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TITLE: Pembrolizumab with standard cytotoxic chemotherapy in treatment naïve non -small cell lung cancer patients with asymptomatic brain metastases

Documentation History Page

Version	Date	Amendment	Summary of Amendment
1.3	**22 February 2021**	**Original**	
2.0	**10 August 2021**	**Non-Substantial amendment**	**Modifications to the pregnancy test, Addition to Visiting**
2.1	**31 March 2022**	**Non-Substantial amendment**	**Change of Sample Collection**
2.2	**26 April 2023**	**Non-Substantial amendment**	**Change of Tumor Imaging, Sample Collection**

TABLE OF CONTENTS

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab in non-small cell lung cancer patients with brain metastases
Trial Phase	II
Clinical Indication	Non-small cell lung cancer
Trial Type	Prospective single arm single center study
Type of control	Historical control
Route of administration	Intravenous
Treatment Groups	Non-small cell lung cancer
Number of trial participants	50
Estimated enrollment period	Mar 2022 – Sep 2024
Estimated duration of trial	42 months
Duration of Participation	18 months
Estimated average length of treatment per patient	7 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase II single center, open-label, single arm study in patients with advanced non-small cell lung cancer (stage IV) with brain metastases. Patients will be treated with combination of Pembrolizumab 200mg plus platinum doublet based on histology subtypes. After the 4 cycles of combination phase with cytotoxic chemotherapy, maintenance phase will be followed for maximum of 35 cycles. If the disease progression is observed in CNS only which can be controlled with local treatment, systemic treatment can be continued as beyond disease progression.

Non-squamous cell carcinoma:

4 cycles of pemetrexed 500mg/m2 + carboplatin AUC 5.0 + pembrolizumab 200mg every 3 weeks

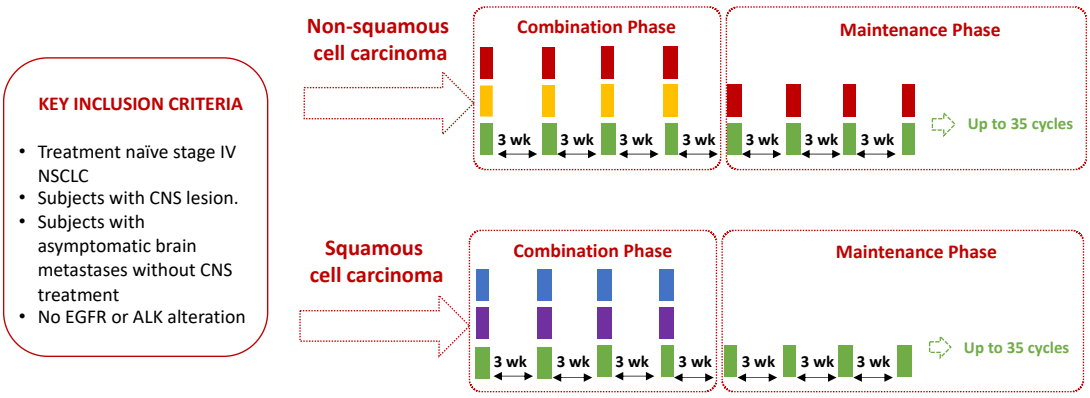
Followed by pemetrexed 500mg/m2 + pembrolizumab 200mg every 3 weeks up to 35 cycles

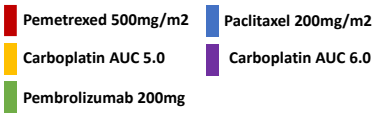
Squamous cell carcinoma:

4 cycles of paclitaxel 200mg/m2 + carboplatin AUC 6.0 + pembrolizumab 200mg every 3 weeks

Followed by pembrolizumab 200mg every 3 weeks up to 35 cycles

2.2 Trial Schema





Primary endpoint: Intra cranial response rate
Secondary endpoint:
Progression-free survival, Intracranial progression-free survival, intracranial duration of response, overall survival, objective response rate
Exploratory analysis: Exploratory biomarker study based on WES, WTS and PD-L1 expression

2.3 Schedule of Activities

Table 1 Study Flow Chart

Study Period:	Screening		Treatment cycles								Post-treatment		
Visit Number/Title:	Screening		Combination phase (C1 to C4)				Maintenance phase (To be repeated to C35)				EOT (Safety F/U)	Follow up visit	Survival F/U
		C1 D1	C1 D8	C2	C3	C4	C5	C6	C7	C8			
Scheduled Hour, Day, Week, etc., and Window:	-28 to -1			± 3	± 3	±3	± 3	± 3	± 3	± 3	28 day post discontinue	Every 12 weeks post EOT	Every 12 weeks post EOT
Administrative Procedures													
Informed Consent (Including consent for the treatment of beyond disease progression)	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Trial treatment administration		X		X	X	X	X	X	X	X			
Post study anticancer therapy status											X		X
Efficacy Procedures[a]													
Tumor imaging (Chest +/- Abdomen CT)	X				X		X		X		X	X	
PET-CT (Optional)	X				X		X		X		X	X	
Brain MRI	X				X		X		X		X	X	
Laboratory procedure and Safety Procedures													
Full physical examination	X												
Height	X												
Weight	X	X		X	X	X	X	X	X	X			
Directed Physical Examination		X		X	X	X	X	X	X	X	X		
Vital Signs (heart rate, blood pressure), ECOG	X	X		X	X	X	X	X	X	X	X		
12-lead ECG	X												
Chest X-ray			X										
HIV, hepatitis B and C screen	X												
CBC with differential	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis (every 4 cycles during the maintenance phase)	X				X		X				X		
Comprehensive serum chemistry profile	X	X	X	X	X	X	X	X	X	X	X	X	
hCG test for female patients with possibility of pregnancy[b]	X				X		X		X		X		

Study Period:	Screening		Treatment cycles								Post-treatment		
Visit Number/Title:	Screening		Combination phase (C1 to C4)				Maintenance phase (To be repeated to C35)				EOT (Safety F/U)	Follow up visit	Survival F/U
		C1 D1	C1 D8	C2	C3	C4	C5	C6	C7	C8			
Scheduled Hour, Day, Week, etc., and Window:	-28 to -1			± 3	± 3	±3	± 3	± 3	± 3	± 3	28 day post discontinue	Every 12 weeks post EOT	Every 12 weeks post EOT
Thyroid Function Tests (TSH, T3, free T4; periodically) (every 4 cycles during the maintenance phase)	X				X		X				X		
PT and aPTT (baseline only)	X												
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	
Survival status													X
Exploratory biomarker study[c]													
PD-L1 status, Correlative studies blood collection (Optional)	X		X	X	X						X (Disease Progression)		
Correlative studies tissue collection (optional)	X										X (Disease Progression)		

a. CT/PET-CT/Brain MRI will be conducted with window period of ± 7 days.
CT and Brain MRI will be conducted every 2 cycles(6 weeks) for the first 12 months and every 3 cycles(9 weeks) thereafter.
PET-CT during the study can be conducted based on investigator's decision as optional method.
At the time of treatment discontinuation(±4 weeks window). Every 12 weeks for follow up visit.

b. WOCBP should be a maximum of 24-hours before the first dose/vaccination.

c. Blood Sample(Optional): 30cc blood at the time of screening. 20cc blood at the time of C1D8, C2D1, C3D1, and disease progression
Tissue Sample(Optional): Fresh tumor tissue sample or up to 15 Unstained slide at the screening and disease progression

3.0 OBJECTIVE(S), HYPOTHESIS(ES), AND ENDPOINT(S)

3.1 Primary Endpoint: Intracranial response rate by RECIST v1.1

3.2 Secondary Endpoint(s)

Progression-free survival

Overall survival

Intracranial duration of response

Intracranial progression-free survival

Objective response rate

Safety profile

3.3 Exploratory Objective(s)

Exploratory analyses based on PD-L1 expression

- Subgroup analysis of clinical efficacy based on PD-L1 result

Exploratory analysis based on genomic profile

- Exploratory analysis using scRNA and TCR sequencing from tissue and blood to identify the subset of immune cells correlated with clinical outcomes

Drug sensitivity test based on organoid culture
- Develop patient derived organoid pre-clinical model to validate the drug sensitivity and explore the tumor characteristics in-depth using organoid.

4.0 BACKGROUND & RATIONALE

4.1 Background

Despite the recent advance in cancer therapy, central nervous system (CNS) metastases remain a devasting complication and major hurdles for the treatment selection. Especially, brain metastases occur in up to 30% of non-small cell lung cancer (NSCLC) at the time point of initial diagnoses. The current treatment of NSCLC with CNS metastases can be different based on molecular profiles and neurology symptoms. To date, if the patients have neurology symptom due to the CNS lesion, upfront local therapies such as stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT) or surgical resection is recommended as an initial treatment. However, if the patient has minimal neurology symptoms, treatment can be different based on molecular profiles. In patients with driver oncogenes which have the potential option with blood-brain barrier (BBB) penetrable small molecules, such as EGFR or ALK tyrosine kinase inhibitor (TKI), upfront treatment with TKI can be considered as an initial treatment. On the contrary, first-line treatment for the patients without driver oncogenes remains controversial.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure (IB).

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)

that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in non-small cell lung cancer with brain metastases.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

There has been a report from the small and retrospective studies which showed clinical efficacy of immune checkpoint inhibitor in CNS metastases. Clinical efficacy of pembrolizumab monotherapy for patients with brain metastases in 18 NSCLC is first reported in 2016 (Lancet Oncol. (2016) 17:976–83). In this study, a cut-off of up-front local treatment was decided based on the size of the CNS lesion (20mm) and other concerning issues. Among the 18 patients, 33% of patients (n=6) showed either CR (4 patients) or PR (2 patients) with durable response ranges from 3 to 7 months.

Efficacy Outcomes in Subjects with Melanoma or NSCLC (Interim Analysis [Data cutoff: June 30, 2015])

	NSCLC (n=18)	Melanoma (n=18)
Brain metastasis response rate, % (95% CI)	33 (14-59)[a]	22 (7-48)[b]
Complete response, n (%)	4 (22)	0
Partial response, n (%)	2 (11)	4 (22)
Stable disease, n (%)	2 (11)	2 (11)
Progressive disease, n (%)	6 (33)	8 (44)
Mixed response	1 (6)[c]	1 (6)[d]
Systemic response rate, % (95% CI)	33 (14-59)	22 (7-48)
Complete response, n (%)	0	2 (11)
Partial response, n (%)	6 (33)	2 (11)
Stable disease, n (%)	1 (6)	4 (22)
Progressive disease, n (%)	10 (56)	8 (44)
Overall survival, median (95% CI), months	7.7 (3.5-NR)	NR

[a]Four subjects were not assessable for brain metastases response due to rapid systemic progression. [b]Four subjects were not assessable for brain metastases response due to rapid extracerebral progression and intralesional hemorrhage. No *BRAF* mutations were detected in those who had a response; however, one subject expressed a *NRAS* mutation. [c]The subject had 30% shrinkage in target lesions but progression in non-target lesions. [d]The subject had 30% shrinkage of target lesions and development of new brain metastases.[1]
NSCLC, non-small cell lung cancer; CI, confidence interval.

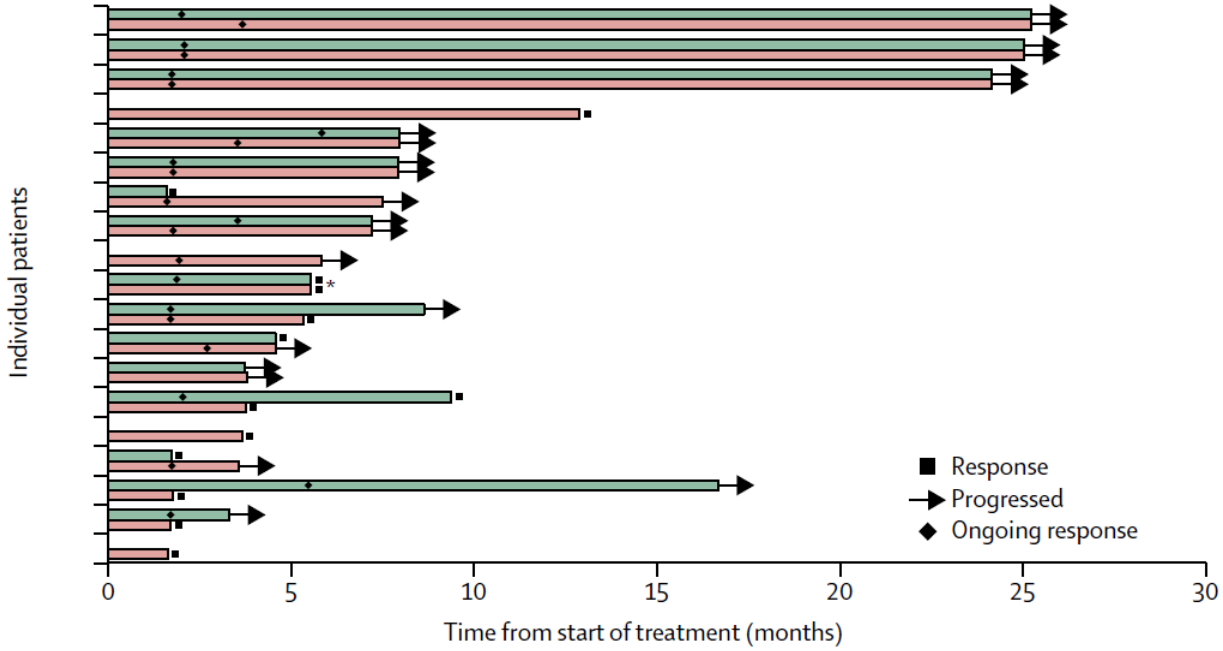
In the updated analysis, the median follow-up duration in 42 subjects with NSCLC was 8.3 months (IQR, 4.5-26.2 months). Confirmed brain response was 29.7% in cohort 1 and 0% in cohort 2. The systemic response in cohort 1 was also 29.7%. Six of 27 subjects had discordant outcomes when evaluated for both CNS and systemic response. Of these subjects, 3 subjects (11%) who had a response in the body developed progression in the brain and 3 subjects (11%) had the opposite results.

Brain Metastasis Response Rates in Subjects with NSCLC (Updated Analysis [Data cutoff: May 21, 2018])

	PD-L1 expression ≥1% (cohort 1; n=37)	PD-L1 expression <1% (cohort 2; n=5)[b]
Brain metastasis response rate, % (95% CI)	29.7 (15.9-47)	0
Complete response, n (%)	4 (11)	0
Partial response, n (%)	7 (19)	0
Stable disease, n (%)	4 (11)[a]	1 (20)
Progressive disease, n (%)	16 (43)	3 (60)

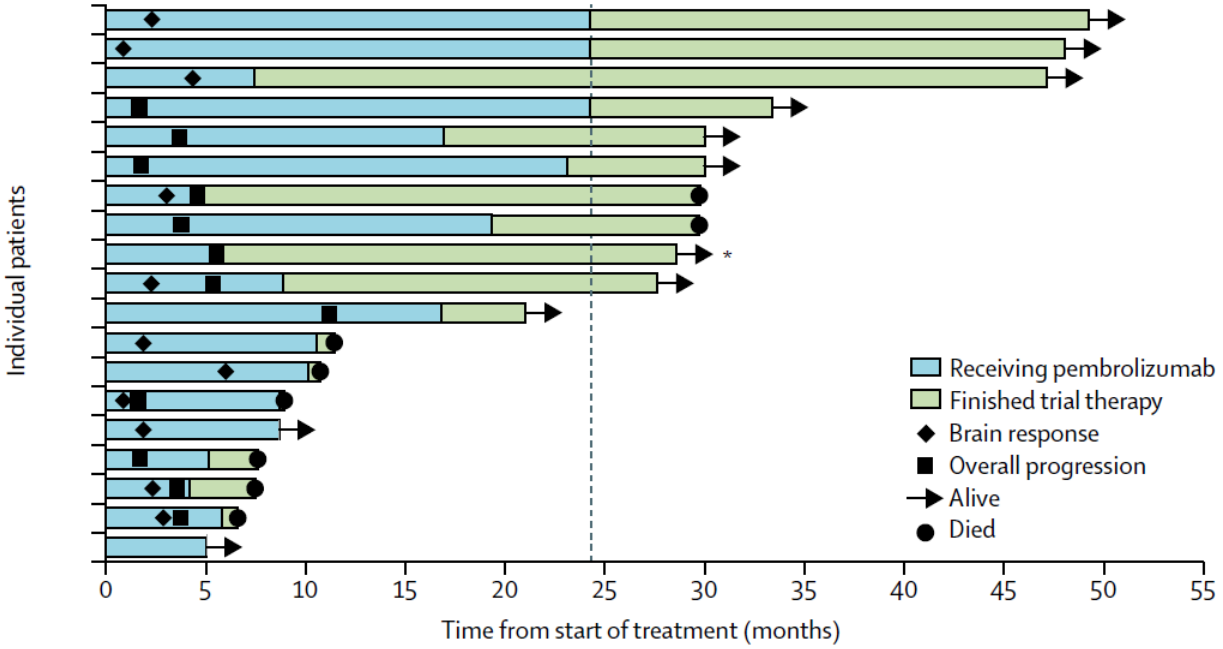
[a]Two subjects were not confirmed. [b]One subject was unevaluable.
NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; CI, confidence interval.

In the updated analysis, 19 of 42 subjects remained on the study for at least four months or had a brain metastasis response. These subjects were assessed for time to and duration of response in extracerebral and brain lesions. (*Lancet Oncol.* 2020;21(5):655-663)



In the updated analysis, each subject's overall course among those who had a brain metastasis response or remained on trial for at least four months was evaluated. All subjects with discordant outcomes lived for longer than six months, with two of the three subjects who had a partial response in the body but progressive disease in the brain living more than two years.

Time of Brain Metastasis Response, Overall Progression, and Death (Updated Analysis [Data cutoff: May 21, 2018]



*Subjects in cohort 2.
The end of the study period is indicated by the dashed line at 24 months.
Figure reprinted from Goldberg SB, et al. Pembrolizumab for management of subjects with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. Lancet Oncology 2020;21(5):655-663, with permission from Elsevier.

In the updated analysis, 37 subjects with NSCLC and PD-L1 expression ≥1% (cohort 1) were assessed for survival outcomes. Among the 37 subjects in cohort 1, 31 subjects progressed or died, and the median PFS was 1.9 months (95% CI 1.8-3.7). Twenty-six of the 37 subjects in cohort 1 had died by the time of data lock with a median OS of 9.9 months (95% CI 7.5-29.8). Estimated 1-year OS was 40% (95% CI 30-64) and estimated 2-year OS was 34% (21-54).

PFS and OS Outcomes in Subjects with NSCLC and Brain Metastases (Updated Analysis [Data cutoff: May 21, 2018])

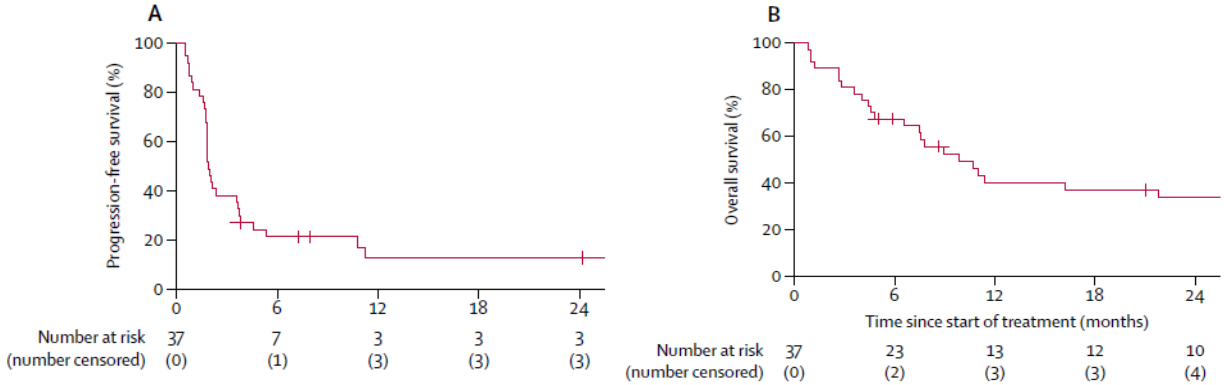


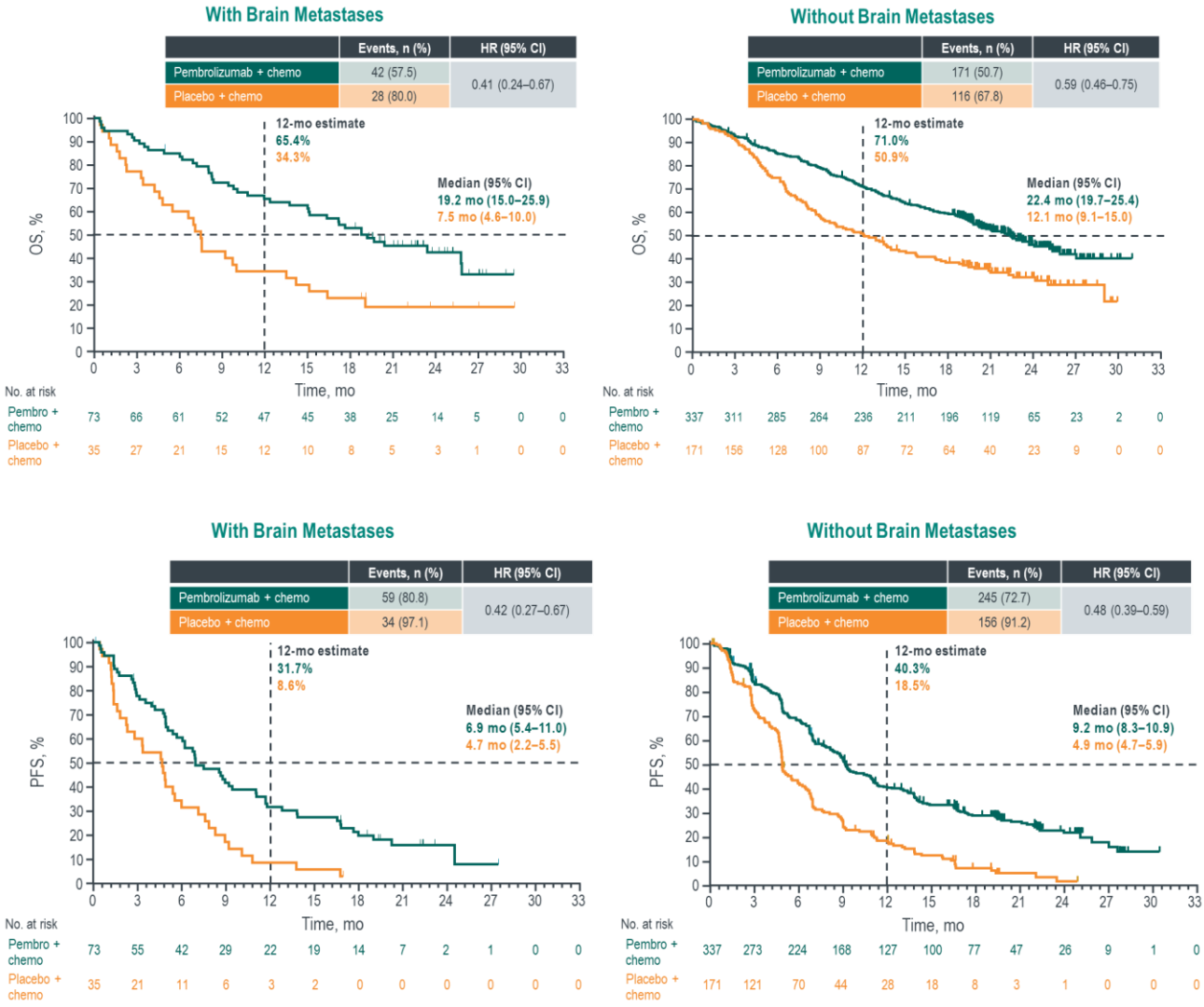
Figure reprinted from Goldberg SB, et al. Pembrolizumab for management of subjects with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. Lancet Oncology 2020;21(5):655-663, with permission from Elsevier.

Another retrospective study conducted from 2011-2017 found that in 94 patients with brain metastases from NSCLC who underwent immunotherapy combined other treatment (such as whole-brain radiation therapy, surgery, stereotactic radiosurgery or systemic chemotherapy) showed the one-year survival rate of 48.3% (J Clin Oncol. 2018;36:214). Moreover, pembrolizumab based treatment demonstrated similar result in the retrospective study (n=134) by showing no difference in median PFS (9.0 vs. 7.9 months; HR, 0.93, P = .7) and OS (18 vs. 21 months; HR, 1.03, P = .8) between patients with brain metastases and no brain metastases(IASLC 2019 North America Conference on Lung Cancer; October 12, 2019; Chicago, Ill. Abstract OA03.02.)

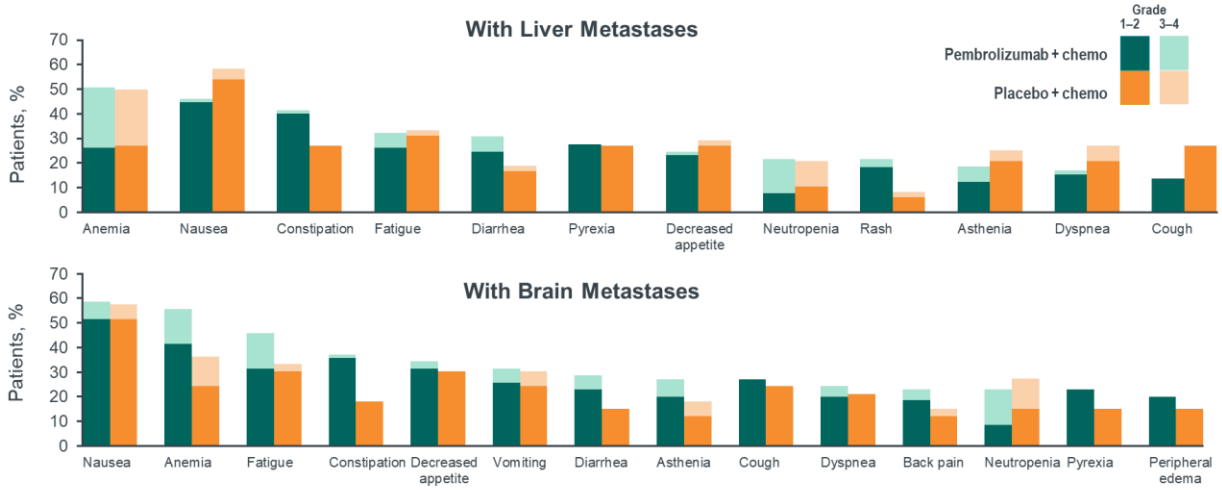
Refer to the landmark 1st line trials using pembrolizumab as monotherapy in PD-L1 > 50% (Keynote-024), 11.7% of the patients with brain metastasis were included in pembrolizumab treated arm (N Engl J Med 2016; 375:1823-1833). For this subset, the hazard ratio (HR) was 0.55 favoring the pembrolizumab treatment compared with chemotherapy although statistical significance was not reached.

In non-squamous non-small cell lung cancer, the Keynote-189 trial included 17.8% of brain metastases patients in pembrolizumab and chemotherapy-treated arm. Interestingly, patients with brain metastases showed HR of 0.41 (95%CI 0.24-0.67) in overall survival. Although it is difficult to make the direct the comparison, the HR of OS in number was slightly lower in patients with brain metastases than HR of patients without brain metastases (HR 0.53, 95%CI 0.39-0.71). HR of PFS was 0.42 (95% CI 0.26-

0.68) in brain metastases arm. Among patients with brain metastases, the ORR was 37.0% in the pembrolizumab plus chemotherapy arm and 17.1% in the chemotherapy arm.



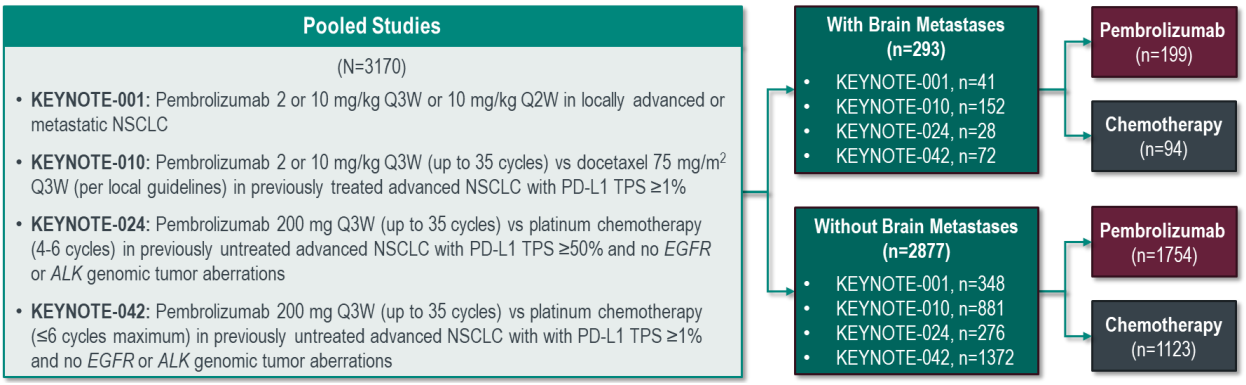
The most common adverse events of any cause for pembrolizumab plus chemotherapy arm vs chemotherapy alone arm was similar in both groups (N Engl J Med 2018; 378:2078-2092, Gadgeel S et al. J Clin Oncol 2020; Epub ahead of print. doi: 10.1200/JCO.19.03136.).



Pooled analyses results

Pembrolizumab monotherapy (Mansfield AS, Herbst RS, Castro G. Jr, et al. Outcomes with pembrolizumab monotherapy in patients with PD-L1–positive NSCLC with brain metastases: pooled analysis of KEYNOTE-001, 010, 024, and 042. Oral presentation presented at European Society for Medical Oncology (ESMO) Congress; September 27-October 1, 2019; Barcelona, Spain.)

Pooled Analysis Study Design



Among subjects allocated to pembrolizumab vs chemotherapy across all the studies, 3 vs 4 with brain metastasis and 11 vs 57 without brain metastasis did not receive treatment.
Q3W, every 3 weeks; Q2W, every 2 weeks; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

Baseline Characteristics of the Pooled Analysis Population

	With Brain Metastases		Without Brain Metastases	
	Pembrolizumab (n=199)	Chemotherapy (n=94)	Pembrolizumab (n=1754)	Chemotherapy (n=1123)
Age, median (range), years	59 (31-88)	60 (31-81)	64 (20-93)	64 (32-90)
Male, %	49.7	56.4	65.3	69.3
ECOG PS 1, %	69.8	69.1	66.5	68.7
Nonsquamous histology, %	86.9	84.0	67.3	63.1

Current/former smoker, %	79.9	81.9	80.2	79.1
PD-L1 TPS ≥50%, %	56.3	51.1	48.0	53.3
EGFR mutation[a], %	13.6	6.4	4.7	1.9
ALK alteration[a], %	1.0	0	0.7	0.2
Prior systemic therapy[b], %				
1	30.7	30.9	29.0	19.1
≥2	41.7	20.2	20.5	7.7

[a]Subjects with *EGFR* or *ALK* aberrations were not excluded from enrollment in KEYNOTE-001 or KEYNOTE-010. [b]Includes adjuvant and neoadjuvant therapies.
ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

The median duration of follow-up for the overall pooled population was 12.9 months (range, 0.1-43.7 months).

	With Brain Metastases		**Without Brain Metastases**	
PD-L1 TPS ≥50%	**Pembrolizumab (n=112)**	**Chemotherapy (n=48)**	**Pembrolizumab (n=842)**	**Chemotherapy (n=598)**
OS, median (95% CI), months	19.7 (12.1-31.4)	9.7 (7.2-19.4)	19.4 (17.0-22.4)	11.7 (10.1-13.1)
HR (95% CI)	0.78 (0.71-0.85)		0.66 (0.58-0.76)	
12-month, %	59.8	42.5	62.1	49.0
PFS,[a,c] median (95% CI), months	4.1 (2.3-10.6)	4.6 (3.5-8.4)	6.5 (6.1-8.1)	6.1 (5.8-6.2)
HR (95% CI)	0.70 (0.47-1.03)		0.69 (0.62-0.78)	
12-month, %	38.9	13.5	38.0	23.5
ORR[a], n (%)	38 (33.9)	7 (14.6)	321 (38.1)	156 (26.1)
DOR,[a,b] median (range), months	NR (4.0+ to 41.7+)	7.6 (2.9+ to 28.6+)	33.9 (1.4+ to 49.3+)	8.2 (1.6+ to 30.4+)
DOR ≥12 months[b], n (%)	28 (91.7)	1 (25.0)	173 (74.0)	27 (38.1)
PD-L1 TPS ≥1%	**(n=199)**	**(n=94)**	**(n=1754)**	**(n=1123)**
OS, median (95% CI), months	13.4 (10.4-18.0)	10.3 (8.1-13.3)	14.8 (13.4-16.1)	11.3 (10.2-12.0)
HR (95% CI)	0.83 (0.62-1.10)		0.78 (0.71-0.85)	
12-month, %	52.8	45.7	55.3	46.9
PFS,[a,c] median (95% CI), months	2.3 (2.1-3.9)	5.2 (4.2-8.3)	4.3 (4.2-5.1)	6.1 (6.0-6.3)
HR (95% CI)	0.96 (0.73-1.25)		0.91 (0.84-0.99)	
12-month, %	28.3	19.1	27.8	23.1
ORR[a], n (%)	52 (26.1)	17 (18.1)	452 (25.8)	249 (22.2)
DOR,[a,b] median (range), months	NR (3.3 to 46.2+)	8.3 (2.0+ to 28.6+)	30.4 (1.4+ to 49.3+)	8.1 (1.1+to 30.4+)
DOR ≥12 months[b], n (%)	36 (83.9)	3 (39.3)	245 (71.2)	39 (33.9)

[a]Response assessed per RECIST version 1.1 by blinded independent central review; [b]Kaplan-Meier estimate; [c]4 subjects had missing data.[3]
PD-L1, programmed death-ligand 1; TPS, tumor proportion score; OS, overall survival; CI, confidence interval; HR, hazard ratio; ORR, objective response rate; DOR, duration of response; NR, not reached; +, ongoing response; PFS, progression-free survival.

Safety Outcomes in the Pooled Analysis Population (Data cutoff: November 5, 2018 for KEYNOTE-001; March 16, 2018 for KEYNOTE-010; July 10, 2017 for KEYNOTE-024; and September 4, 2018 for KEYNOTE-042)

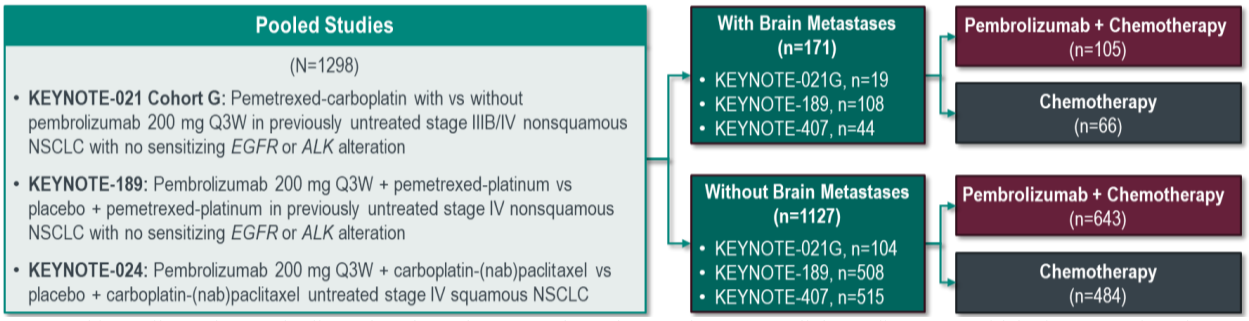
	Pembrolizumab		**Chemotherapy**	
	With Brain Metastases (n=196)	**Without Brain Metastases (n=1743)**	**With Brain Metastases (n=90)**	**Without Brain Metastases (n=1066)**
Treatment duration, median (range), months	2.8 (0.03-39.6)	4.7 (0.03-75.9)	2.9 (0.03-29.5)	3.5 (0.03-34.8)
Treatment-related AEs, %	66	67	84	88
Grade 3-5	15	18	46	43

Leading to death	2	1	3	2
Leading to discontinuation	6	8	10	11
Affecting CNS	10	7	27	27
Immune-mediated AEs and infusion reactions, %	21	25	9	8

Safety was assessed per treatment actually received.
AE, adverse event; CNS, central nervous system.

Pembrolizumab and chemotherapy combination therapy (Powell SF, Rodrǵuez -Abreu D, Langer CJ, et al. Pembrolizumab plus platinum-based chemotherapy in NSCLC with brain metastases: pooled analysis of KEYNOTE-021, 189, and 407. Poster presented at European Society for Medical Oncology (ESMO) Congress; September 27-October 1, 2019; Barcelona, Spain.)

Pooled Analysis Study Design



Among subjects allocated to pembrolizumab + chemotherapy vs chemotherapy alone across all the studies, 3 vs 2 with brain metastasis and 3 vs 4 without brain metastasis did not receive treatment.[4]
Q3W, every 3 weeks.; NSCLC, non-small cell lung cancer.

Overall, 1298 subjects were included in the analysis across all 3 studies. The data cutoff dates were December 1, 2017 for KEYNOTE-021; September 21, 2018 for KEYNOTE-189; and April 3, 2018, for KEYNOTE-407.

Baseline Characteristics of the Pooled Analysis Population[4]

	With Brain Metastases		Without Brain Metastases	
	Pembrolizumab + Chemotherapy (n=105)	Chemotherapy (n=66)	Pembrolizumab + Chemotherapy (n=643)	Chemotherapy (n=484)
Age, median (range), years	63 (35-82)	63.5 (47-81)	65 (29-87)	65 (34-88)
Male, %	66.7	54.5	66.3	69.0
ECOG PS 1, %	61.0	74.2	61.6	62.2
Nonsquamous histology, %	77.1	62.1	57.7	44.0
Current/former smoker, %	93.3	93.9	87.9	89.9
PD-L1 TPS, %				
≥50%	31.4	34.8	29.9	28.3
1%-49%	23.8	25.8	35.0	34.7
Prior therapy, %				
Adjuvant/neoadjuvant	7.6	4.5	5.3	6.8
Radiotherapy	49.5	51.5	12.4	14.0

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

The median follow-up duration for subjects with vs without brain metastasis was 10.9 months (range, 0.1-35.1 months) vs 11.0 months (range, 0.1-34.9 months).

Efficacy Outcomes in the Pooled Analysis Population (Data cutoff: December 1, 2017 for KEYNOTE-021; September 21, 2018 for KEYNOTE-189; and April 3, 2018, for KEYNOTE-407)

	With Brain Metastases		Without Brain Metastases	
	Pembrolizumab + Chemotherapy (n=105)	Chemotherapy (n=66)	Pembrolizumab + Chemotherapy (n=643)	Chemotherapy (n=484)
OS, median (95% CI), months	18.8 (13.8-25.9)	7.6 (5.4-10.9)	22.5 (19.8-25.2)	13.5 (11.3-15.8)
HR (95% CI)	0.48 (0.32-0.70)		0.63 (0.53-0.75)	
12-month, %	62.9	34.9	70.2	53.6
PFS,[a] median (95% CI), months	6.9 (5.7-8.9)	4.1 (2.3-4.6)	8.8 (8.1-9.5)	5.3 (4.8-6.1)
HR (95% CI)	0.44 (0.31-0.62)		0.55 (0.48-0.63)	
12-month, %	29.9	6.6	39.2	20.1
ORR[a,b], n (%)	41 (39.0)	13 (19.7)	351 (54.6)	154 (31.8)
DOR,[a,b] median (range), months	11.3 (1.1+ to 27.9+)	6.8 (1.3+ to 9.4+)	12.2 (1.1+ to 29.3+)	6.0 (1.4+ to 30.1+)
DOR ≥12 months[b], n (%)	15 (45.7)	0	101 (50.8)	21 (37.0)

[a]Response assessed per RECIST version 1.1 by blinded independent central review. [b]Kaplan-Meier estimate.[4]
OS, overall survival; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; ORR, objective response rate; DOR, duration of response; +, ongoing response.

Safety Outcomes in the Pooled Analysis Population (Data cutoff: December 1, 2017 for KEYNOTE-021; September 21, 2018 for KEYNOTE-189; and April 3, 2018, for KEYNOTE-407)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	With Brain Metastases (n=102)	Without Brain Metastases (n=640)	With Brain Metastases (n=64)	Without Brain Metastases (n=480)
Treatment duration, median (range), months	7.0 (0.03-29.1)	6.9 (0.03-30.4)	4.2 (0.03-18.5)	4.3 (0.03-30.7)
Treatment-related AEs, %	88.2	94.5	82.8	90.6
Grade 3-5	59.8	50.5	45.3	46.9
Led to death	5.9	2.0	1.6	1.9
Led to discontinuation	25.5	21.4	10.9	8.1
Affecting CNS	32.4	36.4	17.2	33.5
Immune-mediated AEs and infusion reactions, %	25.5	27.8	9.4	10.6
Grade 3-5	13.7	9.7	1.6	3.8

Safety was assessed per treatment actually received.[4]
AE, adverse event; CNS, central nervous system.

Rationale of pembrolizumab and chemotherapy combination therapy in asymptomatic brain metastasis

Most of previous studies with pembrolizumab monotherapy or pembrolizumab combined with chemotherapy include patients with previously treated, stable brain metastases if clinically stable ≥ 4 weeks without corticosteroids ≥3 days before study entry, which include KEYNOTE 001,

KEYNOTE 024, KEYNOTE 010, KEYNOTE 042, KEYNOTE 021G, KEYNOTE 189, and KEYNOTE 407.
In contrast, only KEYNOTE 189 and KEYNOTE 407 studies allow patients with asymptomatic brain metastasis, where no neurologic symptoms, no need for corticosteroid, and no lesion > 1.5 cm. Although the clinical outcome such as overall survival was improved with pembrolizumab monotherapy or pembrolizumab with combination chemotherapy compared with control group irrespective of brain metastasis, the data on efficacy of these regimens in untreated brain metastasis is very limited and it has not been fully established. Given that, in our study, we will investigate pembrolizumab and combination chemotherapy in patients with untreated brain metastases to evaluate the intracranial response, intracranial response duration and intracranial progression free survival.

4.2.2 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

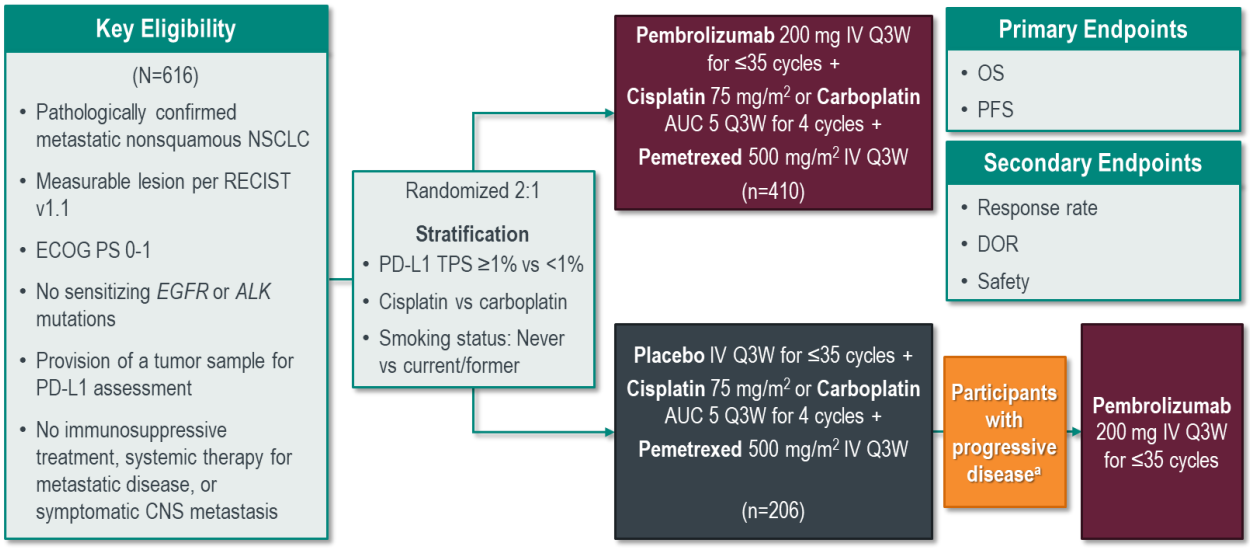
- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD -L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.
Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

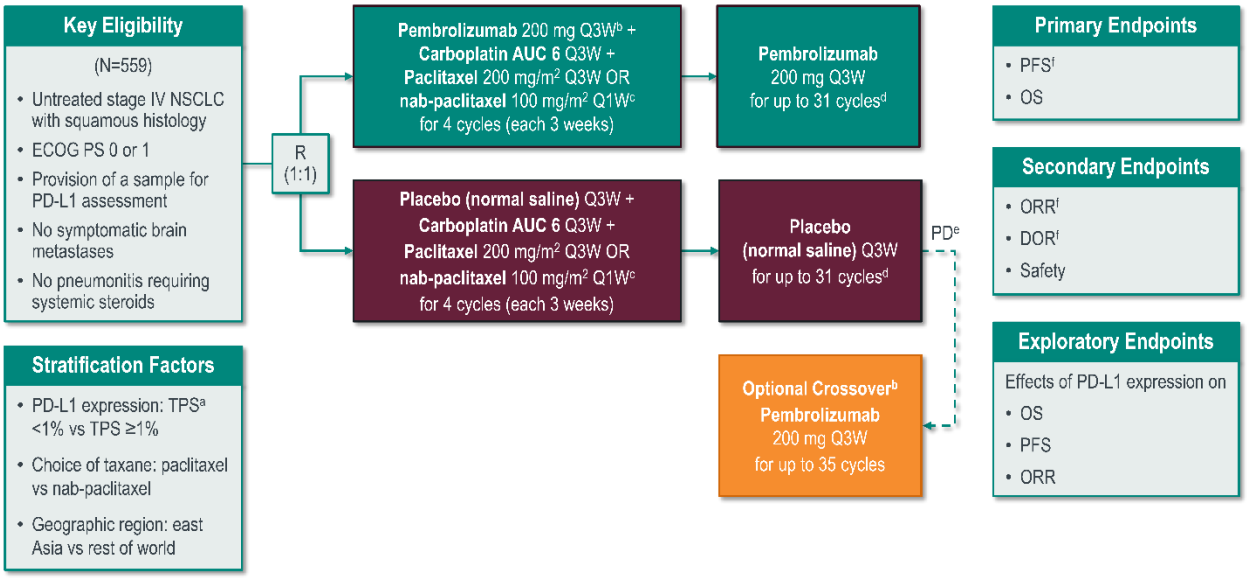
Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

Based on the previous justification for the dose of pembrolizumab monotherapy, this study is designed to combine the pembrolizumab with cytotoxic chemotherapy. The dosage used for this study is already validated for its safety through 2 major landmark trial

The first study keynote 189 study is designed to evaluate the clinical efficacy of 200mg pembrolizumab with combined with pemetrexed and carboplatin which is same regimen used for this trial. As shown below, this trial will adopt same dosage pemetrexed 500mg/m2 with Carboplatin AUC 5.0 for the non-squamous patients.



The second study Keynote 407 study is designed to evaluate the clinical efficacy of 200mg pembrolizumab with paclitaxel and carboplatin. In this study we will evaluate the clinical efficacy with Paclitaxel 200mg/m2 and carboplatin AUC 6.0 for squamous patients



4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Primary endpoint:

Intracranial overall response rate

In this study, we will evaluate the intracranial overall response rate of pembrolizumab with cytotoxic chemotherapy agent to evaluate the effectiveness of combination regimen in intracranial lesion. The overall response rate will be measured by RECIST v1.1 criteria.

Secondary endpoint:

1. Progression-free survival
   Progression free survival defined by the date of either disease progression or the all-cause mortality from the date of IP administration will be calculated.

2. Overall survival
   Overall survival defined by date of all-cause mortality from the date of IP Administration will be calculated.

3. Intracranial duration of response
   In addition to overall progression-free survival, the intracranial response will be evaluated separately. The duration for intracranial response will be calculated separately to evaluate the intracranial efficacy of IP drug

4. Intracranial progression-free survival
   Progression free survival of intracranial disease defined by the date of disease progression of intracranial lesion from the date of IP administration will be calculated.

5. Objective response rate
   Objective response rate of disease will be measured by RECIST v 1.1 criteria.

6. Safety profile
   Adverse event will be evaluated using CTCAE v5.0

4.2.3.2 Planned Exploratory Biomarker Research

The exploratory analyses based on the PD-L1 expression (by DAKO PD-L1 22C3 assay) and genomic profile (using scRNA and TCR sequencing) from the baseline samples will be used for the exploratory analyses in subjects who are available for the PD-L1 test and genomic profiling. Also organoids derived from obtained tissue will be used for development to validate the drug sensitivity and explore the tumor characteristics in-depth using organoid.

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 19 years of age on the day of signing informed consent with histologically confirmed diagnosis of stage IV non-small cell lung cancer with asymptomatic brain metastases will be enrolled in this study.

2. Must have at least one intracranial target lesion. Intracranial lesion must be equal or greater than the 10mm in longest diameter.

3. Have confirmation that EGFR or ALK-directed therapy is not indicated (documentation of absence of tumor activating EGFR mutations AND absence of ALK gene rearrangements OR presence of a K-Ras mutation. However, patients with squamous histology are eligible without genomic data)

4. Have measurable disease based on RECIST 1.1 as determined by the local site investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Otherwise, previously treated with radiation is not considered as measurable lesion.

5. Have not received prior systemic treatment for their advanced/metastatic NSCLC. Subjects who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 6 months prior to the development of metastatic disease.

6. Have a life expectancy of at least 3 months

7. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status.

8. Have adequate organ function

9. Male participants:
   A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

10. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
    OR

b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days after the last dose of study treatment.

11. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

Table 2. Adequate Organ Function Laboratory Values

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

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

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

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

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

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to IP administration (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

3. Has received prior systemic anti-cancer therapy including investigational agents prior to IP administration as a metastatic disease treatment, including tyrosine kinase inhibitor.

4. Had major surgery < 3 weeks prior to first dose

5. No measurable CNS lesion other than CNS lesion treated with stereotactic radiotherapy or surgery

6. Had received whole brain radiotherapy or stereotactic radiotherapy to CNS disease.

7. Has received prior radiotherapy within 1 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation to non-CNS disease.

8. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

9. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.

10. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

11. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, thyroid cancer or early gastric cancer or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

12. Has known active carcinomatous meningitis.

13. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

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

15. Has a history of (non-infectious) pneumonitis that currently required steroids or has current pneumonitis.

16. Has an active infection requiring systemic therapy.

17. Has a known history of Human Immunodeficiency Virus (HIV) infection.

18. Has a active Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive with HBV DNA positive) or known active Hepatitis C virus (defined as HCV RNA is detected) infection. These patients can be participated with appropriate treatment and prophylactic treatment based on the investigator's decision.

19. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

20. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

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

22. Has had an allogenic tissue/solid organ transplant.

5.1.3 Lifestyle Considerations

5.1.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.
For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study intervention(s). The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to principal investigator within 2 working days 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 principal investigator. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to principal investigator and followed as described in Section 6.2.

5.2 Trial Intervention(s)

The intervention(s) to be used in this trial is outlined below in below **Table**3

Table 3. Trial Intervention(s)

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle	Experimental
Pemetrexed	500mg/m^2	Q3W	IV infusion	Day 1 of each 3-week cycle	Experimental
Paclitaxel	200mg/m^2	Q3W	IV infusion	Day 1 of each 3-week cycle	Experimental
Carboplatin	AUC 5.0 or 6.0	Q3W	IV infusion	Day 1 of each 3-week cycle	Experimental
Carboplatin dosage will use Calvert formula and dose not to exceed 750mg Total Dose (mg) = target AUC x (CrCl + 25)					

5.2.1 Timing of Dose Administration

Trial interventions should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Schedule of Activities, Section 2.3. Trial interventions may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.
All trial interventions will be administered on an outpatient basis.

Pembrolizumab
Pembrolizumab 200 mg 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).

Pemetrexed
Pemetrexed 500 mg/m2 will be administered as an IV infusion over 10 minutes Q3W until progression or unacceptable toxicity. All subjects should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below:
- Folic Acid 350-1000 µg oral: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.

• Dexamethasone prophylaxis 4 mg, orally twice per day (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during cycles 1-4 but not to exceed doses in MASCC guidelines.

Paclitaxel
Paclitaxel 200 mg/m2 will be administered as an IV infusion over 3 hours Q3W for 4 cycles as per local practice and labels. All subjects should be pre-medicated with oral or intravenous steroid and anti-histamines according to the approved product label and/or standard practice. Additional pre-medications should be administered as per standard practice. Paclitaxel should be completely administered before initiating carboplatin dose.

Carboplatin
Carboplatin AUC 5 or 6 mg/mL/min (based on histology) will be administered as an IV infusion over 15-60 minutes Q3W for 4 cycles immediately after pemetrexed as per local practice and labels

Dose modification
Dose modification must be based on the maximum toxicity experienced during a cycle. Toxicity needs to resolve to Grade ≤1 or baseline prior to resuming the subsequent cycle. For individual subjects requiring a dose modification, treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recover to Grade ≤1 or the baseline status of the subject.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Subjects can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. If a subject experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Subjects who require a 3rd dose modification to any particular component will have that agent discontinued. Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the treatments. If, in the e opinion of the Investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of three agents, all three agents should be reduced (if applicable), interrupted or discontinued according to the recommended dose modifications.

Subjects may have chemotherapy discontinued and continue on pembrolizumab alone. Similarly subjects may discontinue pembrolizumab and continue on chemotherapy alone if appropriate.

Chemotherapy may be interrupted for a maximum of 6 weeks; pembrolizumab may be interrupted for a maximum of 12 weeks. The Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0) must be used to grade the severity of adverse events. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 4 and please refer to approved product labels for dose modification regarding the cytotoxic agent.

Table 4. Dose modification for Trial medications are as follows.

	Dose level 0	**Dose level -1**	**Dose level -2**	**Dose level -3**
Carboplatin	AUC 5.0	AUC 3.75	AUC 2.5	Discontinue
Carboplatin	AUC 6.0	AUC 4.5	AUC 3.0	Dicontinue
Pemetrexed	500mg/m^2	375mg/m^2	250mg/m^2	Discontinue
Paclitaxel	200mg/m^2	150mg/m^2	100mg/m^2	Discontinue
Pembrolizumab	200mg fixed dose	Dose reduction not permitted	Dose reduction not permitted	Discontinue

5.2.2 Dose Modification and toxicity management <u>for immune-related AEs associated with pembrolizumab</u>

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.

Table 5. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

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

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold		• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus)

	Recurrent Grade 3 or Grade 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold		• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)

	Grade 3 or 4	Withhold or permanently discontinue [d]	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue		

		based on the event [e].		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

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

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6.

Table 6. Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion);	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs	No subsequent dosing

recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug intervention.**	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events and/or unforeseen circumstances not related to study intervention. However, intervention is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the patient's study record.

5.3 Randomization or Treatment Allocation

No randomization is allowed. Treatment allocation is based on the histologic subtype

5.4 Stratification

No stratification is planned.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the participant.

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days prior to the first dose of trial intervention and up to 28 days after the last dose of trial intervention should be recorded. If participants experience an SAE or ECI, concomitant medications administered 28 days after the last dose of trial intervention are to be recorded as defined in Section 6.2.

5.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol

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

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants 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. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator and the participant.
There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [Table 5]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.
It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.6 Participant Discontinuation Criteria

Discontinuation of study intervention does not represent withdrawal from the study.
As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 2.3 unless the participant has withdrawn from the study (Section 5.7).
Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.
A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention
- After prolonged study intervention interruption that prohibits restarting study intervention
- Radiographic disease progression outlined in Section 6.1.4.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 5.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test

5.7 Participant withdrawal From Study

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

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specified details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 6.1.6.1.

5.8 Clinical Criteria for Early Trial 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 drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

In the event of MSD decision to no longer supply study drug, adequate notification will be provided so that appropriate adjustments to participant treatment can be made.

6.0 TRIAL ASSESSMENTS AND PROCEDURES

6.1 Trial Procedures

- Study procedures and their timing are summarized in The Schedule of Activities, Section 2.3.
- Adherence to the study design requirements, including those specified in the Schedule of Activities is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria
- Additional evaluations/testing may be deemed necessary by the principal investigator for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.1.1 Administrative and General Procedures

6.1.1.1 Informed Consent

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

6.1.1.2 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.
A copy of the signed and dated consent form should be given to the participant before participation in the trial.
The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the

participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.
Specifics about a trial and the trial population will be added to the consent form template at the protocol level.
The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations.
If the investigator recommends continuation of study intervention beyond disease progression, the participant or his/her legally acceptable representative will be asked to sign consent.

6.1.1.3 Inclusion/Exclusion Criteria

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

6.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

6.1.1.5 Prior and Concomitant Medications Review

6.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

6.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. In addition, new medication started during the Second Course should be recorded. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 6.2.

6.1.1.6 Disease Details and Treatments

6.1.1.6.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

6.1.1.6.2 Prior Treatment Details

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

6.1.1.6.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 28 days after the last dose of trial treatment, the 28-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 Physical Exam

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.1.2.3 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 2.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.1.2.4 Directed Physical Exam

For cycles that do not require a full physical exam per the Section 2.3, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.1.2.5 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Schedule of Activities (Section 2.3). Vital signs should include pulse, , blood pressure and weight. Height will be measured at screening only.

6.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Schedule of Activities (Section 2.3).

6.1.2.7 Electrocardiograms

Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and [QTc] intervals.

6.1.3 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from non protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered

clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Refer to the Study Flow Chart (Section 2.3) for the timing of laboratory assessments.

6.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

6.1.3.2 Pregnancy Testing

WOCBP should be a maximum of 24-hours before the first dose/vaccination. Other women must be tested for pregnancy within 72 hours before the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulation.(Appendix3)

6.1.4 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT) for extracranial lesion. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

6.1.4.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of allocation and can be assessed by the central imaging vendor.

Brain imaging should be by MRI if possible.

6.1.4.2 Tumor Imaging During the Study

Tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated for first 12 months and 9 weeks (63 days ±7 days) thereafter. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

6.1.4.3 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.
For participants who discontinue study treatment without documented disease progression, start follow-up visit. Every 12 weeks tumor image assessment.

6.1.4.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment

6.1.5 Tumor Tissue Collection and Correlative Studies Blood Sampling

Collects 30cc of blood samples at the time screening. Collects 20cc of blood C1D8, C2D1, C3D1 and disease progression. Collects Fresh tumor tissue sample or up to 15 unstained slide at the screening and disease progression. Tumor tissue collection and correlative blood sampling is not mandatory.

If participants agree with the purpose of secondary usage and has an identifiable residual sample among samples obtained through other studies before participating in this trial, the tissue sample may be used.

6.1.6 Other Procedures

6.1.6.1 Discontinuation and withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 6.1.7.3.
Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2.

6.1.7 Visit Requirements

Visit requirements are outlined in Section 2.3 – Schedule of Activities. Specific procedure-related details are provided above in Section 6.1 - Trial Procedures.

6.1.7.1 Screening

6.1.7.1.1 Screening Period

Screening should be conducted within 28 days from the expected date of allocation

6.1.7.2 Treatment Period

Treatment will follow the study protocol until disease progression or unacceptable toxicity. Beyond treatment is allowed based on the investigator's decision

6.1.7.3 Post-Treatment Visits

6.1.7.3.1 EOT (Safety Follow-Up Visit)

The mandatory Safety Follow-Up Visit should be conducted approximately 28 days after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first.

6.1.7.3.2 Follow-up Visits

Participants who complete the protocol-required cycles of study intervention of who discontinue study intervention for a reason other than disease progression will begin the Follow-Up Phase Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

6.1.7.3.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.1.7.3.4 Post Study

Participants will be required to return to clinic approximately 28 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less then 28 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 28 days post the last dose of study intervention to determine of any AEs have occurred since the poststudy clinic visit.

6.2 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 4.
Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).
The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.
The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

6.2.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation must be reported by the investigator if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 28 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 90 days following cessation of study intervention or 28 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through 120 days following cessation of study intervention, or 28 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to principal investigator if the event is considered drug-related.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify principal investigator.
All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to principal investigator within the time frames as indicated in

Table

Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** **Consent to Allocation**	**Reporting Time Period:** **Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period:** **After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to principal investigator:**
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 2 business days but no longer than 3 calendar days of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of learning of event

6.2.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

6.2.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up. In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated or randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

6.2.4 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable country specific regulatory requirements, global laws and regulations.

6.2.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to principal investigator.
All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

6.2.6 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to principal investigator.

Events of clinical interest for this study include:

1. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant 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 MSD product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.0 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan Summary

Based on the pooled analyses from Keynote-189 and 407 study, overall response rate of pembrolizumab with chemotherapy was around 40%. Overall response rate of chemotherapy alone was around 20% in patients with CNS metastases. In this study, we expect this number can be reproduced in the intracranial overall response.

H0: 20% of intracranial response rate by historical control treated with cytotoxic chemotherapy alone
H1: 40% of intracranial response rate by treated with pembrolizumab and cytotoxic chemotherapy

Accrual time: 18 months
Follow-up time: 12 months
One-sided alpha: 0.05
Power: 0.9

Using the Simon's two stage design, a total of 45 patients is needed for the minimax statistical analyses. Considering the 10% of dropout rate, a total of 50 patients is needed for final analyses.

7.2 Statistical Analysis Plan

This study will not conduct interim analyses and final analyses will be conducted after last patient reached at least 6 cycles of the treatment. Intracranial overall response rate will be measured by RECIST v1.1 and patients with best response of partial response and complete response will be calculated as responder. Progression-free survival will be calculated by the date of either disease progression or the all-cause mortality from the date of IP administration. Overall-survival will be calculated by date of all-cause mortality from the date of IP Administration. The duration for intracranial response will be calculated separately to evaluate the intracranial efficacy of IP drug.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 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.
Pembrolizumab will be provided by MSD as summarized in Table 8.

Table 8. Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

8.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

8.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, designee are not blinded to treatment.

8.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.
Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.
Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from MSD or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.
Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9.0 REFERENCES

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10.0 APPENDICES

Appendix 1: ECOG Performance Status

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

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

Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9. Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose [Indicate if fasting, or nonfasting]	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• [Highly sensitive serum or urine] hCG pregnancy test (as needed for WOCBP)			
Other Screening Tests	• FSH (as needed in WONCBP only) • [Serum or urine] [alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) if applicable] • [Serology [(HIV antibody, HBsAg, and hepatitis C virus antibody)] [or specify other tests] [if applicable] •			
	•			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)
Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:
Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 5.11:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:
Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10 during the protocol-defined time frame in Section 5.11.

Table 10. Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 30 days after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose/vaccination.
Following initiation of treatment additional pregnancy testing will be performed at 2 cycle interval (approximately 6 weeks) intervals during the treatment period and at 30 days after the last dose of study treatment and as required locally.
Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.1.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as MSD product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by MSD for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

10.1.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.1.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to principal investigator in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by principal investigator for collection purposes.

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

10.1.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- There may be instances when copies of medical records for certain cases are requested by the MSD. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the MSD.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

1. The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
    - Grade 4: Life threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.

Assessment of causality

1. Did MSD product cause the AE?

2. The determination of the likelihood that MSD product caused the AE 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 product and the AE based upon the available information.

3. The following components are to be used to assess the relationship between MSD's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely MSD product caused the AE:

    - **Exposure:** Is there evidence that the participant was actually exposed to MSD 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 MSD product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies 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.
- **Dechallenge:** Was MSD 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 MSD product; (3) the study is a single-dose drug study; or (4) MSD product(s) is/are only used 1 time.)
- **Rechallenge:** Was the participant re-exposed to MSD 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 study is a single-dose drug study; or (3) MSD product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY MSD PRODUCT, OR IF RE-EXPOSURE TO MSD'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

4. **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding MSD product or drug class pharmacology or toxicology?
5. 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.
6. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of MSD product relationship).

- Yes, there is a reasonable possibility of MSD product relationship:
- There is evidence of exposure to the MSD product. The temporal sequence of the AE onset relative to the administration of MSD product is reasonable. The AE is more likely explained by MSD product than by another cause.
- No, there is not a reasonable possibility of MSD product relationship:
- Participant did not receive the MSD product OR temporal sequence of the AE onset relative to administration of the MSD product is not reasonable OR the AE is more likely explained by another cause than the MSD product. (Also entered for a participant with overdose without an associated AE.)

7. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

8. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the MSD. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to MSD.

9. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

11. For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to principal investigator within 2 business days but no longer than 3 calendar days of receipt of the information.

10.1.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Principal investigator

SAE reports and any other relevant safety information are to be forwarded to the Principal investigator based on the local regulation.