TITLE: Phase 2 Multi-center Study of Anti-Programmed-Death-1 [anti-PD-1] during Lymphopenic State After High-Dose Chemotherapy and Autologous Hematopoietic Stem Cell Transplant [HDT/ASCT] for Multiple myeloma

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1.0 STUDY SUMMARY

Abbreviated Title	Phase 2 Study of Anti-PD-1 After Autologous Transplant for Multiple Myeloma
Trial Phase	*2*
Clinical Indication	Multiple myeloma patients with inadequate response from prior therapy
Trial Type	Multi-Center Phase 2
Type of control	None
Route of administration	Intravenous
Trial Blinding	None
Treatment Groups	Single Treatment Group
Number of trial subjects	A total of 50 subjects
Estimated duration of Study	*2 years*
Duration of Participation	7 months (Enrollment to End-of-Study Safety Evaluation)

2.0 STUDY SYNOPSIS

2.1 Study Design

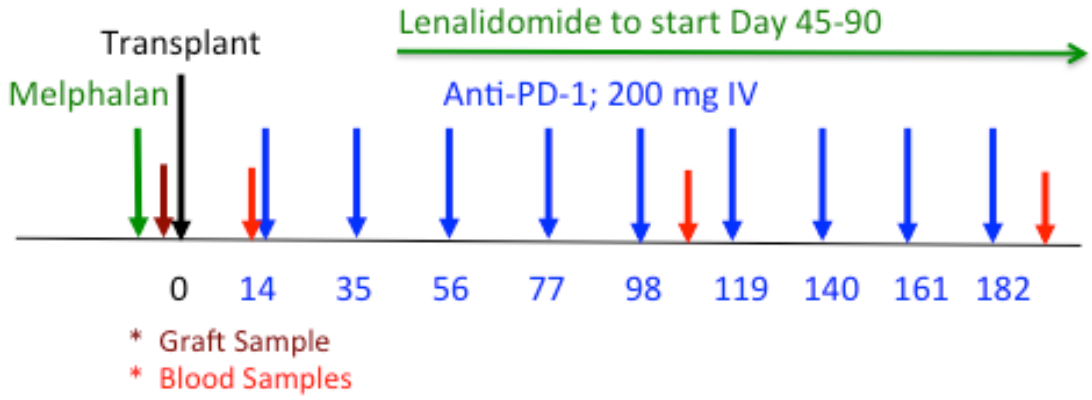
Phase 2 Multi-center Single-arm Study

2.2 Treatments

1. **Standard Multiple Myeloma Treatments**
   - **1.1 High-dose Melphalan and Autologous Stem Cell Transplantation**
     High-dose melphalan 140-200 mg/m^2 (<200 mg/m^2 for age >70 years)
   - **1.2 Post-transplant Maintenance**
     Lenalidomide 5-15 mg/day, starting day 45-90 post-transplant

2. **Study Treatment:** 200 mg/day of MK-3475 will be administered every 3 weeks, starting day 14 post-transplant (or after engraftment) for a total of 9 doses or ~180 days after transplant. Treatment days are +/- 4 days flexible.

2.3 Treatment Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objectives & Hypothesis

Objectives:

(1) To investigate the feasibility (safety and tolerability) of the addition of anti-PD1 after high dose therapy and autologous hematopoietic stem cell transplant in patients with multiple myeloma.

(2) To investigate the efficacy of the addition of anti-PD1 after high dose therapy and autologous hematopoietic stem cell transplant in improving complete response (CR) conversion rate for patients with multiple myeloma

Hypothesis: The administration of anti-PD-1 during the lymphopenic state after high dose therapy and autologous hematopoietic stem cell transplant is safe and tolerable and will enhance recognition and eradication of multiple myeloma by the recovering immune system and will result in a higher CR conversion rate.

See Appendix 13.3 for the definition of complete response (CR).

3.2 Secondary Objective & Hypothesis

Objective:
To investigate the efficacy of this strategy in improving other transplant outcomes especially 2-year progression-free and overall survival (PFS and OS).

Hypothesis: The intervention increases other transplant outcomes especially 2-year PFS among patients achieving CR by day 180.

See Section 5.10 for the definition of PFS and OS.

3.3 Exploratory Objectives

(1) To perform correlative studies of the effects of anti-PD-1 on T-cell and NK-cell function.

Hypothesis: Enhanced Th1-type and cytotoxic immune responses following anti-PD-1 treatment will correlate with prolonged remission, while relapse will correlate with reduced Th1 response or increased regulatory immune response.

(2) To measure immune cell phenotypes in the autologous graft tissue being transplanted.

Hypothesis: Remission and relapse rates will correlate with differences in cell types present in the graft

4.0 BACKGROUND & RATIONALE

4.1 Background

1 Multiple Myeloma [MM]

Multiple myeloma (MM) is a common hematologic malignancy with high disease morbidity burden in the western hemisphere. It was estimated that 70,000 new patients were diagnosed and 21,700 patients died of MM in the US in 2012.[1] MM is a clonal neoplastic proliferation of plasma cells and is considered chronic and incurable, with current novel chemo-biologic targeted agents. In the previous conventional chemotherapy era, the median overall survival was ~4-5 years for average-risk patients while this has been estimated to be much improved to >7 years in the current targeted era.[102-108] However, outcomes of high-risk or advanced MM therapy remain poor, with a median survival only ~8-14 months after therapy.[2-6]

The current standard therapy for MM is partly based on the pre-biologic targeted era when high dose therapy and autologous stem cell transplant (HDT/ASCT) was proven to improve myeloma progression-free and overall survival. This consists of 3 phases: 1) primary induction therapy 2) consolidative HDT/ASCT and 3) maintenance therapy. The immune modulating agents, thalidomide and lenalidomide, and proteasome inhibitor bortezomib, are used in the induction and maintenance, while conditioning with high-dose melphalan, a conventional chemotherapeutic agent with high anti-MM activity, remains the standard agent.[7] Despite these measures, relapse or progression during maintenance is inevitable. Retreatment with or without second HDT/ASCT is often used but of less efficacy. Few effective treatment options are available for advanced relapsed MM.

In addition, MM with certain cytogenetic abnormalities [17p-, t(4;14), t(14;16), (14:20), 13-, hypodiploidy and plasma cell leukemia] are of extremely poor prognosis, with a median survival of 8-14 months and 1-year and 2-year overall survival rates of 50% and 25% only, respectively, after HDT/ASCT [2-6]. These high risk MMs constitute ~30% of MM. Certain novel biologic agents e.g. bortezomib have been shown to overcome the resistance of these high risk MMs [8,9] but response is temporary and none is proven to be curative or to provide meaningful long-term MM control.

In the initial pioneer stage ~30 years ago, full-intensity allo-HCT was extensively explored in advanced or relapsed/refractory MM but these resulted in high early TRM, regimen related toxicities and GVHD, up to 50% in the first 6 months post transplant.[10] However, those patients who had survived subsequently enjoyed a sustained long-term MM control and likely a cure of MM. These led to the use of reduced-intensity allo-HCT in an attempt to decrease TRM in the past 15-20 years. However, the success in decreasing TRM was at the expense of increasing MM relapse, thus resulting in no improvement of overall outcomes.[11-14]

Failure of the use of allo-HCT in the advanced MM setting led to studying of its role in an upfront setting. And to improve MM control, high-dose therapy and autologous HCT was incorporated prior to reduced-intensity allo-HCT (tandem auto-allo HCTs). Several genetically randomized controlled trials (RCT) comparing tandem auto-allo HCTs versus tandem double auto-HCTs, according to the availability of matched siblings. As expected, auto-allo arms experienced increased TRM but a trend towards a better MM control after 3 years. However, there was still no definite improvement in the overall survival.[15-18]

University of Michigan experience on allo-HCT for high-risk multiple myeloma showed a marginal improvement in outcomes, with 1-year and 2-year survival rates of 65% and 35%, respectively. Relapse rates were very high, with 1-year and 2-year progression-free survival rates of 40% and 15% only, respectively. In addition, most surviving patients suffered debilitating chronic graft-versus-host disease.[19,20]

The use of novel targeted biologic agents in primary MM therapy has improved the outcome significantly. In addition, bortezomib has been reported to overcome the poor risk karyotype t(4;14).[21] Nonetheless, recent studies of primary novel targeted biologic agents, followed by HDT/ASCT reported 1-year progression-free survival of ~50% only.[21-23]

2. Immunotherapy for Cancer

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [24]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in malignant tissue and favorable prognosis in various malignancies [25-29]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major 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 Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [30; 31]. The structure of murine PD-1 has been resolved 32]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is 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 (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [30; 33;-35]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [36; 37]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [38; 39]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [40]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [36; 41-43]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [36]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1

has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL)[44]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Similarly, dysfunction of immune surveillance of transformed cells leads to hematologic malignancies.[45,46] Chemotherapy is curative in a small proportion of patients. HDT/ASCT and allo-HCT have a curative potential in only some of these advanced refractory malignancies. In addition, allo-HCT may result in multiple debilitating or fatal complications. Thus, a safer approach of immune therapy is needed.

Passive immunotherapy includes administration of target specific monoclonal antibody e.g. anti-CD20 [rituximab] or tumor-specific effector T cells, while active immunotherapy involves the administration of tumor specific cell-based vaccines. These therapies are effective but of very short duration. The main mechanism of intolerance involves the regulatory elements e.g. immune check points [cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) receptor/PD-1-Ligand (PD-1-L) axes) and myeloid derived suppressor cells (MDSC). Other contributing factors in the case of cell-based therapies are poor access of effector cells to activating cytokines due to presence of competitors of cytokines [cytokine sinks] and the lack of essential “space niche”.[45-48]

3. The PD-1/PD-L1 axis

PD-1 belongs to the B7 family and is a key immune check-point receptor in peripheral tissues.[28] Its ligands are the more common PD-1-L1 (B7-H1) and PD-L2 (B7-DC). It is expressed on antigen-activated T and B cells, which then become immunologically exhausted, resulting in termination of immune response after antigen activation. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1 receptors, which are expressed on the cell surface of activated T-cells under healthy conditions, are to down-regulate unwanted or excessive immune responses, including autoimmune reactions.

PD-1, which is encoded by the gene *PDCD1*), is an Ig superfamily member related to CD28 and CTLA-4 and has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [49; 50]. The structure of murine PD-1 has been resolved [51]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is 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 (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [49; 52-54]. The mechanism by which PD-1 down-regulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [55,56]. PD-1 is expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [57,58]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [59]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [55,60-62]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions

with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [63]. Although healthy organs express no or little PD-L1, a variety of cancers express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [64]. This suggests that the PD-1/PD-L1 axis plays a critical role in tumor immune evasion and is an attractive target for therapeutic intervention.

For T cells, PD1 is a surface inhibitory molecule and is a receptor for its ligands, PD1-L1 and PD1-L2, which are expressed by tumor or virally infected cells.[46-48, 65] Like CTLA-4/ligand interaction, binding of PD-1 and its ligand results in inhibition of T-cell receptor (TCR) signaling and thus down-regulates T cell function (IFN-γ and IL-2 secretion) and survival/proliferation (BLC-XL). In contrast, inhibition of PD-1/PD-1-L axis by either anti-PD-1 or anti-PD1-L1 leads to enhancement of T-cell response in vitro and preclinical anti-tumor activity.[66,67]

4. Clinical Trials Targeting Cancer Immune Check Points

The largest randomized controlled trial of anti-CTLA4 to leverage anti-tumor activity in patients with advanced melanoma revealed objective response but high incidence of 46% severe grade 3/4 adverse reactions in the anti-CTLA4 alone arm.[68]

In contrast, a pilot study of a fully humanized IgG4 anti-PD-1, later known as nivolumab, as a single administration on 39 patients with advanced solid tumor, including non-small cell lung cancers, showed safety and feasibility.[69] There were no serious adverse reactions and most immune reactions were of mild severity. The plasma half-life was 12-20 days after one single infusion, with >70% sustained PD-1 receptor occupancy for >2 months. Lastly, the clinical response was sustained.

The success led to a larger phase 1 study of nivolumab on 296 patients with advanced solid tumor receiving one infusion (0.1 to 10 mg/kg) every 2 weeks for up to 2 years.[70] Nivolumab was well tolerated and MTD was not reached. The median T_{max} was 1-4 hours after the start of infusion. The PK was linear, with a dose proportional increase in the C_{max} and AUC calculated from day 1 to day 14 in the dose range 0.1-10 mg/kg. The median PD-1-receptor occupancy was 64-70% for the dose of 0.1-10 mg/kg every 2 weeks. The incidence of grade 3/4 adverse events was 14%, with 3 deaths from pulmonary toxicity. The cumulative response rate (CR/PR) was 20-25% and 20 of 31 responders had durable response for >1 year. Some had response for >2 years. Common adverse reactions were grade 1 or 2 and mainly immunologic skin events (rash, pruritus, urticaria, vitiligo) and diarrhea.

A more recent second phase 1 study of another anti-PD-1 (lambrolizumab; a humanized IgG4 kappa anti-PD-1 antibody) at a dose of 10 mg/kg IV every 2 or 3 weeks or 2 mg/kg IV every 3 weeks in patients with advanced melanoma for patients who had received prior treatment with the anti-CTLA-4, ipilimumab, and those who had not.[71] Steady-state serum trough concentration was 20% higher in the patients receiving 10 mg/kg every 2 weeks, compared to the same dose every 3 weeks. The serum half-life time of lambrolizumab was 2-3 weeks. Common adverse events were low-grade fatigue rash, pruritus and diarrhea. The overall response rate was 38%, with the highest response rate of 52% in the cohort receiving 10 mg/kg every 2 weeks. The

response was sustained, with a median follow-up time of 11 months. There was no difference in the response rates of those having or not having had received anti-CTLA-4, ipilimumab.

The most recent phase 1 study of combination of anti-PD-1 nivolumab and anti-CTLA-4 ipilimumab has recently been reported.[72] The concurrent regimen for those not having had received ipilimumab consisted of IV doses of both agents in patients with advanced melanoma every 3 weeks for 4 doses followed by anti-PD-1 nivolumab alone every 3 weeks for 4 doses, followed by maintenance combined treatment every 12 weeks for up to 8 doses. The optimal doses being nivolumab at a dose of 1 mg/kg and ipilimumab at a dose of 3 mg/kg resulted in a 53% objective response rate, with all tumor reduction of 80% or more. This study revealed a more rapid and deeper degree of response with the combination of both agents targeting two different immune checkpoints.

A phase 1 study of anti-PD-L1 against the ligand PD-L1 on tumor cells was also performed on 207 patients with advanced solid tumors. [73] The dose ranged from 0.3 to 10 mg/kg every 2 weeks on a 6-week cycle basis up to 16 cycles. This agent was also very well tolerated and MTD was not reached. The grade 3/4 toxicities were only 9%. With a mean follow-up period of 12 weeks (range, 20-111 weeks), the objective response rate was 6-17% and 8 of 16 responders had a durable response (>1 year).

5. Multiple Myeloma Immune Evasion

MM is an incurable malignancy due to its intrinsic chemotherapy- and immunotherapy-refractoriness. In contrast to myeloid malignancies, allogeneic hematopoietic cell transplant and donor lymphocyte infusion have limited role in controlling or cure of MM, implicating the underlying MM-specific immune evasion. The two major possible mechanisms include[74,75]

1) Immunologically hostile microenvironment: MM cells produce multiple cytokines that promote their own survival advantage, angiogenesis and osteoclast activity leading to osteolytic lesions and resultant impaired immune response. These cytokines include TFG-β, IL-10, MUC-1, VEGF, IL-6, Fas/FasL, COX-2 and MMP.
2) Cellular immune defect: Dysfunction of T-cells, NK-cells, NKT-cells, B-cells, dendritic cells.

6. PD-1/PD-L1 axis and T cell Function in MM

A MM mouse model study showed that PD-1 expression on T cells from MM-bearing mice was up-regulated in the tumor site, compared with non-tumor sites [peripheral blood and spleen].[76] PD-1 was expressed on CD8+ and CD4+ T cells and NK cells at the tumor sites. The CD8+ T cells expressing PD-1 showed immunologically exhausting phenotype as evidenced by the impairment of IL-2, TNF-α and IFN-γ secretion and increased Tim3 expression, compared with PD-1 negative CD8+ T cells from tumor site and non-tumor sites. In addition, PD-1 was up-regulated in primary CD4+ and CD8+ T cells collected before HDT/ASCT from bone marrow and peripheral blood of MM patients. The peak of PD-1 expression occurred ~day 30 post transplant in these MM patients.[77]

Blockade of PD-1/PD-L1 axis by anti-PD-L1 against PD-L1 ligands on tumor cells enhanced efficacy of post-transplant cell based vaccine.[49] In another mouse model, it was demonstrated that anti-PD-L1 facilitated sub-ablative radiation in MM killing, which was CD8+ and CD4+ T cell dependent. With a more intensive therapy, anti-PD-L1 synergized with ablative radiation and adoptive T cell transfer.[77]

In a similar way, blockade of this axis by anti-PD1 against PD-1 on T cells was shown to enhance T cell migration *in vitro*.[78] In a mouse model, anti-PD1 increased the efficacy of dendritic cell/myeloma fusion cell vaccine following HDT/ASCT.[79] The T cell response was enhanced ex vivo.[80] In another mouse model, anti-PD1 synergized with low-dose cyclophosphamide on enhancing the effect of vaccine therapy.[81]

7. PD-1/PD-L1 axis and NK cell Function in MM

Clinical observation revealed increasing NK cell dysfunction with the advancing stages of plasma cell neoplasm from MGUS to advanced stage multiple myeloma.[82] Moreover, absolute number of NK cell recovery after HDT/ASCT for patients with MM correlated with PFS and OS.[83-85]

In addition to the general immunologically hostile microenvironment – increased levels of TGF-β, IL-10, IL-6 and PGE_2, which inhibits MM killing abilities by NK cells, specific mechanisms against NK function include 1) direct interference by excessive MM monoclonal immunoglobulin 2) depletion of essential cytokines by secretion of decoy soluble IL-2 receptor and expression of surface IL-15 receptors 3) modulation of NK receptor ligations including loss or down-regulation of membrane MICA, NKG2D and DNAM-1 in advanced MM, increased membrane MHC class I expression and secretion of soluble MHC class I and beta-2-microglobulin 4) down-regulation and loss-of-function mutation of membrane Fas receptors on MM cells and 5) increased expression of PD-1-ligand on MM cells.[82,86]

Pre-clinical data showed that NK cell lines were able to kill clonogenic MM cell lines *in vitro* and *in vivo*.[87] In addition, PD-1 was demonstrated to be up-regulated on primary NK cells from MM patients and MM bearing mice as a the function of MM burden.[88] *In vitro* data revealed that anti-PD-1 enhanced NK cell cytotoxicity against and trafficking towards $PD\text{-}L1^+$ MM cell lines. In addition, anti-PD-1 enhanced immune complex formation between NK and MM cells. Interestingly, lenalidomide was also shown to down-regulate PD-L1 expression on MM cells and this effect was synergistic with NK cytotoxicity against PD-L1+ MM cell lines.[88]

8. Clinical Data on Leveraging NK cell versus MM effect

Two activating lymphokines, IFN-α and IL-2, were investigated in clinical trials. IFN-α was shown to have activity against MM *in vitro*, *ex vivo* and in patients. It was found to mobilize peripheral NK cells into bone marrow, the MM site.[89,90] Two large meta-analyses of these randomized controlled trials revealed a 20% response rate and prolonged PFS and OS.[91,92] Thus, IFN-α has remained a standard option for MM treatment. However, significant adverse events precluded its long-term use. Similar outcomes were seen in studies using IL-2, which increased the number of lymphokine-activated killer [LAK] cells, with modest response rate.[93-96] Unfortunately, IL-2 was associated with more unacceptable toxicities, preventing long-term use.[95-97]

Observation studies of HDT/ASCT for MM reported consistent correlation between early lymphocyte recovery and progression-free survival.[83-85,98,99] The dose of lymphocytes infused, especially the NK cell dose, predicted overall lymphocyte and NK cell recovery, which, in turn, correlated with survival.[85] Day-15 absolute lymphocyte count [ALC] $\geq$500/μL and day-30 ALC $\geq$1000/μL correlated with PFS and OS.[81,82,96,97] More specifically, day-15 absolute NK-cell count $\geq$80/μL correlated with PFS.[100] Mayo Clinic group demonstrated an augmentation of *ex vivo* day-14 primary NK cell cytotoxicity by IL-2 and IFN-α early post HDT/ASCT in patients with MM.[95] Lastly, Meehan *et al* conducted a phase 1/2 study of post-HDT/ASCT immunomodulation of NK cell function in MM patients with IL-2 therapy during lymphopenic state

from day 0 for 4 weeks, in conjunction with GM-CSF. There was a significant increase in the number of $CD3^+$T cells, $CD4^+$Tcells, $CD8^+$T cells and $CD25^+$ and $CD8^+CD56^+T_{reg}$ cells, compared with control.[101] Ex vivo cytotoxicity of peripheral blood mononuclear cell against MM cell lines increased significantly, compared with control.[101]

9. Homeostatic Proliferation of Lymphocytes

Active immunotherapy e.g. adoptive T cell transfer and cell based vaccines have been limited in sustained efficacy due to immune check point and other regulatory components and competition with native immune cells for space niche and essential homeostasis lymphokines.[45-48, 65]

Lympho-depletion state occurring after irradiation or chemotherapy creates a suitable condition for transferred or newly activated lymphocytes to proliferate and be activated due to depletion of competitors for space niche, cytokines (cytokine sinks) and suppressors or regulators.[102-107]

This effect is potentiated by higher intensity ablation and infusion of hematopoietic stem cells. With a higher degree of depletion of competitors or suppressor components, transferred lymphocytes proliferate and become activated more efficiently, with less intensity of antigen and co-stimulatory signals. In addition, infused hematopoietic stem cells provide more effector and precursor cells, which produce or induce other cells to secrete essential cytokines, growth factors and anti-apoptotic factors, nourishing transferred lymphocytes.[108,109] Condomines *et al* demonstrated a nadir of absolute lymphocyte count occurring ~day 3-8 post high-dose melphalan/HSCT in patients with MM and coinciding with the peak of serum IL-6, IL-7 and IL-15 levels.[110]

10. Previous Related Clinical Studies on Lymphoid Malignancies

A phase 2 study of a humanized anti-PD-1 monoclonal antibody, MK-3475 (Pembrolizumab), in 66 patients with diffuse large B-cell lymphoma post-HDT/ASCT.[89] MK-3475 was administered at 1.5 mg/kg every 6 weeks for 3 cycles, starting between 30-90 days post transplant. This intervention was safe and feasible. The 18-month progression free survival was 72% (95%CI; 60-82%) overall and 70% (95% CI; 51-82%) in 24 high-risk patients with PET+ disease prior to transplant. The results were very promising, when compared with historical data. Treatment was associated with increases in circulating lymphocyte subsets including PD-L1+ lymphocytes, suggesting an on-target *in vivo* effect of MK-3475. [111]

A more recent phase 2 study of a combination of MK-3475 and the anti-CD20 rituximab in 32 patients with advanced rituximab-sensitive follicular lymphoma at 3 mg/kg intravenously every 4 weeks for 4 infusions, plus additional 8 optional infusions every 4 weeks for patients with stable disease or better. Rituximab was added on day 17 at 375 mg/m^2 intravenously weekly for 4 weeks. The combination of MK-3475 and rituximab was well tolerated, with no autoimmune or treatment-related adverse events of grade 3 or 4. The most common adverse events of grade 1 were anaemia (14 patients) and fatigue (13 patients), and the most common adverse event of grade 2 was respiratory infection (5 patients). Of the 29 patients evaluable for activity, 19 (66%) achieved an objective response: complete responses were noted in 15 (52%) patients and partial responses in four (14%).[112]

11. Anti-PD-1: MK-3475 (Pembrolizumab)[113]

MK-3475 (previously known as SCH 900475) is a potent and highly selective humanized

monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2 without ADCC or CDC activity.

MK-3475 strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC_{50} (concentration where 50% of the maximum effect is achieved) has been ~0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFN**g**), and levels of other cytokines were modulated by MK-3475. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells. Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy results in increased complete tumor regression rates *in vivo*.

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo 114-119]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

Based on preclinical *in vitro* data, MK-3475 has high affinity and potent receptor blocking activity for PD-1. MK-3475 has an acceptable preclinical safety profile and is being advanced for clinical development as an immunotherapy for advanced malignancies.

Clinical data from PN001 is presented in the report with a visit cut-off date of 26-Jul- 2013. As of 26-Jul-2013, there have been 789 patients treated in PN001 with MK-3475 as a 30-minute IV infusion. Of these 789 patients, preliminary data are presented in this report from 479 patients. Data from 200 patients in Part B3 and 110 patients in Part F that were treated as of the cut-off data were not included in the analyses yet. Based upon this safety database consisting of patients treated up to 10 mg/kg once every two to three weeks, MK-3475 has been generally well-tolerated at doses up to 10 mg/kg every other week without DLTs. One (0.002%) patient assayed to date had samples confirmed positive for ADA, but no impact on safety has been observed. Five other clinical studies (PN002, PN006, PN010, PN011, and PN012) are ongoing however preliminary data analyses are not yet available. For these 5 studies, the number of treated patients indicated in this report is based on a visit cut-off date of 18-Oct-2013 to allow for more mature enrollment data and align with the Development Safety Update Report data cutoff
date. MK-3475 PK results have been obtained from PN001 following the first dose at 1, 3 and 10 mg/kg IV of MK-3475 administered to 17 patients with solid tumors. The observed pharmacokinetic profile of MK-3475 was typical of other IgG mAbs with a half-life (t½) of approximately 2 to 3 weeks. There was no indication of dose dependency of half-life in the 3 dose groups and a dose related increase in exposure was observed from 1 to 10 mg/kg. The long half-life supports a dosing interval of every 2 or 3 weeks. Exposure obtained with sparse sampling

after dosing melanoma and non-small cell lung cancer (NSCLC) patients at 2 and 10 mg/kg, every 2 or 3 weeks, is consistent with this profile. As of 18-Oct-2013, PN002 has randomized 497 patients with metastatic melanoma (495 patients were treated) across 3 treatment groups as follows, MK-3475 2 mg/kg Q3W, MK-3475 10 mg/kg Q3W, and chemotherapy (investigator choice of treatment) in a 1:1:1 ratio. PN006 has randomized 68 IPI-naïve patients with unresectable or metastatic melanoma across the 3 treatment groups: 10 mg/kg Q2W, 10 mg/kg Q3W, and ipilimumab in a 1:1:1 ratio. PN010 has randomized three patients with NSCLC across the 3 treatment groups: 10 mg/kg Q3W, 2 mg/kg Q3W, and docetaxel 75 mg/m2 Q3W in a 1:1:1 ratio. In PN011 10 patients have been treated. In PN012, 109 patients have been treated across the three cohorts as of 18-Oct-2013. Durable objective responses have been reported in patients with melanoma and NSCLC. Adverse events have generally been manageable and infrequently require discontinuation of MK-3475 treatment.

12. Significance

This phase 2 study is embarking on leveraging T and NK cell function after standard high-dose therapy and autologous transplant for multiple myeloma by use of anti-PD-1 to disrupt the PD-1/PD-L-1 immune checkpoint axis. This translational concept is based on the extensive pre-clinical data of this axis specifically in myeloma and the positive clinical outcomes and safety profiles from recent phase I studies of this agent in patients with advanced solid tumors. Timing of treatment during post transplant lympho-penic state is expected to further enhance the effect of anti-PD-1.

Multiple myeloma is a very common hematologic malignancy in the US but remains incurable, even with novel targeted agents and high-dose therapy/autologous transplant. Immunotherapy e.g. allogeneic hematopoietic cell transplant has a curative potential but at the expense of high treatment-related mortality (graft-versus-host disease, infection and other transplant specific events). Thus, the positive outcomes of this safer strategy will definitely be a break through and has great impact on the outcomes of therapy for this common cancer.

4.2 Rationale

4.2.1 Rationale for the Study and Selected Subject Population

1. Immunotherapy is highly potent but very short-lived in clinical setting; thus meaningful clinical benefits are lacking. Reasons include: a) presence of immune checkpoints [CTLA4 and PD-1 receptor/PD-1 ligand axes]; b) presence of other suppressor elements [regulatory T cells (T_{reg}), myeloid derived suppressor cells (MDSC)]; c) presence of competitors for essential activating cytokines for T/NK cells [Cytokine Sinks]; and d) the lack of “space niche”.

2. Patients with MM who do not respond adequately with primary therapy and those with high-risk cytogenetic features have worse treatment outcomes, compared with those who achieve a complete response status, which predicts favorable long-term outcomes. Complete response rate after primary therapy with highly effective targeted agents, followed by HDT/ASCT is disappointingly low (30% only).

3. Early lymphocyte, especially NK cells, and antigen-presenting dendritic cell recovery post-transplant is associated with decreased multiple myeloma relapse.

4. Clinical trials using anti-Cytotoxic T-lymphocyte Antigen-4 [Anti-CTLA4] to leverage T cell function resulted in very promising anti-tumor outcomes but high rate of serious autoimmunity.

5. Preclinical studies showed increased PD-1 expression on $CD8^+$ and $CD4^+$ T cells and NK cells at the multiple myeloma sites and their function was impaired. Disruption of the PD-1/PD-L1 axis restored their cytotoxicity against and trafficking towards multiple myeloma. Lastly, in a mouse model, anti-PD1 increased the efficacy of dendritic cell/myeloma fusion cell vaccine following HDT/ASCT and synergized with low-dose cyclophosphamide on enhancing the effect of vaccine therapy.

6. PD-1 was expressed on primary T and NK cells from multiple myeloma patients. In addition, PD-1 was expressed on primary CD4+ and CD8+ T cells collected before and after HDT/ASCT from bone marrow and peripheral blood of MM patients. The time peak of PD-1 expression occurred ~day 30 post-transplant in these MM patients.

7. Phase 1 studies of fully humanized IgG4 anti-PD-1 in advanced cancers showed its feasibility and safety for use in human, with a sustained anti-tumor activity and a more favorable adverse reaction profile, and pharmacokinetics and -dynamics profiles.

8. Post high-dose chemotherapy lympho-depletion state is devoid of suppressor T_{reg} or MDSC and competitors for enriching cytokines, with more available space niches.

9. In addition, transfer of hematopoietic stem cells and T cells with autologous transplant augments the above effects of lympho-depletion to T cell/immune recovery.

10. Based on the above evidence, administration of anti-PD-1 to unleash and augment T and NK cell function during lymphopenic state early post HDT/ASCT when PD-1 expression on effector cells peaks and myeloma tumor burden nadirs may result in a maximal synergy on the cytotoxicity to multiple myeloma. This may then result in the improvement of multiple myeloma relapse post transplant and overall transplant outcomes.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (98). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The dose regimen of 200 mg Q3W of MK-3475 is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, non-small cell lung cancer (NSCLC), and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving MK-3475 at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive MK-3475 at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to MK-3475 to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient

covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumor types and indication settings.

Based on the PK/PD data, and the time peak of PD-1 expression on primary T-cells at day 30 post-transplant in MM patients,[40] we will study anti-PD-1 at a fixed dose of 200 mg MK-3475 intravenously every 3 weeks (+/-4 days), starting on day +14 or later after an engraftment until ~day 182 post-transplant for a total of 9 doses. [See Schema]

4.2.3 Rationale for Endpoints

See Section 5.10 and Appendix 13.3 for the definition of Endpoints.

4.2.3.1 Efficacy Endpoints

We expect that the addition of anti-PD1 during lymphopenic state after high dose therapy and autologous transplant will augment immune reaction against multiple myeloma and increase complete response (CR) conversion rate at day 180.

Primary Efficacy Endpoint: CR rate at day 180

Secondary Efficacy Endpoints

- CR rate at day 100
- Flow based minimal residual disease (MRD) rate at day 100 and day 180
- Progression-free survival at 2 years
- Overall survival at 2 years
- Compliance with treatment:
    - Median Number of doses administered
    - Dose de-escalation requirements

4.2.3.2 Safety Endpoints

- Regimen-related toxicities (RRT) according to CTCAE v4
- Engraftment
- Treatment-related mortality (TRM)
- Late adverse reactions especially autoimmune disorders

4.2.3.3 Biomarker Research

1) Measurement of immune cell phenotypes in autologous graft tissue pre-transplant

2) Quantification of immune recovery: Quantification of activated and effector $CD4^+$ and $CD8^+$ cells, NK cells, and regulatory T and B cells.
3) Functional T cell subtypes and cytokine profiles: Intracellular IFN-α, IFN-γ, cytokine release spectrum, T_H subset transcription factor profiling
4) NK cell cytotoxicity: Intracellular granzyme B, tumor cell death
5) PD-1-ligand expression on MM cells pre-transplant

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

1. Subjects with multiple myeloma (MM) of <u>any stage</u> and of <u>any cytogenetic risk</u> per International Multiple Myeloma Working Group Criteria (Appendix 13.2).

   Pathology review by Pathology Department of each institution is mandatory.

2. Has no progressive disease (PD; Appendix 13.3) after initial primary therapy

   AND

   Has either of the following suboptimal response with primary therapy

   2.1 <u>Very good partial response (VGPR) or less (Appendix 13.3) after at least 2 cycles of a triple regimen</u>**:**

   An *IMiDs, a proteasome inhibitor and a systemic steroid **OR**

   A conventional chemotherapy, a proteasome inhibitor and a systemic steroid **OR**

   An equivalent triple regimen at the investigator discretion

*IMiDs consists of thalidomide, lenalidomide, pomalidomide and other related –lidomides.

   2.2 <u>VGPR or less after at least 4 cycles of a double regimen</u>:

   An IMiDs and a systemic steroid **OR**

   A proteasome inhibitor and a systemic steroid **OR**

   An equivalent double regimen at the investigator discretion

5.1.2 Subject Inclusion Criteria

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

3. Be $\geq$ 18 years and $\leq$75 of age on day of signing informed consent.

4. Had measurable disease of MM **at diagnosis**, defined as:

    - A monoclonal immunoglobulin spike on serum electrophoresis of at least 0.5 g/dL **and/or**
    - Urine monoclonal protein levels of at least 200 mg/24 hours

    - For subjects without measurable serum or urine M-protein levels, an abnormal free light chain ratio (normal value: 0.26-1.65) with involved FLC level ≥10 mg/dL (≥100 mg/L).

      "Measurable disease" is NOT required at the time of enrollment. See "required MM status at enrollment" in 5.1.1 #2. Final determination of measurable disease requirement is at PI's discretion.

5. Has no other hematopoietic stem cell transplant of any type prior to the current planned autologous hematopoietic cell transplant.

6. Has a performance status of 0 or 1 on the ECOG Performance Scale. (≥70% Karnofsky Performance Score) (Appendix 13.1).

7. Demonstrate adequate organ function per institutional guidelines for high-dose melphalan and autologous transplant at the time of enrollment. See separate laboratory criteria to initiate MK-3475 at day +14 post transplant (Table 1) which are not required at enrollment.

8. Has had a successful peripheral blood stem cell collection with G-CSF (Filgrastim) +/- Plerixafor (Mozobil) only. The target cell dose is ≥2.0 $x10^6$ CD34+ cells/kg.

9. Be willing and able to provide written informed consent/assent for the study.

10. Female subject of childbearing potential should have a negative urine or serum pregnancy per institutional guidelines for high-dose melphalan and autologous transplant. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

11. Female subjects of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study starting with the first dose of MK-3475 through 120 days after the last dose of MK-3475 (Section 5.5.4). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >2 year (Section 5.5.4).

12. Male subjects must agree to use an adequate method of contraception starting with the first dose of MK-3475 through 120 days after the last dose of MK-3475 (Section 5.5.4).

13. Subject is able to swallow capsules and is able to take or tolerate oral medications on a continuous basis.

5.1.3 Subject Exclusion Criteria

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

1. Has any type of amyloidosis, hyperviscosity, plasma cell leukemia, POEMS syndrome, Waldenström's macroglobulinemia, non-secretory multiple myeloma or **IgM myeloma**.
2. Has known clinically active CNS involvement OR history of resolved CNS involvement by multiple myeloma.
3. Has an active autoimmune disease or a documented history of autoimmune disease, or an autoimmune syndrome that requires systemic steroids or immunosuppressive agents.

   Note: Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would NOT be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will NOT be excluded from the trial.

4. Has a history of non-infectious pneumonitis that required steroids or current pneumonitis.
5. Has evidence of interstitial lung disease.
6. Has a diagnosis of immunosuppressive disorder OR is on any other form of immunosuppressive therapy within 7 days prior to transplant admission.
7. Is currently participating in or has participated in any study of an investigational agent or using an investigational device within 4 weeks of transplant admission.
8. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
9. Has had prior monoclonal antibody, chemotherapy (including dexamethasone for MM treatment), targeted small molecule therapy, or radiation therapy within 2 weeks prior to transplant admission (or ~4 weeks prior to the first dose of MK-3475).

   OR

   Has not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent more than 2 weeks prior to transplant admission or more than 4 weeks prior to the first dose of MK-3475.

   Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

   Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to transplant admission.

   Note: Toxicity that has not recovered to ≤ Grade 1 is allowed if it meets the requirements per institutional guidelines for high-dose melphalan and autologous transplant.

10. Has been free of additional malignancy for at least 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

11. Has an active infection requiring systemic therapy or history of repeated infections.
12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the pre-screening or screening visit through 120 days after the last dose of MK-3475 (Section 5.5.4).
14. Has a known Human Immunodeficiency Virus (HIV), Hepatitis B (HBV), or Hepatitis C (HCV) infection.
15. Has a clinically significant coagulopathy per investigator's assessment.
16. Has known symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.
17. Has received any type of hematopoietic cell transplant except for the current planned high dose melphalan and autologous stem cell transplant.
18. Has received a live vaccine within 30 days prior to transplant admission.
19. Is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this study, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

5.2 Inclusion Criteria to initiate on the first dose of MK-3475 on day 14

The subject must demonstrate adequate organ function as defined in Table 1 prior to receiving the first dose of MK-3475 on day+14 (+/-4) post transplant. All labs should be performed within 3 days of MK-3475 treatment initiation.

Table 1: Required Organ Function Laboratory Values Prior to the first MK-3475 Initiation only

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /μL
Platelets	≥20,000 / μL
Hemoglobin	≥8 g/dL
Renal	
Serum creatinine **OR** Measured or calculated[1] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total

	bilirubin levels > 1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[1] Creatinine clearance should be calculated per institutional standard.	

Note: These criteria in Table 1 are not required or applicable to 8 subsequent doses of MK-3475. Refer to 5.3.4.7 (Event of Clinical Interest (ECI) and immune-related Adverse Event (irAE)) and 5.3.4.8 (Dose Modification) for management of 8 subsequent doses.

Subject Screening and Registration Procedure

Subject registration for this study will be centrally managed by the Oncology Clinical Trials Support Unit (O-CTSU) of The University of Michigan Comprehensive Cancer Center as described below:

A potential study subject who has been screened for the study and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log provided by the O-CTSU.

It is the responsibility of the local site investigator to determine subject eligibility prior to submitting subject registration request to the O-CTSU. After subject eligibility has been determined, a copy of the **completed** Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the O-CTSU, by email to CTSU-Oncology-Multisite@med.umich.edu.

A Multi-Site Coordinator (MSC) of the CTSU, who acts as the registrar, will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

An email will be sent by the registrar to the requesting site registrar to confirm patient registration and to provide the study identification number that has been assigned to the patient. In addition,

a copy of the completed Section of the Eligibility Worksheet signed and dated by the registrar, will be returned to the requesting site registrar.

Subjects found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These subjects will not have study identification number assigned to them, and will not receive study treatment.

Pre-study Documentation Requirements

Informed consent, eligibility checklist and registration forms **shall be** obtained before subjects can receive the first study treatment of MK-3475 (pembrolizumab).

Informed consent, eligibility checklist and registration forms **should be** obtained before "transplantation". Failure to complete the registration before transplantation may be allowed at the discretion of the PI and will not be considered a protocol deviation or violation.

Of note, conditioning chemotherapy (melphalan), autologous hematopoietic cell transplantation and lenalidomide maintenance therapy are standard treatments (see 5.3).

5.3 TREATMENTS

5.3.1 Standard Multiple Myeloma Treatment

5.3.1.1 High-dose Melphalan and Autologous Stem Cell Transplantation

1. High-dose melphalan 140-200 mg/m^2 (<200 mg/m^2 for subjects aged >70 years)

2. The procedure protocol of high-dose melphalan and autologous stem cell transplant follows Institutional Guidelines. The target cell dose is ≥2.0 x10^6 CD34+ cells/kg.

3. Use of filgrastim (Neupogen®) to facilitate engraftment is allowed per Institutional Guidelines

5.3.1.2 Maintenance Treatment

Lenalidomide 5-15 mg/day to start on day 45-90 post-transplant per standard multiple myeloma management as tolerated until multiple myeloma progression.

Venous thromboembolism prevention and contraception required during lenalidomide maintenance treatment will follow standard of care or Institution Guidelines. Of note, warfarin is not allowed (see Section 5.4.2).

Failure to follow the standard multiple myeloma treatment procedures due to appropriate medical indications may not be considered a protocol deviation or violation at the PI's discretion.

5.3.2 Study Treatment with MK-3475 (Pembrolizumab)

A fixed MK-3475 dose of 200 mg/day will be administered as a 30-minute intravenous (IV) infusion every 3 weeks, starting ~day +14 post-transplant (Schema). Dose days are 4 days flexible (+/- 4 days).

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 and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Treatment Schema

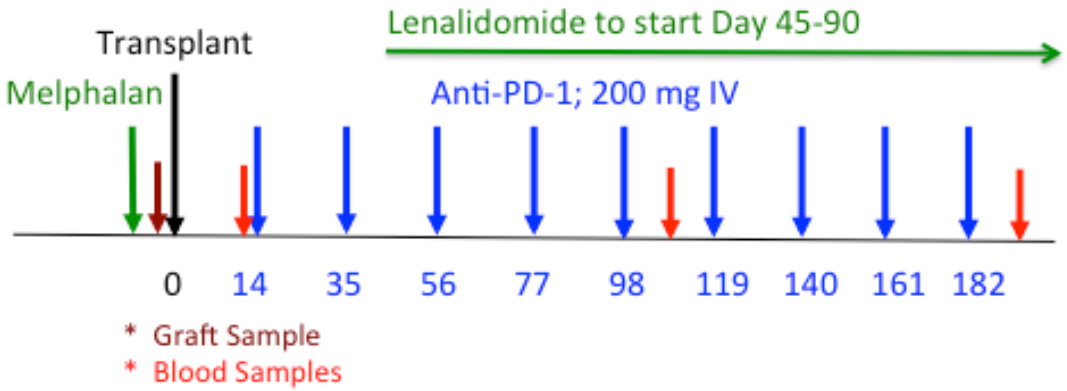


Table 2: Study Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3475 (Pembrolizumab)	200 mg	Every 3 weeks (+/- 4 days)	IV infusion	Starting day +14 for a total of 9 doses	Experimental
The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.3.4.8 (Table 4 and 5)					

Premedication per institutional guidelines for monoclonal antibodies (e.g. acetaminophen and antihistamine) is allowed. Steroid premedication is not indicated and should be avoided.

5.3.3 Standard Transplantation Drugs

1. Melphalan [Evomela, Alkeran]

Formulation: Melphalan (L-phenylanine mustard) is a bifunctional alkylating agent. It forms covalent linkages with susceptible cellular proteins. It induces formation of DNA interstrand and DNA protein cross-links. Alkeran: IV administration of melphalan revealed rapid elimination from plasma with terminal half-life of 1.8 hours. 13% is excreted in the urine. It is rapidly distributed in total body water and eliminated in a biphasic manner. IP administration of 20-30 mg/M2 revealed a peak concentration in the peritoneal cavity of 6.4 ± 2.4 µg/ml and half-life of 85 ± 30 minutes. The peak plasma concentration was 1.22 µg/ml, and half-life was 86 ± 31 minutes. Evomela: IV administration has a comparable PK profile to conventional IV melphalan (Alkeran).

Availability: Alkeran: The drug is available as an injectable kit. This kit contains an ampule of 100 mg (equivalent) melphalan, a 1 ml ampule of acid- alcohol diluent (containing 0.047 ml 37%

HCl, q.s. to 1 ml with alcohol) and a 9 ml ampule of final diluent containing dipotassium phosphate, 108 mg propylene glycol 5.4 ml sterile water for injection q.s. 9.0 ml. Evomela: The drug is available as a lyophilized powder in a single-dose vial for intravenous use. Each vial contains 50 mg melphalan free base equivalent to 56 mg melphalan hydrochloride and 2700 mg Betatex Sulfobutyl Ether Sodium. The Alkeran kits and Evomela vials should be stored at room temperature and projected from light.

Administration: Alkeran: The 100 mg injectable formulation is put into solution initially with the addition of 1 m acid-alcohol diluent. When dissolution is complete, the 9 ml final diluent is added. This final solution has a pH of > 7 and should be used promptly. According to the manufacturer (8.5% hydrolysis 24 hours after mixing) a further dilution in D5W is also reportedly stable for 24 hours. Evomela: Each 50 mg vial is reconstituted with 8.6 mL of normal saline solution (0.9% Sodium Chloride Injection, USP) to make a 50 mg/10 mL (5 mg/mL) nominal concentration of melphalan. The reconstituted Evomela drug product is stable for: 24 hours at refrigerated temperature (5^{o}C) without any precipitation due to the high solubility, and for 1 hour at room temperature. Add the required volume of Evomela to the appropriate volume of 0.9% Sodium Chloride Injection, USP to a final concentration of 0.45 mg/mL. The Evomela admixture solution is stable for 4 hours at room temperature in addition to the 1 hour following reconstitution.

Potential and Expected Toxicities: Human Toxicology: Melphalan's major systemic toxicity is bone marrow depression with secondary anemia, leukopenia and thrombocytopenia, usually occurring within three to five weeks of the onset of therapy and lasting four to eight weeks. These effects are exacerbated by prior chemotherapy or radiotherapy. Other adverse reactions include nausea, vomiting, diarrhea, stomatitis, esophagitis, colitis, increases in liver function and kidney function tests, renal/bladder necrosis, pulmonary fibrosis, respiratory distress, peripheral neuropathy, paresthesia, alopecia, fever and hypersensitivity including edema, rash and anaphylaxis. At high doses, supraventricular arrhythmias, including atrial fibrillation, may occur. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

2. FILGRASTIM (r-metHuG-CSF, NEUPOGEN®)

Formulation: Filgrastim, (recombinant human granulocyte-colony stimulating factor, r-metHuG-CSF), is a protein produced by E. coli into which has been inserted the human granulocyte colony-stimulating factor gene. Filgrastim differs from the natural protein in that the N-terminal amino acid is a methionine and it is not o- glycosylated. G-CSF functions as a hematopoietic growth hormone; it increases the proliferation, differentiation, maturation and release of precursor cells into mature blood cells of the neutrophil lineage. G-CSF has demonstrated in vitro effects on mature neutrophils, including an increased expression of chemotactic receptors, enhanced phagocytosis and intracellular killing of certain organisms, as well as enhanced killing of target cells that are bound by antibodies.
Approximately 6,400 patients in U.S. and international based trials have participated in clinical trials of filgrastim to date, and the worldwide commercial populations receiving filgrastim totaled approximately 190,000. The drug has been found to be well tolerated at dosages up to 69 µg/kg/day given IV or SC, with no toxic effects attributable to filgrastim. A maximum tolerated dose has not yet been determined.

Availability: Recombinant G-CSF, filgrastim, NEUPOGEN®, is supplied as a clear, colorless preservative-free liquid for parenteral administration. Single use vials contain filgrastim 300 µg/ml in a preservative-free solution with 0.59 mg/ml acetate, 50 mg/ml sorbitol, 0.004% Tween® 80, 0.035 mg/ml sodium, and water for injection, USP, pH 4.0 to make 1 ml filgrastim Neupogen® is

commercially available in 2 vial sizes: 300 µcg/1 ml and 480 µg/1.6 ml. Dilution: If required, filgrastim may be diluted in 5% dextrose. Filgrastim diluted to concentrations between 5 and 15 µg/ml should be protected from adsorption to plastic materials by addition of albumin (Human) to a final concentration of 2 mg/ml. When diluted in 5% dextrose or 5% dextrose plus albumin (Human), filgrastim is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Dilution of filgrastim to a final concentration of less than 5 µg/ml is not recommended at any time. Do not dilute with saline at any time; product may precipitate. Storage and Stability: Filgrastim should be stored in the refrigerator at 2 - 8°C (36 - 46°F). Avoid shaking. Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours Any vial left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulates or discoloration are observed, the container should not be used.

Administration: Filgrastim is administered as a single daily injection by SC bolus injection, by short IV infusion (15 - 30 minutes), or by continuous SC or continuous IV infusion.

Potential and Expected Toxicities: The most frequently reported adverse effect was medullary bone pain, occurring in 20 - 25% of patients in Phase II and III trials. When bone pain was reported it often preceded a rise in the circulating neutrophil count; it occurred more frequently in patients treated with 20 - 100 µg/kg/day of intravenously administered filgrastim and less often in lower subcutaneous doses. The pain was generally mild to moderate in severity, and usually controlled with non-narcotic analgesics such as acetaminophen. Other side effects include transient but reversible increases of alkaline phosphatase, lactate dehydrogenase and uric acid levels. These occurred in 27-58% of patients, without clinical sequelae observed. Elevations of leukocyte alkaline phosphatase levels have also been noted but the significance is not yet known. Less frequently reported adverse events related to filgrastim administration include subclinical splenomegaly, exacerbation of pre-existing skin rashes, alopecia, and thrombocytopenia, and cutaneous vasculitis. Rarely, allergic-type reactions have occurred. Since the commercial introduction of filgrastim there have been reports (< 1 in 4,000 patients) of symptoms suggestive of an allergic-type reaction, but in which an immune component has not been demonstrated. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (rash, urticaria, edema), respiratory (wheezing, dypsnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first thirty minutes after administration and appeared to occur more frequently in those patients who received filgrastim intravenously. Rapid resolution of symptoms occurred in most cases after administration of standard supportive care, and symptoms recurred in more than half the patients when rechallenged.

3. LENALIDOMIDE (REVLIMID®)

Formulation: A thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2H-isoindol-2-yl) piperidine-2,6-dione and the gram molecular weight is 259.3. The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of proinflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro. Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration

(Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Availability: Lenalidomide (REVLIMID®) is available in 5, 10, 15 and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink. Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

Administration: Lenalidomide (REVLIMID®) is administered as an oral route, preferably at the same time.

Potential and Expected Toxicities: Hematologic: anemia, neutropenia, leucopenia, lymphopenia and thrombocytopenia; thromboembolic events (deep vein thrombosis and pulmonary embolism). Neurologic: Somnolence, dizziness, headache, confusion, tremor, loss of co-ordination, asthenia, paresthesia, numbness, and leukoencephalopathy (radiographic findings). Gastrointestinal: Constipation, dehydration, dry mouth, diarrhea, dyspepsia, nausea, vomiting and stomatitis. Constitutional: Weakness, insomnia, rigors, chills, sweating, weight loss and fever. Reproductive: teratogenicity and miscarriage. Musculoskeletal: arthralgia, back/neck pain, joint pain, muscle cramp and weakness. Cardiac: hypotension. Dermatologic: rash, dry skin, itching. Endocrine: hypothyroidism. Infection. Pulmonary: cough, dyspnea. Metabolic: hypokalemia, liver damage. Renal: increased creatinine, renal failure.

Note: Pregnancy reporting: Due to its structural similarities to thalidomide, a known human teratogen**, lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant.** When there is no alternative, females of childbearing potential may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (e.g., IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with REVLIMID® (lenalidomide), during therapy with REVLIMID® (lenalidomide), during therapy delay, and continuing for 4 weeks following discontinuation of REVLIMID® (lenalidomide) therapy. If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.

Note: Deep Venous Thrombosis and Pulmonary Embolism: lenalidomide has demonstrated a significantly increased risk of DVT and PE in patients with multiple myeloma who were treated with **REVLIMID® (lenalidomide) combination therapy.** Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to

seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

5.3.4 Study Drug: MK-3475 (Pembrolizumab)

5.3.4.1 Description

MK-3475 is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, MK-3475 has high affinity and potent receptor blocking activity for PD-1.
MK-3475 has an acceptable preclinical safety profile.

MK-3475 is a humanized anti-PD-1 mAb of the IgG4/kappa isotype with a stabilizing S228P sequence alteration in the fragment crystallizable (Fc) region. MK-3475 binds to human PD-1 and blocks the interaction between PD-1 and its ligands. The theoretical molecular weight of the polypeptide is 146,288 Da and its theoretical pI is 7.5. The parental murine anti-human PD-1 antibody (hPD-1.09A) was produced by immunizing mice with hPD-1 DNA. The MK-3475 antibody was generated by humanization of the parental antibody by the Medical Research Council (Cambridge, UK) using complementarily-determining region (CDR) grafting technology (U.S. Patent No. 5,225,539). The gene segments encoding the variable heavy and light chains of MK- 3475, as well as human IgG4, were codon-optimized, synthesized, and ligated into a vector.

A single expression plasmid, pAPD11V1-GA was constructed for the expression of both the heavy and light antibody chains of MK-3475. The nucleotide sequences encoding the heavy and light chains, along with their respective promoters and poly A signal sequences have been confirmed by DNA sequence analysis. The pAPD11V1-GAexpression vector was subsequently used to transfect CHO-DXB-11 cells for the development of the MK-3475-producing cell line.

5.3.4.2 Formulation

MK-3475 Solution will be used. Refer to the Investigator Brochure (IB).

5.3.4.3 Storage

MK-3475 Solution is stored under refrigerated conditions (2°C - 8°C). Refer to the IB.

5.3.4.4 Administration

MK-3475 is administered as a 30-minute IV infusion. Refer to the IB.

5.3.4.5 Dose Selection

Dose Selection Rationale

The dose regimen of 200 mg Q3W of MK-3475 is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related

SAEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to MK-3475 to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumor types and indication settings.

The treatment to be used in this study is outlined below in **Table 2**.

Table 2: Study Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3475 (Pembrolizumab)	200 mg	Every 3 weeks (+/- 4 days)	IV infusion	Starting day +14 for a total of 9 doses	Experimental
The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.3.4.8 (Table 4 and 5)					

A fixed dose of 200 mg/day will be administered as a 30 minute IV infusion every 3 weeks. 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 and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Premedication per institutional guidelines for monoclonal antibodies (e.g. acetaminophen and antihistamine) is allowed. Steroid premedication is not indicated and should be avoided.

5.3.4.6 Timing of Dose Administration

MK-3475 will be started on "day +14 post-transplant" AND "after all assessments prior to the first dose of MK-3475" have been completed as detailed in Table 1 and the Study Flow Chart (Section 6.0).

The criteria to initiate the first dose of MK-3475 on day 14 in Table 1 are NOT required or applicable to 8 subsequent doses of MK-3475. Refer to the Study Flow Chart (Section 6.0), Section **5.3.4.7** (Event of Clinical Interest (ECI) and immune-related Adverse Event (irAE)) and Section **5.3.4.8** (Dose Modification) for required assessments prior to and managements of 8 subsequent doses of MK-3475, respectively.

MK-3475 may be administered up to +/- 4 days of each dose of MK-3475 due to clinical and administrative reasons.

MK-3475 will be administered on an outpatient basis, but may be administered during transplant admission as appropriate.

5.3.4.7 Event of Clinical Interest (ECI) and immune-related Adverse Event (irAE)

An ECI is defined as an immune-related adverse event (irAE) that is considered MK-3475 related, after other causes are excluded.

An irAE is defined as a clinically significant AE of any organ system that is associated with MK-3475 exposure and is consistent with an immune-related mechanism. irAEs were reported in 21.4% of melanoma patients; most of these events (15.8%) were considered drug-related by the investigator. The most commonly reported irAEs across the dose schedules are rash (3.2%), pruritus (2.9%), vitiligo (2.9%), hypothyroidism (2.7%), arthralgia (2.2%), diarrhea (2.2%), and pneumonitis (1.9%). The organ most frequently affected by irAEs with MK-3475 is the skin. Less frequently affected tissues include thyroid gland, colon, lung, kidney, and liver. Severe but rare irAEs include Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) and immune-mediated myocarditis.

ECI/irAEs can be categorized according to organ systems or syndromes (see the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document").

ECI/irAEs must be reported to Merck according to the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document" within a specified time period (e.g. within 24 hours according to the Document Version most updated. See Section 7.2.3.2 for reporting procedure.

5.3.4.8 Dose Modification

For **immune-related AEs**, including immune-related hematologic AEs (e.g. autoimmune hemolytic anemia, immune thrombocytopenic purpura etc.), dose modification and management will follow the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document".

For **non-immune-related hematological AEs** (e.g. neutropenia, thrombocytopenia etc.) dose modification and management will follow Table 4 below. Determination of immune related versus non-immune-related etiology is at the investigator's discretion.

For **SJS, TEN and immune-mediated myocarditis**, see the Investigator Brochure for management.

Recommendations to managing irAEs and any AEs not detailed in the Manual are provided in Table 5. (5.5.2)

For subjects who are receiving maintenance treatment, lenalidomide will be withheld before or at the same time of MK-3475 withhold at the investigator's discretion. Determination of cause-effect relationship of AEs (lenalidomide versus MK-3475) is at investigator's discretion.

Table 4: Dose Modification Guidelines for Non-Immune-Related Hematological Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with PI)
Non-immune-related Hematological Toxicity (e.g. neutropenia, thrombocytopenia, etc.)	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week.	Toxicity does not resolve within 4 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The investigator/Institution should discuss any questions regarding this with the Merck. 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 study therapy or vaccination schedule requires the mutual agreement of the Investigator, Merck, and the subject.

5.4.1 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 BMT community standards of medical care. All concomitant medication will be captured in patient medical record including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. Only the concomitant medications taken during any SAEs or ECI/ irAEs will be recorded on the **Case Report Form (CRF).**

All concomitant medications received within 28 days before the first dose of MK-3475 (or ~14 days prior to transplant) and 30 days after the last dose of MK-3475 should be captured in patient medical record.

Glucocorticoid up to an equivalent dose of prednisolone 30 mg/day for 5 days is allowed for the treatment of engraftment syndrome. See glucocorticoid dosing for suspected acute infusion reactions (see 5.5.1 and the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document)) and immune-related adverse reactions (see 5.5.2, 5.5.3 and the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document).

As stated above, any treatments, including systemic glucocorticoid, which the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the BMT community standards of medical care.

Thus, inevitable systemic corticosteroid treatment for a subject's welfare is NOT considered a protocol violation or deviation.

5.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies not specified in the study protocol during the Study Treatment Period:

- Anti-multiple myeloma systemic chemotherapy or biological agents not specified in this protocol:

  IMiDs (lenalidomide other than maintenance therapy specified in this protocol, thalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib) and other new related targeted biologic agents.

- Glucocorticoids for any purpose should be avoided.

  EXCEPT for the following conditions:
  - Engraftment syndrome as specified in this protocol
  - Acute infusion reactions as specified in Section 5.5.1
  - Event of clinical interest / immune-related adverse events (ECI / irAEs) as specified in Section 5.5.2 and Section 5.5.3
  - Adrenal insufficiency supplement with physiologic glucocorticoid dose at an investigator's discretion

  However, as stated above, any treatments, including systemic glucocorticoid, which the investigator considers necessary for a subject's welfare may be administered at the discretion

of the investigator in keeping with the BMT community standards of medical care. Thus, inevitable systemic corticosteroid treatment for a subject's welfare is NOT considered a protocol violation or deviation.

- Sargramostin (Granulocyte/Macrophage-Colony Stimulating Factor: GM-CSF)
- Warfarin
- Immunotherapy not specified in this protocol
- Any chemotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Radiation therapy

  Radiation therapy to a symptomatic solitary lesion may be allowed after consultation with Investigator/Institution. Disease progression must be investigated accordingly.

- 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

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

The Exclusion Criteria describes other medications that are prohibited in this study.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5 Rescue Medications & Supportive Care

5.5.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator, including but not limited to, the common items outlined below:

1. Diarrhea:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

In symptomatic subjects, standard post-transplant workup e.g. infectious etiologies must be performed, and if symptoms are persistent and/or severe, endoscopic evaluation should be

considered before the diagnosis of MK-3475-related immunologic reaction is made. Information on how to identify and evaluate irAEs has been developed and is included in "the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document" located in the Administrative Binder.

All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be replaced via IV infusion.

2. **Nausea/vomiting**:
Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

3. Infections:
Subjects with a documented or suspicious infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

4. Immune-related adverse events:
See Section 5.5.2 and the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document in the administrative binder regarding diagnosis, report and management of adverse experiences of a potential immunologic etiology.

5. Acute Infusion Reactions:
Acute infusion reactions, which may include cytokine release syndrome, angioedema and anaphylaxis, are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs.

Signs and symptoms usually develop during or shortly after MK-3475 infusion and generally resolve completely within 24 hours of completion of infusion.

Signs/symptoms of acute infusion reactions may include:
- Allergic reaction/hypersensitivity (including drug fever), rigors/chills, pruritus/itching, myalgia, urticaria (hives, welts, wheals)
- Arthralgia (joint pain), fatigue (asthenia, lethargy, malaise)
- Rash/desquamation
- Bronchospasm; Cough; Dyspnea (shortness of breath)
- Dizziness
- Headache
- Hypertension, hypotension, tachycardia
- Nausea/ vomiting
- Sweating (diaphoresis)
- Tumor pain (onset or exacerbation of tumor pain due to treatment)

See the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document for diagnosis, report and management of acute infusion reactions.

5.5.2 Supportive Care Guidelines for Events of Clinical Interest (ECI) and Immune-related Adverse Events (irAEs)

An Event of clinical interest (ECI) of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with MK-3475 exposure and is consistent with an immune phenomenon.

irAEs may be predicted based on the nature of the MK-3475 compound, its mechanism of action, and reported experience with other immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs.

An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document located in the Administrative Binder.

Subjects who develop a Grade 2 or higher irAE should be discussed immediately with Investigator/Institution and Merck.

**For subjects who are receiving maintenance treatment, lenalidomide will be withheld before or at the same time of MK-3475 withhold at the investigator's discretion. Determination of cause-effect relationship of AEs (lenalidomide versus MK-3475) is at investigator's discretion.

Recommendations to managing irAEs not detailed elsewhere in the protocol or the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document are detailed in Table 5.

Table 5: General Approach to Handling irAEs and any AEs NOT specified in the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document"

irAE	Withhold/Discontinue	Managements
Grade 1	No action	Provide symptomatic treatment.
Grade 2	Withhold until resolving to Grade 1.	Consider systemic corticosteroids as per Grade 3, irAEs in addition to appropriate symptomatic treatment. May increase dosing interval by 1 week (every 4 weeks) after resolving to Grade 1 or less.

Grade 3	Withhold until resolving to Grade 1. Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. Prednisone 1-2 mg/kg/day or equivalent Add anti-inflammatory e.g. infliximab, if not improving in 48-72 hours. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. May increase dosing interval by 1 week (every 4 weeks) after resolving to Grade 1 or less.
Grade 4	Discontinue permanently	Systemic corticosteroids are indicated Methylprednisolone 125 mg IV or prednisone 1-2 mg/kg/day or equivalent, then follow the ECI Guidance Document. Add anti-inflammatory e.g. infliximab, if not improving in 48-72 hours.

5.5.3 Management Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving MK-3475 and have an evaluation. The evaluation may include bronchoscopy with bronchoalveolar lavage to rule out other causes such as infection. Management, report and dose modification will follow the Manual "Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document"..

**For subjects who are receiving maintenance treatment, lenalidomide will be withheld before or at the same time of MK-3475 withhold at the investigator's discretion. Determination of cause-effect relationship of AEs (lenalidomide versus MK-3475) is at investigator's discretion

5.5.4 Diet/Activity/Other Considerations

1. Diet

Subjects should maintain a diet according to institutional guidelines for autologous transplant, unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

2. Contraception

In general, pregnancy is a contraindication for receiving high-dose melphalan and autologous transplant; however, becoming pregnant after transplant is not impossible in the first 6-12 months post-transplant.

MK-3475 may have adverse effects on a fetus *in utero*. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm.

Non-pregnant, non-breast-feeding women of child-bearing potential may be enrolled 1) if they are willing to use 2 methods of birth control until 120 days after the planned last dose of MK-3475 or 2) if they are considered highly unlikely to conceive.

Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) not heterosexually active for the duration of the study.

Subjects should start using birth control from study visit 1 (first dose of MK-3475 treatment) throughout the study period up to 120 days after the last dose of MK-3475 therapy.

The two birth control methods can be either

1) two barrier methods or
2) a barrier method plus a hormonal method to prevent pregnancy

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide.

Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking MK-3475 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 **must** adhere to the contraception requirement as described above for the duration of the study and during the follow-up period defined in the section 7.2.2 – "Reporting of Pregnancy and Lactation to the Investigator/Institution and to Merck". If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Subjects receiving standard lenalidomide maintenance therapy must strictly follow contraception requirement per lenalidomide program as a standard of care.

3. Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475, the subject will immediately be removed from the study. 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 Investigator/Institution and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., 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 Investigator/Institution and to Merck.

If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Investigator/Institution and to Merck and followed as described above and in Section 7.2.2.

4. Use in Nursing Women

It is unknown whether MK-3475 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 breast-feeding are not eligible for enrollment.

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be removed from the study at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4.

Subjects who complete 9 doses of MK-3475 will be considered having completed the study treatment.

A subject must be discontinued from the study for any of the following reasons:

- Current planned autologous hematopoieitic cell transplant does not occur.
- The subject or legal representative (such as a legal guardian) withdraws consent.
- Confirmed disease progression
- Unacceptable adverse experiences as described.
- Intercurrent illness that prevents further administration of treatment
- Noncompliance with study treatment or procedure requirements
- Investigator's decision to withdraw the subject
- The subject is lost to follow-up
- The subject has a confirmed positive serum pregnancy test
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Study Visit Requirements).

Evaluable subjects who received at least 2 doses of MK-3475 will have End of Treatment Evaluation (Table 8). They will have Follow-up visit and Survival Follow-up procedures per Table 8, starting 8 weeks after End of Treatment Evaluation.

Non-evaluable subjects who received less than 2 doses of MK-3475 will not have the "Efficacy Assessments" or the "Tumor Biopsies/Archival Tissue Collection/Correlative Studies" as parts of End of Treatment Evaluation (Table 8). They will have Follow-up visit and Survival Follow-up procedures per Table 8, starting 8 weeks after End of Treatment Evaluation.

Non-evaluable subjects who have never received MK-3475 will NOT have End of Treatment Evaluation or Follow-up visit or Survival Follow-up procedures per Table 8.

All subjects will be followed for disease status for at least 3 years after transplant (See Table 6: Study Flow Chart) or until disease progression, initiating a non-study multiple myeloma treatment (except maintenance therapy as specified in this protocol), withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.7 Subject Replacement Strategy

The following subjects will be replaced:

1. Subjects who were screened and signed consent but received less than 2 doses of MK-3475 (non-evaluable subjects).
2. Subjects who are poor adherence to protocol and regulatory requirements or who are lost to follow-up prior to the end-of-study evaluation after the completion of MK-3475 treatment
3. Quality or quantity of data recording is inaccurate or incomplete

5.8 Clinical Criteria for Early Study Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete.
2. Poor adherence to protocol and regulatory requirements.
3. Incidence or severity of adverse reaction indicates a potential health hazard to subjects.

5.9 Plans to Modify or Discontinue the Development of the MK-3475

In the event of Merck decision to no longer supply MK-3475, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

5.10 Definition of Endpoints

5.10.1 SAFTY ENDPOINTS

1. ENGRAFTMENT and GRAFT FAILURE

Neutrophil engraftment day will be defined as the first day of the 3 consecutive days (or of the 3 consecutive tests for >3 day-duration) of achieving an absolute neutrophil count (ANC) ≥500/uL.

Platelet engraftment day will be defined as the first day of the 2 consecutive days (or of the 2 consecutive tests for >2 day duration) of achieving platelet count ≥20,000/uL, without transfusion support.

Primary graft failure will be defined as the inability to maintain an ANC >500/uL AND a platelet count >20,000/uL, without transfusion support and without other causes, e.g. viral infection, other known myelosuppressive medication or multiple myeloma progression, **in a subject who survives 35 days after transplant**.

Secondary graft failure will be defined as a decline of ANC to <500/uL after having engrafted that is unresponsive to growth factors, without other causes, e.g. viral infection, other known myelosuppressive medication or multiple myeloma progression.

2. REGIMEN-RELATED TOXICITY [RRT]

An RTT is defined as an adverse event (AE) that occurs during the period right after the first dose of MK-3457 (day 14 +/- 4) until 14 days thereafter (day 28 +/-4), and is considered to be a direct consequence and a related event as a result of the combination of conditioning chemotherapy,

and MK-3475.

3. TREATMENT-RELATED MORTALITY [TRM]

TRM is defined as any death due to the transplant procedure, including death attributable directly to MK-3475 therapy. Death due to, but not limited to, the following events are considered a TRM: general transplant complications (e.g. infection, graft failure), RRT and Event of Clinical Interest (ECI) and immune-related AEs (irAEs)..

5.10.2 EFFICACY ENDPOINTS

1. RELAPSE / PROGRESSION

See **Appendix 13.3** for the definitions of Multiple Myeloma Response Criteria, including relapse/progression.

2. PROGRESSION-FREE SURVIVAL [PFS]

PFS is defined as the period from transplant day 0 to the day of the first Progression /Relapse.

3. OVERALL SURVIVAL [OS]

OS is defined as the period from transplant day 0 to the day of death from any cause.

5.10.3 CORRELATIVE STUDIES

The following correlative studies are planned; however, failure to obtain peripheral blood hematopoietic stem cell graft tissue and post transplant blood samples at specified time points is not a study violation as these studies are not primary endpoints.

5.10.3.1 Pre-transplant phenotypic analysis of autologous graft tissue

5.10.3.2 Quantitative *ex vivo* Immune Function Recovery Assays

1) Lymphocyte subset recovery in anti-PD-1 enhanced HDT/ASCT
2) Functional measurements of T cell subtypes and cytokine profiles
3) NK cell cytotoxicity

Table 6: Correlative Study: Medical College of Wisconsin Laboratory of Bryon D. Johnson, Ph.D.

Biomarker name	Assay	Tissue/Body Fluid Tested and Timing of Assay
Lymphocyte content of autologous graft pre-transplant	Flow cytometry: Quantify activated and effector $CD4^+$ and $CD8^+$ cells, NK cells, and regulatory T and B cells.	Graft tissue: pre-transplant day 0 or previously frozen samples

Table 7: Correlative Studies: University of Michigan Laboratory of Steven K. Lundy, Ph.D.

Biomarker name	Assay	Tissue/Body Fluid Tested and Timing of Assay
Lymphocyte recovery in anti-PD-1 enhanced HDT-ASCT	Flow cytometry: Quantify activated and effector $CD4^+$ and $CD8^+$ cells, NK cells, and regulatory T and B cells.	PBMC: pre-chemotherapy, day 14 post-transplant [before first dose of anti-PD-1] and day 100±7 and day 182±7 post-transplant
Functional T cell subtypes and cytokine profiles	Cytokine profiling: Intracellular IFN-α, IFN-γ (flow cytometry), cytokine release spectrum (Luminex), T_H subset transcription factor profiling (Q-PCR)	PBMC: pre-chemotherapy, day 14 post-transplant [before first dose of anti-PD-1], day 100±7 post-transplant, and day 182±7 post-transplant
NK cell cytotoxicity	Intracellular granzyme B (flow cytom), flow cytometric analysis of tumor cell death	PBMC: day 100±7 post-transplant, and day 182±7 post-transplant

5.10.3.3 Sample collection

We will obtain heparinized (green top; approximately 15 mL total/sample) peripheral blood hematopoietic stem cell graft tissue sample on day 0 or previously frozen graft sample and peripheral blood samples approximately on day +14 [or before the first dose of MK-3475], day 100±7 post-transplant and at early termination, if any, or day 182±7 post-transplant from each patient for the flow cytometric study of immune recovery and *ex vivo* T cell function. NK cytotoxicity measurements will be performed on the day +100±7 and day 182±7 time points using an additional 15 mL/patient blood draw. [Schema]

Samples [a 15-30 mL extra blood draw each; limit to maximal volume allowed per Institutional Policy)] will be collected coincidently with routine daily blood draws on the patients during transplant admission and clinic visits. All University of Michigan samples will be processed on the day of collection. Additional samples received from the Medical College of Wisconsin will be shipped overnight on wet ice and processed within 24 hours of being drawn. Plasma will be banked and frozen for analysis of anti-PD-1 antibody titers and other parameters if indicated. Leukocytes will be isolated by Ficoll gradient centrifugation and used for phenotypic and functional analyses described below. Previously frozen graft samples will be shipped frozen.

5.10.3.4 Flow cytometry

Lymphocyte repopulation in peripheral blood and analysis of the peripheral blood graft tissue specimens will be assessed by multi-color flow cytometry using the cell surface and intracellular markers. For surface marker only staining, 2×10^5 PBMC will be stained with each panel and 2×10^4 cells will be analyzed. Antibody panels are designed to include markers of activated T cells, as well as regulatory and cytotoxic T and B cell subsets. CXCR4 expression will be determined as a marker for bone marrow homing potential. For intracellular cytokine staining, 5×10^6 PBMC will be stimulated for 3 days with anti-CD3 and anti-CD28 with the addition of brefeldin A for the last 5 hours to stop cytokine release. Cytotoxic cells will be stimulated for 3 days with recombinant human IL-2 prior to staining for intracellular granzyme B and Fas ligand expression. Isotype control antibody staining will be used as control for non-specific binding of the intracellular markers.

5.10.3.5 Cytokine release

Cytokine production by PBMC will be analyzed at all time points. Culture supernatants will be collected from anti-CD3 and anti-CD28 stimulated PBMC (1×10^6 cells/mL) after 5 days of culture.

Released cytokines will be measured by Luminex Cytokine Human 10-Plex Panel (Life Technologies). This panel simultaneously quantifies GM-CSF, IFNg, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, and TNFa in a single sample.

5.10.3.6 Quantitative PCR
The relative presence of $CD4^+$ T_H cell subsets (T_H1, T_H2, T_H17, and Treg) in fresh 1 million freshly isolated PBMC will be determined at all time points using the Human T Helper Cell RT^2 Profiler PCR Array (Qiagen-SABiosciences).[82] This array sensitively measures the mRNA levels of 84 genes involved in T_H cell differentiation without need of *ex-vivo* stimulation.

5.10.3.7 Cytotoxicity assays
Killer function of NK cells will be determined in patient samples collected on day 100±7 and day 182±7 post-transplantation by flow cytometry.[83] Human multiple myeloma target cell lines (U266 and RPMI-8226) will be cocultured with CalceinAM-FITC-labeled patient PBMC for 4 hours. At the end of the coculture, NK cytotoxicity will be measured by labeling apoptotic cells with 7AAD and AnnexinV-APC and analysis by flow cytometry.

5.10.3.8 Partnering PI experience and credentials:

The laboratory correlative studies will be performed in the laboratories of Steven K. Lundy, Ph.D. and Bryon D. Johnson, Ph.D.

Dr. Lundy is a Research Assistant Professor in the Department of Internal Medicine of the University of Michigan Medical School. Dr. Lundy has over 27 years of experience as a technician, trainee and faculty member working in the field of immunology research. He has a particularly high level of expertise in the cellular immunological assays outlined in this proposal. Dr. Lundy spent the earliest parts of his career performing chromium release assays to measure NK cell cytotoxicity of tumor target cells and mixed lymphocyte reactions. He has extensive experience in the cloning and functional characterization of human $CD4^+$ and $CD8^+$ T cells, as well as assays related to human prostate and lung cancer cell metastasis.[120,121] His doctoral work focused on T_H cell death mediated by B cells in the *S. mansoni* worm egg granuloma model, with an emphasis on the role of Fas ligand-positive B cell subsets.[122,123] Dr. Lundy's work continues to be focused on the interactions between killer lymphocytes and their targets.[124,125] His laboratory is well-equipped to compare the effects of treatment with anti-PD-1 antibodies on the phenotypes and functions of human T cells,[126] and the cytotoxic potential of NK cells in these patients. His laboratory is well-equipped to compare the effects of treatment with anti-PD-1 antibodies on the phenotypes and functions of human T cells,[127] and the cytotoxic potential of NK cells in these patients[128].

The Lundy laboratory does not have CLIA certification, and therefore, results will not be used for clinical diagnostics or for any purposes other than the research endpoints outlined in the protocol.

Dr. Johnson is a Professor in the Department of Pediatrics at the Medical College of Wisconsin in Milwaukee. His laboratory recently generated new data using an animal model that shows blocking PD-1-Ligand on myeloma cells can promote elimination of the myeloma cells during lymhodepleted state in animals that had just been treated with a low dose of whole body irradiation. He was a recipient of 2012 Senior Research Grant Award from the Multiple Myeloma Research Foundation.

6.0 STUDY FLOW CHART

Table 8: Study Flow Chart

Study Period	**Screening Phase**	**Treatment Doses (Transplant Days)[a]**									**Early Discontinu-ation (if any)**	**Post-Treatment**		
Treatment Dose/Title:	Screening visit Days -30 to -2 [a] (except all bone marrow and imaging studies allowed -42 to -2) [c, d]	Day +14	Day +35	Day +56	Day +77	Day +98	Day +119	Day +140	Day +161	Day +182	Early Discontinu-ation	End-of-treatment Safety Evaluation	Follow Up Visits	Survival Follow-Up[e]
Scheduling Window for dosing (+/- Days):		± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	30+/-7 days after early disconti-nuation	30+/- 7 days post day 182 dose	Every 8 weeks (+/- 7 days) Until 1 years post transplant	Every 12 weeks (+/- 14 days) After 1 year Until 3 years post transplant
Administrative Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History	X													
Prior and Concomitant Medication Review (Day -14 to consenting)	X													
Post-study anti-MM therapy status											X	X	X	
Survival Status											X	X	X	
Clinical Procedures/Assessments (To be performed on the same day prior to MK-3475 dosing)														
MK-3475 Administration		X	X	X	X	X	X	X	X	X				
Toxicity/adverse reaction Assessment		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		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG or Karnofsky Performance Status	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X		

Study Period	Screening Phase	Treatment Doses (Transplant Days)[a]									Early Discontinu-ation (if any)	Post-Treatment		
Treatment Dose/Title:	Screening visit Days -30 to -2 [a] (except all bone marrow and imaging studies allowed -42 to -2) [c, d]	Day +14	Day +35	Day +56	Day +77	Day +98	Day +119	Day +140	Day +161	Day +182	Early Discontinu-ation	End-of-treatment Safety Evaluation	Follow Up Visits	Survival Follow-Up[e]
Scheduling Window for dosing (+/- Days):		± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	30+/-7 days after early discontinuation	30+/- 7 days post day 182 dose	Every 8 weeks (+/- 7 days) Until 1 years post transplant	Every 12 weeks (+/- 14 days) After 1 year Until 3 years post transplant
[g]Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG	X	X			X			X			X		Until 120 days after last dose	
PT/INR and aPTT	X	X			X			X			X			
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X		X	
Comprehensive Serum Chemistry Panel including LDH	X	X	X	X	X	X	X	X	X	X	X		X	
Urinalysis	X	X			X			X			X			
T3 or FT3, FT4 and TSH	X	X			X			X			X		X	

Study Period	Screening Phase	Treatment Doses (Transplant Days)[a]									Early Discontinu-ation (if any)	Post-Treatment		
Treatment Dose/Title:	Screening visit Days -30 to -2 [a] (except all bone marrow and imaging studies allowed -42 to -2) [c, d]	Day +14	Day +35	Day +56	Day +77	Day +98	Day +119	Day +140	Day +161	Day +182	Early Discontinu-ation	End-of-treatment Safety Evaluation	Follow Up Visits	Survival Follow-Up[e]
Scheduling Window for dosing (+/- Days):		± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	30+/-7 days after early discontinuation	30+/- 7 days post day 182 dose	Every 8 weeks (+/- 7 days) Until 1 years post transplant	Every 12 weeks (+/- 14 days) After 1 year Until 3 years post transplant
Efficacy Measurements														
Multiple Myeloma Blood/Urine Workup and serum β2 microglobulin [b]	X					X (Day 100+/-7)					X		X[f]	X[f] 2 year Anniversary is Mandatory
Bone Marrow Aspiration per institutional guidelines for Morphology [c]	X										X		2 year Anniversary only	
Bone Marrow flow Cytometry-based minimal residual disease (MRD)	X										X			
Imaging Study: Skeletal Survey [d]	X					(X) If indicated					(X) If indicated		2 year Anniversary only	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Graft Sample Collection (Previously frozen sample is allowed)	X until Day 0													
Blood Sample Collections		X pre-MK-3475				X (Day 100+/-7)				X Day 182 +/- 7)	X (+/- 7 days after discontinu-ation)			

a Transplant day when day 0 is the day of stem cell infusion. The specified reference date of dosing (day +14, +35, etc) may be further adjusted +/-3 days to represent a NEW reference date, according to medical and administrative indications within 200 days following transplant at investigator's discretion. However, any interval between adjacent dosing dates shall be at least 14 days.

The screening window for subjects who is receiving or has received high-dose melphalan and autologous transplant is allowed to be as late as day-1 until the day of enrollment.

b Peripheral blood and urine quantification of monoclonal protein including serum protein electrophoresis (SPEP)/serum immunofixation (IFIX), serum free light chain levels, serum β2 microglobulin (at screening only), 24-hour urine protein electrophoresis (UPEP) and 24-hour urine Bence-Jones protein quantification.

c Bone marrow Morphology and bone marrow flow cytometry-based minimal residual disease (MRD) are mandatory. Bone marrow Immunohistochemistry (IHC), Cytogenetics by standard karyotyping, and FISH panel should be performed. FISH panel should include del 1p, del 13, del 17p13, t(4;14), t(11;14), t(11;16), and 1q21 amplification. Screening bone marrow studies may be performed between day -42 and -2.

d Only skeletal survey is mandatory while other imaging studies may be performed as indicated per standard of care. Skeletal survey should include a chest (PA or AP; lateral), skull (lateral), upper extremities (shoulder to elbow), lower extremities (hip to knee; AP), pelvis (AP), cervical/thoracic/lumbar spine (AP and lateral) or per institutional guidelines. A skeletal survey and/or MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) performed as standard of care prior to signing consent can be used for screening if performed within 42 days of Day 0.

For suspected progression to bone disease bidirectional measurement of the target lytic lesions must be performed. During the course of the trial or if a subject develops bone pain a skeletal survey and/or MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) should be performed annually or as clinically indicated. When clinically indicated MRI is required for subjects with bony disease and should just include the bony lesions.

Subjects with measurable plasmacytomas only at baseline should have appropriate imaging study performed at day 100+/-7, end of study evaluation and every 8 weeks until year per standard of care- at investigator's discretion.

e After 1 year, subjects will be further followed by phone or letter every 12 weeks until 3 years post-transplant or until MM progression/relapse, whichever occurs earlier, for secondary efficacy endpoints (MM relapse/progression, late immune adverse reactions and survival). Subjects will be evaluated and managed in clinic as indicated. However, a 2-year anniversary visit is mandatory (see **f**). After 1 year, subjects will follow with his/her primary oncologist per standard of care.

f After end-of-treatment evaluation until 1 year, blood and urine MM workups (see **b**) will be performed every 8 weeks or per standard of care (allowed to be performed locally). Subjects may follow with his/her primary oncologist per standard of care.

After 1 year, blood and urine MM workups (see **b**) will be performed every 12 weeks or per standard of care (allowed to be performed locally). After 1 year, subjects will follow with his/her primary oncologist per standard of care.

However, a 2-year anniversary visit is mandatory for an official evaluation of the secondary endpoint 2-year PFS. All Efficacy Measurements (Blood and urine MM workups, bone marrow aspiration for morphology and flow-cytometry based MRD study and required imaging study) are mandatory at 2-year anniversary visit.

g Subjects may receive each MK-3475 dose after the required laboratory tests (e.g. thyroid function tests, PT/PTT, urinalysis) are obtained, at investigator's discretion of safety and administrative reason.

7.0 STUDY PROCEDURES

7.1 Study Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the Investigator/Institution and/or Merck 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 must obtain documented consent from each potential subject prior to participating in a clinical trial.

General Informed Consent

Due to high risk category of the study, consent must be obtained by an Investigator physician and 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 (Investigator physician).

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

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 study. 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 the study and the study population will be added to the consent form template at the protocol level. The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Institution requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

7.1.1.3 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 prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease (multiple myeloma), for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

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 28 days prior to the first dose of MK-347514 treatment (~14 days before transplant). Treatment for the disease (multiple myeloma) for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

2. Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the study and follow-up visits per Table 8. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease (Multiple Myeloma) Details and Treatments

1. Disease Details

The investigator or qualified designee will obtain prior and current details regarding multiple myeloma status. See Appendix 13.3 for Multiple Myeloma response criteria.

2. Prior Treatment Details

The investigator or qualified designee will review all prior multiple myeloma treatments including systemic treatments, radiation and surgeries.

3. Subsequent Anti-Multiple Myeloma Therapy Status

The investigator or qualified designee will review maintenance therapy (starting day+45 to day+ 90) and all subsequent new anti-multiple myeloma therapy initiated after the last dose of study treatment. If a subject initiates a new anti-Multiple Myeloma therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-Multiple Myeloma therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Study Compliance (Medication/Diet/Activity/Other)

Subjects will be followed for compliance to allowed concomitant medications and other activity restriction according to section 5.4.1, 5.4.2 and 5.5.4.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Study Flow Chart and more frequently if clinically indicated.

Adverse events will be graded and recorded from the start of infusion of the first dose of MK-3475 and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendices). 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 MK-3475 exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.5.2, 5.5.3 and the separate guidance document in the administrative binder regarding the identification, evaluation and management of AEs of a potential immunological etiology.

Refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Examination

The investigator or qualified designee will perform a complete physical exam during the screening and other required study visits. Clinically significant abnormal findings should be recorded as medical history.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of MK-3475 and at treatment discontinuation as specified in the Study Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status or KPS (see Appendix 13.1) at screening, prior to the administration of each dose of MK-3475, discontinuation of MK-3475 and post study visits as specified in the Study Flow Chart (Section 6.0).

7.1.2.5 Multiple Myeloma Assessment

Multiple myeloma assessment includes peripheral blood and urine quantification of monoclonal protein including serum protein electrophoresis (SPEP)/serum immunofixation (IFIX), serum β2-microglobulin (at screening only), serum free light chain levels, 24-hour urine protein electrophoresis (UPEP) and 24-hour urine Bence-Jones protein quantification, bone marrow examination, skeletal/bone survey and other imaging studies as indicated. These will be performed as specified in the Study Flow Chart (Section 6).

7.1.2.6 Correlative Study Multiple Myeloma Tissue Sample and Blood Sample Collections

For the flow cytometric study of immune recovery and *ex vivo* **T cell function**, heparinized (green top; approximately 15 mL total/sample) peripheral blood hematopoietic stem cell graft tissue sample on day 0 or previously frozen sample and peripheral blood samples approximately on day +14 [or before the first dose of MK-3475], day 100±7 post-transplant and at, if any, or day 182±7 post-transplant from each patient will be obtained. [Schema] **NK cytotoxicity** measurements will be performed on the day +100±7 and day 182±7 time points using an additional 15 mL/patient blood draw. [Schema]

In summary, samples [a 15-30 mL extra blood draw each; limit to maximal volume allowed per Institutional Policy)] will be collected coincidently with routine daily blood draws on the

patients during transplant admission and clinic visits.

All University of Michigan samples will be processed on the day of collection. Additional samples received from the Medical College of Wisconsin will be shipped overnight on wet ice and processed within 24 hours of being drawn. Plasma will be banked and frozen for analysis of anti-PD-1 antibody titers and other parameters if indicated. Leukocytes will be isolated by Ficoll gradient centrifugation and used for phenotypic and functional analyses described below.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in the study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study, including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject, is limit to maximal volume allowed per Institutional Policy.

Of note, some of these blood/tissue tests are already part of standard BMT evaluations for non-study patients.

Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Required laboratory tests for hematology, chemistry, urinalysis, and others will be performed at time points specified in Table 8. The total amount of "additional" study required blood/tissue samples to be drawn/collected over the course of the study (from pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type is limit to maximal volume allowed per Institutional Policy. Of note, some of these blood tests are already part of standard BMT evaluations for non-study patients. Pre-dose laboratory tests can be performed **up to 72 hours** prior to dosing. Results must be reviewed by an investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit, if possible, 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. Subjects who complete 9 doses of MK-3475 will be considered having completed the study treatment.

After discontinuing treatment, these subjects, if possible, should return to the site for a Safety Follow-up Visit (Section 7.1.6.7) and then proceed to the Follow-Up Period of the study (Sections 7.1.6.7 and 7.1.6.8).

7.1.5 Study Visit Requirements

Study visit requirements are outlined in Section 6.0 - Study Flow Chart. Specific procedure details are provided above in Section 7.1 - Study Procedures.

7.1.6 Study Definitions

7.1.6.1 Screening
A subject will be considered to be in the "Screening" period from the time he/she signs consent until the date the subject is determined as either "eligible" or "ineligible" (screen failure) by an investigator. Patients may be consented to this study based on disease eligibility and other criteria at the time of consent, but later removed from the study prior to initiation of high-dose melphalan if the change of disease status makes the subject "ineligible". In the event that this occurs, the subject will be replaced.

7.1.6.2 Enrolled
A subject will be considered to be "Enrolled" onto the study once (1) he/she has signed consent; (2) he/she has successfully met all screening criteria, as documented by the inclusion/exclusion document; (3) all eligibility criteria have been reviewed and accepted by an investigator. The date of enrollment will be documented as the date that an investigator has reviewed and approved the subject's eligibility.

7.1.6.3 Treatment Period
"Treatment Period" is defined as the first day through the last day of treatment with MK-3475 – from 1st to 9th doses or ~ day+14 (+/-4) to day+182 (+/-4) post-transplant.

7.1.6.4 On Study
"On Study period" starts from the day that a subject signs the protocol consent document and subsequently meets the protocol eligibility criteria ("Enrolled"), receives MK-3475 treatment and ends 30 days after the last dose (9th) of MK-3475 or prior to this period if one of the following event occurs earlier:
1. Death
2. Lost to follow-up or non-compliance
3. Withdrawal of consent
4. Entry on to a competing trial
5. Multiple myeloma progression/relapse and its treatment (excluding ongoing maintenance treatment as specified in this protocol) or development of new malignancy and its treatment
6. Unacceptable or dose limiting toxicity or complication
7. Any conditions affecting study integrity

Thirty days after the last (9th) dose of MK-3475, the patient will be considered "Off Study/Off Protocol." But they will be followed for the primary and secondary endpoints off study/off protocol until 3 year as mentioned in "Follow Up Period".

7.1.6.5 Off Treatment
"Off Treatment" period starts after a patient has completed MK-3475 on day +182 (+/-4 days) or prior to day+182 if one of the listed event in 7.1.6.4 occurs earlier, and ends 30 days afterwards.

7.1.6.6 Evaluable
A subject who has received 2-9 doses of MK-3475 will be considered "evaluable" for efficacy endpoint analysis. The number of subjects who are considered not "evaluable" for endpoint analysis will be monitored closely. Additional subjects will be replaced.

A subject who has failed to follow the standard lenalidomide maintenance therapy (5.3.1.2) due to appropriate medical indications will be considered "evaluable" for endpoint analysis.

7.1.6.7 Post-Treatment Safety Follow-Up Visits

"Follow Up period" is defined as the first day a subject is no longer receiving MK-3475 until 1 year post-transplant.

Subjects will have an **End-of-Treatment Safety Follow-Up Visit** for a complete evaluation 30 days after the last dose of MK-3475. After that, subjects will be followed every 8 weeks for follow-up visits until 1 year post-transplant. 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 anti-MM therapy, whichever occurs first.

7.1.6.8 Survival Follow-up

After 1 year, subjects will be further followed by phone or letter until 3 years following transplant for late AEs, SAEs and secondary efficacy endpoints (MM relapse/progression, late immune adverse reactions and survival) (Table 8). Of note, a 2-year anniversary visit is mandatory.

After 1 year, subjects will follow with his/her primary oncologist per standard of care.

Once a subject experiences confirmed MM progression or starts a new anti-MM therapy (excluding ongoing maintenance treatment as specified in this protocol), the subject moves into the "Survival follow-up phase" and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

See 7.2 for Reporting of AEs and SAEs after 1 year until 3 years following transplant.

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 anti-MM therapy, whichever occurs first.

7.2 Assessing and Recording Adverse Events

Definition

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 unfavorable 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 Merck'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.

Merck 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 Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Reporting of AEs and SAEs during study treatment and safety follow-up period until 1 year following transplant

1. Any AEs related to MK-3475 (pembrolizimab)

2. Any events listed in the most recent updated version of the Event of Clinical Interest Guidance Document

3. Any ≥grade 3 AEs related or unrelated to MK-3475 (pembrolizimab)

4. Any SAEs related or unrelated to MK-3475 (pembrolizimab)

The above events will be reported on the Adverse Event (or Severe Adverse Event) Case Report forms/worksheets from the start of infusion of the first dose of MK-3475 through 30 days following cessation of treatment, at each examination and during the follow-up period (until 1 year following transplant) per Table 8 or until the initiation of new anti-multiple myeloma therapy (excluding maintenance treatment as specified in this protocol), whichever is earlier.

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 anti-MM therapy, whichever occurs first.

Reporting of AEs and SAEs after 1 year until 3 years following transplant

After 1 year, subjects will be further followed by phone or letter until 3 years following transplant for late AEs, SAEs and secondary efficacy endpoints (MM relapse/progression, late immune adverse reactions and survival) (Table 8). Subjects will be evaluated and managed for late AEs/SAEs in clinic as indicated and these late AEs/SAEs will be reported.

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 anti-MM therapy, whichever occurs first.

Any AEs or SAEs occurring after 1 year until 3 years following transplant may be reported at an investigator's discretion. Of note, a 2-year anniversary visit is mandatory.

After 1 year, subjects will follow with his/her primary oncologist per standard of care.

The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Investigator/Institution and to Merck

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for MK-3475 by 20% over the prescribed dose. No specific information is available on the treatment of overdose of MK-3475. In the event of overdose, MK-3475 should be discontinued and 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 a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product 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 within 24 hours to the Investigator/Institution and within 2 working days to Merck by the primary site.

7.2.2 Reporting of Pregnancy and Lactation to the Investigator/Institution and to Merck

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 or within 90 days of completing the study, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant 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 Investigator/Institution and within 2 working days to Merck by the primary site.

7.2.3 Immediate Reporting of Adverse Events to the Investigator/Institution and to Merck

7.2.3.1 Serious Adverse Events (SAEs)

A serious adverse event (SAE) is any adverse event occurring at any dose or during any use of Merck'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 a new cancer (that is not a condition of the study)
- Is associated with an overdose
- Is an other important medical event

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

Any serious adverse event (SAE), or follow up to a serious adverse event, including death due to any cause other than progression of multiple myeloma under study that occurs to any subject, whether or not related to MK-3475 (see 7.2) from the start of infusion of the first dose of MK-3475 through 1 year following transplant, or the initiation of new anti-multiple myeloma therapy (excluding maintenance treatment as specified in this protocol), whichever is earlier, must be reported within 24 hours to the Investigator/Institution and within 2 working days to Merck by the primary site

However, any MK-3475 related SAEs occurring until 3 years after transplant may be reported at an investigator's discretion.

A Copy of the SAE form should be sent to the University of Michigan Multi-site coordinator via email at CTSU-Oncology-Multisite@med.umich.edu within 24 hours of the site's knowledge of the event. Follow-up information must also be reported within 1 business day of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites within 5 days of review of the information by the Protocol Chair only in the case that the event(s) is believed to be related (i.e. possibly, probably or definitely) to the study treatment. The Coordinating Center will be responsible for reporting of events to the FDA and supporters as appropriate.

Non-serious Events of Clinical Interest (ECI) will be forwarded to Merck and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck 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 Investigator/Institution and to Merck by the primary site.

SAE reports and any other relevant safety information are to be forwarded to the Merck.

A copy of all 15-Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross-reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

7.2.3.2 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms (CRFs) /worksheets and reported within 24 hours to the Investigator/Institution/primary site and to Merck by primary site, either by electronic media or paper. Investigator/Institution contact information can be found in the Investigator Study File Binder (or equivalent).

A separate guidance document has been provided entitled “Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document”. This document can be found in the administrative binder and provides guidance regarding identification/diagnosis, evaluation, and management of ECIs and irAEs. Additional non-serious and serious ECIs are identified in this guidance document and also need to be reported to the Investigator/Institution/primary site and to Merck by primary site within 24 hours of the event.

Events of clinical interest for this study also include an overdose of MK-3475, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Investigator/Institution and to Merck, that is not associated with clinical symptoms or abnormal laboratory results.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiological causes. If lab results or symptoms indicated a possible immune-related ECI then additional testing should be performed to rule out other etiologic causes. If no other cause was found, then it is assumed to be immune-related.

ECIs that occur to any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anti–multiple myeloma therapy (excluding maintenance therapy as specified in this protocol), whichever is earlier, whether or not related to Merck’s product must be reported within 24 hours to the Investigator/Institution and to Merck by the primary site, either by electronic media or paper. Investigator/Institution Contact Information can be found in the Investigator Study File Binder.

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. See the Manual “Pembrolizumab Program (MK-3475): Event of Clinical Interest Guidance Document” for adverse reactions that are considered ECI or immune-related AEs (irAEs).

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

Table 9: 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 Merck 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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 Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck 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 Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck 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 Merck 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 Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck 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 Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck 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) Merck 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 MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR 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 Merck 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 Merck product relationship).
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

Planned Method of Statistical Analysis

Primary and Secondary Endpoints
The complete response rate will be estimated by the observed proportion of complete responders at day 180 in our study, along with a 95% confidence interval. Secondary endpoints of OS and PFS will be modeled using the Kaplan-Meier method. Treatment-related mortality, graft failure and relapse will be estimated with the cumulative incidence.

The complete response rate at day 180 post HDT/HSCT of the historical cohort receiving lenalidomide maintenance post HDT/ASCT was 30% and the historical secondary efficacy endpoint (2-year PFS in those achieving complete response (CR) post HDT/ASCT) was 70%.[129,130] The historical cumulative incidences of regimen-related toxicity after HDT/ASCT for multiple myeloma was reported to be ~12% [131], that of treatment-related mortality was ~3% [132] and that of relapse was 15% at 2 years.[130]

Laboratory Correlates
The association of the values and percentage change of each variable with the primary and secondary outcomes will be estimated with Cox regression (for OS and PFS) and competing risks regression (TRM, relapse**).**

8.2 Statistical Analysis PlanNull Hypothesis (H0) for Primary Efficacy Endpoint
“Complete response rate at day 180 post HDT/ASCT is not increased by the administration of anti-PD-1.”

Alternative Hypothesis (H1) for Primary Efficacy Endpoint
“Complete response rate at day 180 post HDT/ASCT is increased at least 20% by the administration of anti-PD-1.”

Sample Size and its Justification
Assuming a baseline CR conversion rate of 30%, this study aims to enroll 46 evaluable subjects to detect a 20% difference in CR conversion (30% to 50%) at day 180 with power of 80% with a one-sided and Type I error of 5%. Patients will be enrolled in two cohorts per an optimal Simon two-stage design. The first cohort will consist of 15 patients; if more than 5 of them achieve CR at day 180, an additional cohort of 31 patients will be enrolled. Thus, a total of 50 subjects will be accrued, with the expectation of 4 subjects not evaluable. We require more than 18 responses in 46 evaluable subjects for the study to be considered to have reached its primary aim.

Study Feasibility
University of Michigan Adult BMT Program receives ~100-120 patients with multiple myeloma per year. Medical College of Wisconsin adult BMT Program is of the same size. We expect to finish an enrollment in 1 year.

8.3 Stopping Rules

8.3.1 Stopping Rule for Excessive GRAFT FAILURE

Stopping rules for excessive graft failure will apply to all subjects entered on study.

"Engraftment failure" will be defined as the inability to achieve or maintain an ANC >500/uL and a platelet count >20,000/uL, without transfusion support, within 35 days post transplant. We consider engraftment failure in more than 5% of subjects to be unacceptable.

We will continually monitor the rate of EF35 and stop if one of the followings occurs:

1. There is 1 graft failure after 10 subjects have been enrolled and followed for 35 days post-transplant.
2. There are 2 graft failures after 40 subjects have been enrolled and followed for 35 days post-transplant.
3. There are 2 consecutive graft failures occurring at any time.

Subjects who have not engrafted and die within 35 days of transplant will be considered to have graft failure and contribute to the number of events of EF35. If projected EF35 >5%, enrollment will be halted and the protocol will be re-evaluated and either closed or modified and re-approved before re-opening.

Although this stopping rule requires 35 days of follow-up for each subject, we will not halt accrual to wait for full follow-up of previous enrolled subjects. For example, we will enroll the 11th subject as soon as they are eligible, regardless of whether the first 10 subjects have all been followed for 35 days.

8.3.2 Stopping Rule for Excessive MORTALITY

Stopping rules for excessive mortality will apply to all subjects entered on study. We consider all-cause mortality in more than 5% of all subjects within 100 days of transplant (ACM100) to be unacceptable.

We will continually monitor the rate of ACM100 and stop if one of the followings occurs:

1. There are 2 deaths after 20 subjects have been enrolled and followed for 100 days post-transplant.
2. There are 3 deaths after 40 subjects have been enrolled and followed for 100 days post-transplant.
3. There are 3 consecutive deaths occurring at any time.

If projected ACM100 >5%, enrollment will be halted and the protocol will be re-evaluated and either closed or modified and re-approved before re-opening.

Although this stopping rule requires 100 days of follow-up for each subject, we will not halt accrual to wait for full follow-up of previous enrolled subjects. For example, we will enroll the 20th subject as soon as they are eligible, regardless of whether the first 20 subjects have all been followed for 100 days.

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 Merck as summarized in Table 10.

Table 10 Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 (Pembrolizumab) 100 mg/ 4 mL	Solution for Injection

9.2 Packaging and Labeling Information

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

Vials will be provided in an open label fashion for subject dosing.

9.3 Clinical Supplies Disclosure

This study is open-label; therefore, the subject, the study site personnel, the Investigator 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 study medication must be recorded by an authorized person at the study site.

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

9.5 Returns and Reconciliation

The Investigator/Institution is responsible for keeping accurate records of the clinical supplies received from Merck, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the study.

For all study sites, the site personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

Regulatory Obligations

10.1 Informed Consent

Informed consent shall be obtained prior to an enrollment of a subject into the study.

10.2 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Merck with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee re-approval throughout the duration of the study.
The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected. The Investigator is also required to notify the FDA in writing of any SAE that is both unexpected and related to the study drug, within 15 days of knowledge of the event, and within 7 days of a death related to the study drug.

10.3 Pre-study Documentation Requirements

Informed consent, eligibility checklist and registration forms **shall be** obtained before subjects can receive any study treatments of MK-3475 (pembrolizumab®).

Informed consent, eligibility checklist and registration forms **should be** obtained before transplantation. Failure to complete the registration before transplantation may be allowed at the discretion of the PI and will not be considered a protocol deviation or violation.

Of note, conditioning chemotherapy (melphalan), autologous hematopoietic cell transplantation and lenalidomide maintenance therapy are standard treatments.

10.4 Subject Confidentiality

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by the FDA and/or other applicable regulatory authority. The access may consist of study-related

monitoring, audits, IRB or Ethics Committee reviews, and FDA inspections. Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

11. ADMINISTRATIVE AND LEGAL OBLIGATIONS

11.1 Protocol Amendments and Study Termination

Shall any evidence of safety concerns or lack of efficacy arises, study enrollment will be on hold. Investigation and assessment will be performed for a determination to amend or terminate the study.

11.2 Study Documentation and Archive

Required study documentation and archive will be maintained by institutional Clinical Trial Office.

11.3 Study Monitoring and Data Collection

11.3.1 Data and Safety Monitoring Procedures

The Data and Safety Monitoring Board (DSMB) of The University of Michigan Comprehensive Cancer Center (UMCCC) is the DSMB for this study. This committee is responsible for monitoring the safety and data integrity of the study.

Each participating site is required to have its own Data and Safety Monitoring Committee (DSMC) for the study. This committee will be composed of the local site principal investigator, site co-investigator(s), site data manager or study coordinator and other members of the study staff involved in the conduct of the study. During the committee's **quarterly** meeting, the principal investigator will discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

These meetings are to be documented by the site data manager or study coordinator using the Protocol Specific Data and Safety Monitoring Report (DSMR), signed by the site principal investigator**.** Each site is required to submit the completed DSMR to the Multi-Site Coordinator at the University of Michigan O-CTSU on a **quarterly** basis together with other pertinent documents.

Similarly, protocol deviations are to be documented using the Notice of Protocol Deviation Form and requires the signatures of both the sites data manager or study coordinator and the site principal investigator. These reports are to be sent to the University of Michigan O-CTSU within 7 calendar days of awareness of the event and on a **quarterly** basis with the Protocol Specific Data and Safety Monitoring Report.

The O-CTSU is responsible for collating all the Data and Safety Monitoring Reports from all the participating sites, and providing the information to the Data Safety Monitoring Board.

11.3.2 Clinical Monitoring Procedures

Clinical studies coordinated by The University of Michigan Comprehensive Cancer Center (UMCCC) must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.
This study will be monitored by a representative of the O-CTSU of the UMCCC. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo a site initiation meeting to be conducted by the O-CTSU. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate UMCCC personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the O-CTSU and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes the Day +35 visit. The study site will send the de-identified source documents to the O-CTSU for monitoring. 'Centralized' monitoring may be requested by the O-CTSU if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the O-CTSU for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the O-CTSU. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the O-CTSU representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The O-CTSU expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the O-CTSU, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit if all of the following apply:

- No patient has signed the Informed Consent Form and has enrolled into the study
- Investigational agent has not been dispensed
- All investigational agent and materials have been returned as defined for the study or destroyed and accounted for properly.

11.3.3 Multi-Site Data Management

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based Velos data management system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the multi-site coordinator (MSC) during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of registration
    - Subject entry into Velos
        - Subject Status
        - Demographics
- During study participation
    - All data should be entered online within 10 business days of data acquisition. *[Information on dose limiting toxicity events must be entered within one business day.]* Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 7 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

11.3.4 Lack of Efficacy

Subjects will be followed closely for AEs and SAEs, which will be reported to IRB and MERCK per required interval. Once 15 subjects have been enrolled and followed for 180 days post-transplant, which is the time of expected primary efficacy endpoint, we will perform an interim analysis to evaluate whether the projected primary endpoint will be potentially achieved.

Although this Lack of Efficacy evaluation requires 180 days of follow-up for each subject, we will not halt accrual to wait for full follow-up of previous enrolled subjects. For example, we will enroll the 16th subject as soon as they are eligible, regardless of whether the first 15 subjects have all been followed for 180 days.

11.4 Quality Assurance and Audits

The Data Safety Monitoring Board can request a ‘for cause’ audit of the study if the board identifies a need for a more rigorous evaluation of study-related issues. A “for cause” audit

would be conducted by the Quality Assurance Review Committee (QARC) of the University of Michigan Comprehensive Cancer Center.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the O-CTSU that such a request has been made.

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13. APPENDICES

13.1 PERFORMANCE STATUS CLASSIFICATION SYSTEMS

ECOG Performance Status

Grade	Description	KPS Equivalent
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	90%-100%
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).	70%-80%
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.	50%-60%
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	30%-40%
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	10%-20%
5	Dead.	

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. . The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.*Am J Clin Oncol 5:649-655, 1982*

KARNOFSKY PERFORMANCE SCALE (KPS)

Scale %	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor symptoms of disease
80	Normal activity with effort, some signs of symptoms of disease
70	Cares for self (consistent with age), unable to carry on normal activity or do active work/school/play
60	Requires occasional assistance (beyond age-appropriate care), but is able to care for most of their needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization is indicated although death is not imminent
20	Hospitalization is necessary, very sick, active support treatment is necessary
10	Moribund, fatal processes progressing rapidly

13.2 DIAGNOSIS OF SYMPTOMATIC MUTIPLE MYELOMA

Active (Symptomatic) multiple myeloma
- M-protein in serum and/or urine
- Bone marrow (clonal) plasma cells or plasmacytoma
- Related organ or tissue impairment (end organ damage, including bone lesions)

Myeloma-related organ or tissue impairment (end organ damage)
- Calcium levels increased: serum calcium > 2.75 mmol/L (11.5 mg/dL)
- Renal insufficiency: creatinine >173 mmol/L (>2 mg/dL)
- Anaemia: haemoglobin 2 g/dL below the lower limit of normal or hemoglobin <10 g/dL
- Bone lesions: lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
- Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

Non-secretory multiple myeloma (Excluded from this study)
- No M-protein in serum and/or urine with immunofixation
- Bone marrow clonal plasmacytosis $\geq$ 10% or plasmacytoma
- Related organ or tissue impairment (end organ damage, including bone lesions)

International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol.* 2003 Jun;121(5):749-57.

13.3 RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Response subcategory	*Response criteria*
Complete response[a] (CR)	Negative immunofixation of serum and urine and Disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow
Stringent complete response (sCR)	CR as defined above plus Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial response (VGPR)[a]	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ⩾90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h
Partial response (PR)	⩾50% reduction of serum M protein and reduction in 24-h urinary M protein by ⩾90% or to <200 mg per 24 h If the serum and urine M protein are unmeasurable, a ⩾50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M protein criteria If serum and urine M protein are unmeasurable, and serum free light assay is also unmeasurable, ⩾50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ⩾30% In addition to the above criteria, if present at baseline, ⩾50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease (PD)[a]	Increase of 25% from lowest response value in any one or more of the following: Serum M-component (absolute increase must be ⩾0.5 g/100 ml)[c] and/or Urine M-component (absolute increase must be ⩾200 mg per 24 h) and/or Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >100 mg/l) Bone marrow plasma cell percentage (absolute % must be ⩾10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/100 ml) that can be attributed solely to the plasma cell proliferative disorder

[a]Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.
All response categories (CR, sCR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy; complete, PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.
Adapted with permission from Durie *et al*. [29]
c for progressive disease, serum M-component increases of ⩾1 gm/100 ml are sufficient to define relapse if starting M-component is ⩾5 gm/100 ml.

Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia* 2009 Jan;23(1):3-9.

13.4 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)