and blood pressure. If a subject's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose. Height will be measured at screening only.
6. A 12-lead ECG will be performed at Screening and at every fourth cycle starting on Cycle 4.
7. Routine laboratory tests (serum or plasma chemistry and hematology) for screening must be performed within 10 days prior to administration of the first dose. If a subject starts screening > 10 days prior to administration of trial treatment, a second screening visit is required to collect the lab specimens within the specified timeframe.
8. Testing will be performed by the local laboratory at Screening: Hepatitis B and C serologies should be obtained for subjects without a known history of hepatitis B or C. Those with a known history are ineligible. Include HCV RNA (qualitative) and HbsAg.
9. For females of reproductive potential, urine or serum pregnancy test should be performed within 72 hours prior to day 1 of each treatment cycle and 30 days post treatment if required or as specified per local regulatory guidance. A serum test can be done if urine is not appropriate. Additionally, if urine test is positive or is not evaluable, a serum test is required. Subjects must be excluded/discontinued in the event of a positive test result.
10. PT/INR and aPTT should be collected at Screening and at the Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters will be determined throughout the study if clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
11. Routine laboratory tests (e.g., CBC with differential, comprehensive serum or plasma chemistry panel, and urinalysis) will be performed by the local study site laboratory or their contract laboratory. Additionally, CBC with differential and comprehensive serum or plasma chemistry panel are to be collected up to 48 hours prior to Day 1 dosing of any Cycle.
12. Following baseline and Cycle 2, urinalysis should be performed every fourth cycle.
13. Analysis of T3, FT4, and TSH will be performed by the local study site laboratory or their contract laboratory. Following Cycle 2, testing will be performed every other cycle.

	Screening	Week/Cycle (21-day Cycle)									Visit 10 and Beyond (21-day Cycle)	End of Treatment (EOT)[17] Treatment Discontinuation	Safety Follow-up[17]
												At time of treatment discontinuation	(30 days after EOT or prior to start of new antineoplastic therapy)
Treatment Cycle	-30 to -1	1	2	3	4	5	6	7	8	9	10-35		
Week (approximate)		0	3	6	9	12	15	18	21	24			
Scheduling Window: Days			±3	±3	±3	±3	±3	±3	±3	±3	±5	+7	+7

14. Tumor imaging will be performed within 30 days prior to enrollment. CT scans are the required modality for measurable disease unless a subject has a contraindication (e.g. severe contrast allergy), in which case MRI is acceptable. Premedication for contrast allergy, including steroids, is permissible. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should be performed 12 weeks (±7 days) after the first cycle of treatment and then every 9 weeks (±7 days), or as clinically indicated. Brain MRI should be performed at screening, 12 weeks (±7 days) after the first cycle of treatment, and then every 18 weeks (±7 days), or as clinically indicated. For subjects for whom an MRI is contraindicated, brain CT scan is acceptable. In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. This is the final required tumor imaging.
15. This test is only required for NSCLC subjects (1st line, 2nd line, and beyond treatment subjects). This test is not required for melanoma subjects. Site must be able to provide documentation of the subject's tumor EGFR mutation and ALK translocation status. If the site is unable to provide this source documentation, then the Sponsor will offer this molecular testing of the tumor.
16. Tumor tissue from NSCLC subjects only (1st line, 2nd line, and beyond treatment subjects) for biomarker analysis from an archival tissue sample (acceptable for EGFR and ALK testing) or newly obtained formalin fixed tumor tissue from a recent biopsy of a tumor lesion not previously irradiated (required for PD-L1 determination; acceptable for EGFR and ALK testing) must be provided and evaluated by the laboratory before randomization. No systemic antineoplastic therapy may have been received by the subject between the time of the biopsy for PD-L1 testing and the first administration of study medication. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. Biopsy should be obtained of a non-target lesion, but if obtained from a target lesion then a new baseline scan should be acquired.
17. EOT and Safety Follow-up visits may be combined if a decision is made to end treatment 30 or more days since the last dose of treatment.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

An audio-video recording of the informed consent process shall be maintained by the Investigator for record if required by applicable regulatory guidelines. Sufficient measures will be taken to maintain the confidentiality of the recordings of the trial subjects.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee as well as the Sponsor to ensure that the subject qualifies for the trial prior to enrollment.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides documented informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

Medical history will include all active conditions, and any condition diagnosed within the previous 10 years that are considered to be clinically significant by the investigator. Disease details regarding the subject's melanoma or NSCLC will be recorded separately and not listed as medical history.

7.1.1.4.1 Subsequent Antineoplastic Therapy Status

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new antineoplastic therapy within 30 days after the last dose of trial treatment, the "30-day Safety Follow-up visit" should occur prior to starting the new antineoplastic therapy.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before first dose of trial medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All concomitant medication will be recorded on the eCRF, including all prescription, OTC, herbal supplements, and IV medications and fluids. If changes occur

during the study period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment number. The treatment number identifies the subject for all procedures occurring after treatment allocation. The assigned screening number will become the subject's treatment number. Once a treatment number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment number.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified treatment for >12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

See Section 7.1.2.6.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Review Adverse Events

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs specified in the Trial Flow Chart (Section 6.0) and more frequently, if clinically indicated. Adverse experiences will be graded and recorded throughout the trial and during the follow-up period as defined by CTCAE, Version 4.0 (see [Section 12.4]). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of a potentially immunologic etiology; see Section 5.6.1 regarding the identification, evaluation, and management of AEs of a potential immunological etiology.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs. Subjects should be assessed for possible ECIs prior to each dose. Laboratory results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related adverse event. Subjects who develop an adverse event thought to be immune-related should have additional testing to rule out other etiologic causes. If laboratory

results or symptoms indicate a possible immune-related adverse event, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.1.2.2 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG Performance Status (see [Section 12.5]) at screening, prior to dosing on Day 1 of each treatment cycle, at EOT, and during the safety follow up, as specified in the Trial Flow Chart (Section 6.0).

7.1.2.3 Physical Examination

The investigator or clinical designee will perform a complete physical examination during the screening period, Day 1 of each cycle, EOT, and the 30-day safety follow-up visit. Clinically significant abnormal findings should be recorded as medical history. Additional full physical examinations should be performed as specified in the Trial Flow Chart (Section 6.0). After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 Vital Signs and Weight

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and weight. Height will be measured at screening only.

7.1.2.5 12-Lead Electrocardiograms

Baseline ECGs will be obtained at screening, with additional ECGs obtained every fourth cycle, starting on Cycle 4 Day 1, EOT, the safety follow-up visit and as clinically indicated for all subjects. Clinically significant abnormal findings found at screening should be recorded as medical history. Clinically significant abnormal findings after the screening ECG must be recorded as an adverse event.

7.1.2.6 Administration of Pembrolizumab (30-minute Infusion)

Administration of pembrolizumab will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood volumes drawn/collected by visit and by sample type per subject can be found in Section 12.2.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT/INR
Platelet count	Alanine aminotransferase	Protein	aPTT
WBC (total and differential)[e]	Aspartate aminotransferase	Specific gravity	Total T3 or free T3, FT4, and TSH[b,d]
RBC	Bicarbonate[c]	Microscopic exam, if abnormal results are noted	Anti-HCV
Absolute lymphocyte count[e]	Calcium		HCV viral load[d]
Absolute neutrophil count[e]	Chloride		HCV genotype[d]
	Creatinine		anti-HBs[d]
	Glucose		HbsAg
	Phosphorus		Anti-HBc (total and IgM)[d]
	Potassium		HbeAg[d]
	Sodium		anti-Hbe[d]
	Total bilirubin		HBV viral load[d]
	Direct bilirubin		Anti-HDV[d]
	Total protein		AFP
	Blood urea nitrogen		CRP
			GGT

[a] Perform on women of childbearing potential only 72 hours prior to Day 1 of Cycle 1. Pregnancy tests must be repeated prior to every cycle if required or as specified per local regulatory guidance.
[b] T3 is preferred; if not available free T3 may be tested.
[c] If this test is not done as part of local standard of care, this test does not need to be performed.
[d] If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Procedure Manual.
[e] Report % or absolute results per standard of practice. Report the results in the same manner throughout the trial.

AFP=alpha-fetoprotein; aPTT=activated partial thrombin time; CRP=C-reactive protein; FT4=free thyroxine; GGT=gamma-glutamyl transferase; HBc=Hepatitis B core; HbeAg=Hepatitis B e antigen; Hbe=hemoglobin E; HBs=hepatitis B surface; HbsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDV=hepatitis D virus; IgM=gamma M immunoglobulin; INR=insulin receptor; PT=prothrombin time; RBC=red blood cells; T3= triiodothyronine; TSH=thyroid-stimulating hormone (thyrotropin); WBC=white blood cells.

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. An exception is hepatitis and thyroid serologies, which may be performed within 30 days prior to first dose. After Cycle 1, pre-dose laboratory safety tests can be conducted up to 72 hours prior to dosing unless otherwise noted on the flow charts.

Laboratory test results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to administration of each dose of trial treatment. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory

tests do not need to be repeated after the end of treatment if laboratory results are within the normal range.

7.1.3.2 Pregnancy Test

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of each cycle of trial treatment and 30 days post-treatment, if required or as specified per local regulatory guidance. If a urine test is positive or not evaluable, a serum test will be required. Subjects must be excluded/discontinued from the trial in the event of a positive or borderline-positive test result.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue treatment prior to completion of the trial should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the EOT should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events and subjects will return to the clinic for a safety follow-up visit 30 days after EOT or prior to start of the new antineoplastic therapy, whichever occurs first.

7.1.4.1.1 Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

- Note: A subject is not considered lost to follow-up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

7.1.4.2 Subject Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical trial that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site**.**

7.1.4.4 Tumor and Brain Imaging

Initial tumor imaging will be performed within 30 days prior to enrollment. Computed tomography (CT) scans are the required modality for measurable disease unless a subject has a contraindication (eg, severe contrast allergy), in which case MRI is acceptable. Premedication for contrast allergy, including steroids, is permissible. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should be performed 12 weeks (±7 days) after the first cycle of treatment and then every 9 weeks (±7 days), or as clinically indicated.

Brain MRI must be performed at screening, 12 weeks (±7 days) after the first cycle of treatment, and then every 18 weeks (±7 days), or as clinically indicated. For subjects for whom an MRI is contraindicated, brain CT scan is acceptable.

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. This is the final required tumor imaging.

Participants may be permitted to continue treatment beyond confirmed RECIST 1.1-defined progression as long as investigator-assessed clinical stability is observed, and the participant is tolerating study drug following Sponsor consultation and approval.

Clinical stability is defined as the following:

- Absence of symptoms and signs (including worsening of laboratory values) indicating progression of disease
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Detailed instructions for tumor and brain imaging are provided in the Site Imaging Manual.

7.1.4.5 Tumor Biopsy/Archival Tissue Collection, NSCLC Subjects Only

Tumor tissue, for NSCLC subjects only, for biomarker analysis from formalin fixed paraffin-embedded tumor tissue sample or newly obtained formalin fixed biopsy of a tumor lesion not previously irradiated must be provided in the form of a tissue block or unstained slides and evaluated before allocation. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous.

To perform testing for PD-L1, the laboratory (local or central) must use the PD-L1 IHC 22C3 pharmDx in strict accordance with the manufacturer's instructions, which is the only assay acceptable for this study.

For 1st line NSCLC subjects only, subjects whose tumors demonstrate PD-L1≥50% expression is eligible for enrollment. 2nd line treatment and beyond NSCLC subjects must demonstrate PD-L1≥1% expression for eligibility. A fine needle aspirate, EBUS or cytologic specimen will not be acceptable. Needle or excisional biopsies, or resected tissue is required. Newly obtained formalin fixed specimens are encouraged.

Detailed instructions for NSCLC subject tissue collection, processing and shipment are provided in the Procedures Manual. Older biopsy material or surgical specimens may be used to assess EGFR mutation status and ALK translocation status, if not already documented when the subject provides documented informed consent.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Approximately 30 days prior to treatment allocation/randomization, potential candidates to be enrolled in this trial will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

If additional time is needed for screening procedures, an extension of the screening window by up to 7 days may be approved following mandatory Sponsor consultation.

7.1.5.2 Treatment Period

The treatment period will continue every 21 days for up to 35 cycles (approximately 2 years) as long as subjects are receiving benefit from trial treatment and have not had disease progression or met any criteria for study withdrawal. Please refer to section 5.8.2.

7.1.5.3 Safety Follow-Up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anticancer treatment, whichever comes first. This visit may be combined with the EOT visit if a decision is made to end treatment 30 or more days since the last dose of treatment.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

7.1.5.4 Discontinued Subjects Continuing to be Monitored in the Trial

Subjects will be required to return to the clinic approximately 30 days after the last dose of trial treatment for a safety follow-up visit. Subjects should report any AEs up to 90 days after the last dose of the trial treatment. A serious adverse event considered drug-related by the investigator should be reported regardless of how long has elapsed since treatment cessation.

7.2 Assessing and Recording Adverse Events

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

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

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

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the Investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations in subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the Investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Immediate Reporting of AEs to the Sponsor must be done. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as a serious adverse event within 24 hours of determination that the event is not progression of the cancer under study

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 7 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes are made to the primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	A Prospective, Open-label, Phase 4 Study to Evaluate the Safety of Pembrolizumab (Keytruda®) in Subjects with Unresectable or Metastatic Melanoma or PD-L1 positive Non-Small Cell Lung Cancer (NSCLC) in India
Treatment Assignment	All subjects to be assigned to the same dose/schedule of pembrolizumab
Analysis Populations	ASaT
Primary Endpoint(s)	Safety and tolerability of the protocol treatment as characterized by the adverse event experience
Statistical Methods for Key Safety Analyses	Descriptive statistics will be provided for the rate of safety endpoints.
Interim Analyses	An ongoing safety review will be conducted for this study. An interim data listing for safety evaluation will be conducted at 1 year from the date at which the first subject is enrolled into the study.
Multiplicity	Not applicable
Sample Size and Power	The planned sample size is approximately 150 subjects (with a minimum of 25 subjects with unresectable or metastatic melanoma, and ~125 NSCLC subjects who are either untreated (PD-L1 ≥50%) or have experienced disease progression after a platinum-containing systemic therapy (PD-L1 ≥1%). No hypothesis testing will be performed. The goal is to characterize the AEs associated with the use of pembrolizumab in the treatment of subjects, as described above, in India.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This trial is being conducted as a non-randomized, open-label study, i.e., subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0

8.4 Analysis Endpoints

The safety endpoints that will be evaluated are listed below.

8.4.1 Safety Endpoints

See Section 4.2.3.2 for the initial description of safety measures.

8.5 Analysis Populations

8.5.1 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all subjects who received at least 1 dose of trial treatment.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 Statistical Methods

8.6.1 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory parameters.

The proportion of subjects with AEs of elevated laboratory values that are reported as ECIs described in Section 7.2.3.2 during the study therapy period will be provided along with the corresponding 95% Cs, which will be calculated using the Clopper Pearson method.

In addition, the broad AE categories consisting of the percentage of subjects with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and those who discontinued due to an AE will be summarized in the same manner Table 8.

Table 8 Analysis Strategy for Safety Parameters

Safety Endpoint	Within Group 95% CI	Descriptive Statistics
Any AE	X	X
Any Serious AE	X	X
Any Drug-Related AE	X	X
Any Serious and Drug-Related AE	X	X
Discontinuation due to AE	X	X
Specific AEs, SOCs, or PDLCs‡ (incidence ≥1% of participants)	X	X
Specific AEs, SOCs or PDLCs† (incidence <1% of participants)		X
Change from Baseline Results (Labs, ECGs, Vital Signs)		X
Note: SOC=System Organ Class; X = results will be provided. 95% Cis will be calculated using the Clopper Pearson method.		

For continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values may be provided in table format. Mean change from baseline over time may also be plotted with the corresponding standard errors.

8.6.2 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

8.7 Interim Analyses

8.7.1 Safety Interim Analyses

An ongoing safety review will be conducted for this study and upon request by the Regulatory Agency. The objective of this safety review is to assess the safety data collected over the duration of the study; the results obtained will be submitted to the Regulatory Agency to seek further direction on the continuation of the study. An interim data listing for safety evaluation will be conducted at 1 year from the date at which the first subject is enrolled into the study.

8.8 Multiplicity

This study does not involve multiplicity adjustments.

8.9 Sample Size and Power Calculations

8.9.1 Sample Size and Power for Safety Analyses

Safety is the primary endpoint. No formal sample size calculations are performed for this study since the primary objective is not to test a predefined hypothesis, but to collect and assess adverse events occurring in subjects treated in a routine clinical setting (see Section 4.2.1). If the planned 150 subjects are enrolled, then, if a certain number of subjects

experience a specific adverse event, serious adverse event, Grade 3+ adverse event, adverse event of special interest (AEOSI) etc. a 95% CI for the true adverse event rate would be:

Number of subjects (%) with AEs	95% confidence interval
8/150 (5.33%)	(2.3%, 10.2%)
15/150 (10.00%)	(5.7%, 16.0%)
23/150 (15.33%)	(10.0%, 22.1%)
30/150 (20.00%)	(13.9%, 27.3%)
38/150 (25.33%)	(18.6%, 33.1%)
45/150 (30.00%)	(22.8%, 38.0%)
53/150 (35.33%)	(27.7%, 43.5%)

8.10 Subgroup Analyses

No subgroup analyses are planned.

8.11 Compliance (Medication Adherence)

For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Doses on Therapy}}{\text{Number of Doses Should be on Therapy}} \text{ x } 100.$$

Summary statistics will be provided on percent compliance for the ASaT population.

8.12 Extent of Exposure

The extent of exposure to trial treatment will be evaluated by summary statistics (N, mean, median, standard deviation) and frequencies for the "Number of Doses on Therapy".

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 9.

Table 9 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-3475 25 mg/ mL	Solution for Infusion	Provided centrally by the Sponsor.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive an open-label kit. The kit provided will contain 2 vials.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IRT system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IRT system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

Select the appropriate text option(s) below as applicable to the given trial. Delete those options that do not apply. If none of the options apply to the given trial, delete this section.

For probe Bioequivalence (BE)/Bioavailability (BA) trials, where reference comparators are sourced by the trial site:

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in Section 12.1 - Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/IEC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The Sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

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

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

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

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. MSD will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to

the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

12.2 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Screening	Cycle 1	C2	C3	C 4	C5	C6	C7	C8	C9	C10-35	EOT	Follow up
15 ml		10.5 ml	5.5 ml	5.5 ml	5.5 ml	10.5 ml	5.5 ml	5.5 ml	5.5 ml	10.5ml	10.5ml	13.5 ml

12.3 Common Terminology Criteria for Adverse Events v4.

The descriptions and grading scales found in the revised NCI CTCAE version 4.0 will be used for adverse event reporting (http://ctep.cancer.gov).

12.4 Eastern Cooperative Oncology Group

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

12.5 Response Evaluation Criteria in Solid Tumors

RECIST 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer [62]

12.6 List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ASaT	All Subjects as Treated
AST	Aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
β-hCG	β-human chorionic gonadotropin
CD28	Cluster of differentiation 28
CD3ζ	CD3 zeta
CI	Confidence Interval
CNS	Central nervous system
CT scan	Computed tomography
CTCAE	Common Terminology for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
EBUS	Endobronchial Ultrasound
eCRF	Electronic case report form
ECI	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EOT	End of treatment
ERC	Ethical review committee
FDA	Food and Drug Administration
FVC	Forced vital capacity
GCP	Good Clinical Practices
HBsAg	Hepatitis B
HIV	Human immunodeficiency virus
HR	Hazard ratio

Abbreviation	Definition
IB	Investigator's brochure
IFU	Instructions for use
Ig	Immunoglobulin
IgG4	Immunoglobulin G4
IL-2	Interleukin-2
INR	International normalized ratio
IPI	Ipilimumab
IRB	Internal review board
IRC	Independent review committee
IV	Intravenous
LDH	Lactate Dehydrogenase
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
NSAIDS	Non-steroidal anti-inflammatory drugs
OS	Overall survival
ORR	Overall response rates
OTC	Over-the-counter
PD	Progressive Disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PEF	Peak expiratory flow
PFS	Progression-free survival
PKCθ	Protein kinase C-theta
PO	By mouth
PT	Prothrombintime
Q3W	Every 3 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	Serious adverse event

Abbreviation	Definition
SOP	Standard operating procedures
T1DM	Type 1 Diabetes Mellitus
TKI	Tyrosine kinase inhibitor
TPS	Tumor proportion score
T-regs	Regulatory T-cells
TB	Tuberculosis
ULN	Upper limit of normal
US	United States
WBC	White blood cell
ZAP70	Zeta-chain-associated protein kinase

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	