MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2017-0339
Protocol Title	A phase Ib/II trial of M7824 in solid tumors with microsatellite instability, with Consensus Molecular Subtype 4 metastatic colorectal cancer in combination with radiation, or in colorectal cancer patients with detectable circulating tumor DNA following definitive therapy
Phase	Ib/II
Protocol Version	9.0
Version Date	June 25, 2020
Protocol PI	Van Morris, MD
Department	GI Medical Oncology
IND Sponsor	MD Anderson Cancer Center
IND #	137789

Clinical Trial Protocol

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IND Number	137789
Principal Investigator	Van Morris, MD The University of Texas – MD Anderson Cancer Center Houston, TX USA
Sponsor	MD Anderson Cancer Center, Houston, TX USA
Clinical Trial Protocol Version	June 25, 2020/ Version 9.0
Replaces Version	May 23, 2019/Version 8.0

Protocol Table of Contents

Table of In-Text Tables

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CIMP	CpG Island Methylator Phenotype
CMS	Consensus Molecular Subtype
CRF	Case Report Form
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
DFS	Disease-Free Survival
DLT	Dose Limiting Toxicity
EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
Hgb	Hemoglobin
IB	Investigator's Brochure
ICH	International Conference on Harmonization
iCPD	Immune Confirmed Progressive Disease
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention To Treat
iUPD	Immune Unconfirmed Progressive Disease
IV	Intravenous
IVRS	Interactive Voice Response System
LA	Locally advanced
mCRC	Metastatic Colorectal Cancer

MoA	Mechanism of Action
MSI	Microsatellite Instability
MSI-L	Microsatellite Instability – Low
MSI-H	Microsatellite Instability - High
MSS	Microsatellite Stable
NCI	National Cancer Institute
NFkB	Nuclear Factor Kappa Light Chain Enhanced of Activated B cells
NK	Natural Killer
OS	Overall Survival
ORR	Objective Response Rate
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	Programmed Death - 1
PD-L1	Programmed Death Ligand 1
PDx	Pharmacodynamics
PGx	Pharmacogenetics/Pharmacogenomics
PFS	Progression Free Survival
PK	Pharmacokinetics
PO	Per Os
PR	Partial Response
PS	Performance Status
RECIST	Response Evaluation Criteria in Solid Tumors
ROS	Reactive oxygen species
RR	Response Rate
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
T_{reg}	T-regulatory
TGF-β	Transforming Growth Factor β
WBC	White Blood Cell
ULN	Upper Limit of Normal
UR	Unresectable

Table 1: Schedule of Assessments (Cohort A-C)

Test		Cycle 1		Cycle 2		Cycle 3 (and all subsequent cycles)		End-of-Treatment	28-day follow up after progression	Long term follow up
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of dis-continuation or within 7 days after**		**Every 3 months after 28 day follow up**
Inclusion/exclusion criteria	X	X								
Demographic data	X									
Medical history	X									
Cancer disease history	X									
Prior anticancer drug/ radiotherapy/ procedures	X									
Concurrent medications	X									
Written informed consent	X									
Enrollment (if eligible)[a]	X									

Test		**Cycle 1**		**Cycle 2**		**Cycle 3[l]and all subsequent cycles)**		**End of Treatment**	**28day follow-up after progression**	**Long-term follow-up**
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of discontinuation or within 7 days after**		**Every 3 months after 28-day follow up**
Physical examination[b,p]	X	X	X	X	X	X	X	X	X	
Vital signs including weight[p] and height (latest height on record acceptable; height is only performed at screening)	X	X	X	X	X	X	X	X	X	X
ECOG PS[p]	X	X	X	X	X	X	X	X	X	X
Toxicity assessment[p]	X	X	X	X	X	X	X	X	X	X[r]
12-lead EKG[c,d, p]	X				X				X	
Full serum chemistry[e, p]	X	X	X	X	X	X	X	X	X	
Complete blood count[e, p]	X	X	X	X	X	X	X	X	X	
Free T4, TSH[e, f, p]	X					X			X	
ANA, RF[e,]	X								X	
Urinalysis (dipstick)[e, p]	X	X		X		X		X	X	

β-HCG pregnancy test, FSH [e, f,p]	X	X		X		X			X[o]	
Test		**Cycle 1**		**Cycle 2**		**Cycle 3 (and all subsequent cycles)**		**End of treatment**	**28 day follow up after progression**	**Long-term follow-up**
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of discontinuation or within 7 days after**		**Every 3 months after 28-day follow up**
HIV, HBV, HCV testing	X									
Documentation of AEs, concomitant medications, and procedures [q]	X	X	X	X	X	X	X	X[q]	X[q]	X
M7824 Administration [p]		X[t]	X[t]	X	X	X	X			
Patient-reported outcomes [p]		X	X	X	X	X	X		X	
Tumor biopsy [g,p]	X			X					X	
MSI testing [h]	X									
Tumor evaluation by imaging (w/collection of available staging imaging prior to study enrollment) [l,j,p]	X					X			X[u]	X[q]

Verification of available specimen for mutation profiling [k]	X									
Test		**Cycle 1**		**Cycle 2**		**Cycle 3 (and all subsequent cycles)**		**End of Treatment**	**28 day follow up after progression**	**Long-term follow-up[r]**
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of discontinuation or within 7 days after**		**Every 3 months after 28-day follow up**
Verification of available specimen for TGFβ 1,2,3 analysis [p]	X	X		X	X	X[s]			X	
Blood biomarkers (including circulating cytokines) [l,p]	X	X		X	X	X			X	
Collection of buccal and fecal swabs for microbiome testing[p]	X			X		X[s]		X		
Verification of available specimen for PD-L1 expression [m]	X			X						
Collection of specimens for analysis of pharmacokinetics of M7824 [n,p]		X	X	X				X		

[a]Enrollment will be done after the confirmation of fulfilling all screening inclusion criteria without matching any exclusion criterion.

[b]Physical examination should include a dermatological examination. If abnormal skin findings are observed, patient should be

referred to a dermatologist for biopsy of suspicious lesions. An ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be conducted at Screening. At subsequent visits, eye signs and symptoms should be checked. If there are any clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days. Starting with C1D15, a focused examination may be performed centered around patient's symptoms at an assigned visit.

[c]12-lead EKG should be performed as soon after completion of infusion as possible.

[d]EKGs are to be performed every 6 weeks.

[e]Laboratory draws may be performed up to 72 hours before a scheduled treatment.

[f]For women of child-bearing potential. FSH should be drawn if clarification of post-menopausal state is warranted. Refer to Appendix 2 for further details.

[g]Mandatory fresh tumor biopsies will be collected prior to treatment and prior to dose 3. An optional tumor biopsy following progression may be offered to the patient.

[h]Performed on archival tissue or fresh biopsy. MSI testing performed in a CLIA certified laboratory is acceptable and does not need to be repeated (see section 6.4.5)

[i]Tumor measurements should occur with CT imaging or MRI. Ideally the same methodology would be used over the course of the study for a given patient. Bone scan should be done at screening if clinically indicated. For collection of those prior imaging studies prior to informed consent, readily available imaging studies since the onset of metastatic/unresectable disease are to be prioritized for collection. If the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the screening CT and/or MRI does not need to be performed.

[j]Tumor measurements are to be assessed every 8 weeks (+/- 5 days). For subjects continuing treatment beyond 12 months, tumor evaluations should take place every 12 weeks (+/- 5 days).

[k]To be performed on archival tissue or fresh biopsy either via hotspot next general sequencing panel in CLIA certified molecular diagnostics laboratory at MD Anderson.

[l]Plasma will be sent for markers including, but not limited to, interleukin (IL) IL-1α, IL-1β, IL-2, IL-5, IL-6, IL-8, IL-13, TNF-α, MCP, MIP-1β, G-CSF, GM-CSF, IFN-γ via a cytokine assay ((Meso Scale Discovery (MSD), 40 Plex). Leukocyte subpopulations and immune activation status will be assessed by flow cytometry (fluorescence-activated cell sorter [FACS]) on PBMC from heparinized blood samples (10 mL, tubes). Additional time points to include for collection after cycle 3, day 1 include C4D1, C5D1, and C6D1. No additional biomarker samples for this analysis will be collected while the patient is receiving treatment on study.

[m]PD-L1 expression by immunohistochemistry on fresh biopsy. Repeat IHC on FRESH biopsy prior to dose 3 of M7824
[n]One 10 mL vial of blood will be drawn prior to M7824 infusion and immediately following completion of M7824 infusion for doses 1 and 3 (cycle 1 day 1 and cycle 2 day 1) for analysis of pharmacokinetics. One 10 mL vial of blood will be drawn prior to M7824 infusion of M7824 infusion for doses 2 (cycle 1 day 15) and dose 6/end of treatment (whichever comes first). Refer to Section 6.4.3 for details on processing of PK samples.
[o]β-hCG (no FSH) at post-progression follow-up visit
[p]Window of +/- 7 days is allowed
[q]Adverse events are recorded and assessed continuously throughout the trial (see Section 6.4.1.3) and are assessed for final outcome at the End of Treatment visit. After the End of Treatment visit only AEs that are deemed attributable to trial drug by the Investigator should be documented until the Safety Follow-up visit.
[r]For up to one year following discontinuation of treatment on study.
[s]Cycle 3, Day 1 collection only.
[t]Patients must remain at the CTRC for two hours of observation following the first two doses of therapy.
[u]Only to be performed if no disease progression was documented previously.

Table 2: Schedule of Assessments (Cohort B)

Test		**Cycle 1**		**Cycle 2**		**Cycle 3 (and all subsequent cycles)**		**End-of-Treatment**	**28 day follow up after progression**	**Long term follow up**
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of dis-continuation or within 7 days after**		**Every 3 months after 28 day follow up**
Inclusion/exclusion criteria	X	X								
Demographic data	X									
Medical history	X									
Cancer disease history	X									
Prior anticancer drug/ radiotherapy/ procedures	X									
Concurrent medications	X									
Written informed consent	X									
Enrollment (if eligible)[a]	X									

Test		Cycle 1		Cycle 2		Cycle 3 (and all subsequent cycles)		End of Treatment	28 day follow-up after progression	Long-term follow-up
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of discontinuation or within 7 days after**		**Every 3 months after 28-day follow up**
Physical examination[b,q]	X	X	X	X	X	X	X	X	X	
Vital signs including weight and height (latest height on record acceptable)[q]	X	X	X	X	X	X	X	X	X	X
ECOG PS[q]	X	X	X	X	X	X	X	X	X	X
Toxicity assessment[q]	X	X	X	X	X	X	X	X[s]	X[s]	X
12-lead EKG[c,d, q]	X				X				X	
Full serum chemistry[e, q]	X	X	X	X	X	X	X	X	X	
Complete blood count[e, q]	X	X	X	X	X	X	X	X	X	
Free T4, TSH[e, f, q]	X					X			X	
ANA, RF[e,]	X								X	
Urinalysis (dipstick)[e, q]	X	X		X		X		X	X	
β-HCG pregnancy test, FSH [e, f,q]	X	X		X		X			X[p]	

Test		**Cycle 1**		**Cycle 2**		**Cycle 3 (and all subsequent cycles)**		**End of treatment**	**28 day follow up after progression**	**Long-term follow-up**
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of discontinuation or within 7 days after**		**Every 3 months after 28-day follow up**
HIV, HBV, HCV testing	X									
Documentation of AEs, concomitant medications, and procedures [q]	X	X	X	X	X	X	X	X[r]	X[r]	X
M7824 Administration [q]		X[u]	X[u]	X	X	X	X			
SBRT Administration[w]			X							
Patient-reported outcomes [q]		X	X	X	X	X	X		X	
Tumor collection [g,q]	X		X[x]	X					X	
MSI testing [h]	X									
Confirmation of CMS status[i]	X									

Test		Cycle 1		Cycle 2		Cycle 3 (and all subsequent cycles)		End of Treatment	28 day follow up after progression	Long-term follow-up[s]
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of discontinuation or within 7 days after**		**Every 3 months after 28-day follow up**
Verification of available specimen for analysis of TGFβ 1,2,3 [q]	X	X		X	X	X[t]			X	
Tumor evaluation by imaging (w/collection of available staging imaging prior to study enrollment) [j,k,q]	X					X			X[v]	X[r]
Verification of available specimen for mutation profiling [l]	X									
Blood biomarkers (including circulating cytokines) [m,q]	X	X		X	X	X			X	
Collection of buccal and fecal swabs for microbiome testing[q]	X			X		X[t]		X		
Verification of available specimen for PD-L1 expression [n]	X			X						

Collection of samples for pharmacokinetics of M7824[o,q]		X	X	X				X		

[a]Enrollment will be done after the confirmation of fulfilling all screening inclusion criteria without matching any exclusion criterion.
[b]Physical examination should include a dermatological examination. If abnormal skin findings are observed, patient should be referred to a dermatologist for biopsy of suspicious lesions. An ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be conducted at Screening. At subsequent visits, eye signs and symptoms should be checked. If there are any clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 weeks, unless an urgent necessity is determined by the treating provider that requires a sooner evaluation. Starting with C1D15, a focused examination may be performed centered around patient's symptoms at an assigned visit.
[c]12-lead EKG should be performed as soon after completion of infusion as possible.
[d]EKGs are to be performed every 6 weeks.
[e]Laboratory draws may be performed up to 72 hours before a scheduled treatment.
[f]For women of child-bearing potential. FSH should be drawn if clarification of post-menopausal state is warranted. Refer to Appendix 2 for further details.
[g]Mandatory fresh tumor biopsies will be collected prior to treatment and prior to dose 2 (i.e., on cycle 1, day 15) and prior to dose 3. An optional tumor biopsy following progression may be offered to the patient.
[h]MSI testing performed in a CLIA certified laboratory is acceptable and does not need to be repeated (see section 6.4.5)
[i]CMS on FFPE at CLIA testing laboratory on archival primary tissue or fresh biopsy.
[j]Tumor measurements should occur with CT imaging or MRI. Ideally the same methodology would be used over the course of the study for a given patient. Bone scan should be done at screening if clinically indicated. For collection of those prior imaging studies prior to informed consent, readily available imaging studies since the onset of metastatic/unresectable disease are to be prioritized for collection. If the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the screening CT and/or MRI does not need to be performed.
[k]Tumor measurements are to be assessed every 8 weeks (+/- 5 days). For subjects continuing treatment beyond 12 months, tumor evaluations should take place every 12 weeks (+/- 5 days).

[l]To be performed on archival tissue or fresh biopsy either via hotspot next general sequencing panel in CLIA certified molecular diagnostics laboratory at MD Anderson.

[m]Plasma will be sent for markers including, but not limited to, interleukin (IL) IL-1α, IL-1β, IL-2, IL-5, IL-6, IL-8, IL-13, TNF-α, MCP, MIP-1β, G-CSF, GM-CSF, IFN-γ via a cytokine assay ((Meso Scale Discovery (MSD), 40 Plex). Leukocyte subpopulations and immune activation status will be assessed by flow cytometry (fluorescence-activated cell sorter [FACS]) on PBMC from heparinized blood samples (10 mL, tubes). Additional time points to include for collection after cycle 3, day 1 include C4D1, C5D1, and C6D1. No additional biomarker samples for this analysis will be collected while the patient is receiving treatment on study.

[n]PD-L1 expression by immunohistochemistry on fresh biopsy. Repeat IHC on FRESH biopsy prior to dose 3 of M7824

[o]One 10 mL vial of blood will be drawn prior to M7824 infusion and immediately following completion of M7824 infusion for doses 1 and 3 (cycle 1 day 1 and cycle 2 day 1) for analysis of pharmacokinetics. One 10 mL vial of blood will be drawn prior to M7824 infusion of M7824 infusion for doses 2 (cycle 1 day 15) and dose 6/end of treatment (whichever comes first). Refer to Section 6.4.3 for details on processing of PK samples.

[p]β-hCG (no FSH) at post-progression follow-up visit

[q]Window of +/- 7 days is allowed

[r]Adverse events are recorded and assessed continuously throughout the trial (see Section 6.4.1.3) and are assessed for final outcome at the End of Treatment visit. After the End of Treatment visit only AEs that are deemed attributable to trial drug by the Investigator should be documented until the Safety Follow-up visit.

[s]For up to one year following discontinuation of treatment on study.

[t]Cycle 3, Day 1 collection only.

[u]Patients must remain at the CTRC for two hours of observation following the first two doses of therapy.

[v]Only to be performed if no disease progression was documented previously.

[w]SBRT administration (total 24 Gy over 3 consecutive business days at a daily fraction of 8Gy to start within 7 days following cycle 1, day 15 and completed prior to cycle 2, day 1). While SBRT is preferred, Intensity-modulated radiation therapy (IMRT) or 3D conformal techniques may be utilized at the discretion of the treating radiation oncologist depending on the dose to surrounding normal tissues. Patient will receive a total dose of 24Gy over three days with one of the following modalities, at the discretion of the treating radiation oncologist: SBRT, IMRT and 3D conformal.

[x]Biopsy to be performed cycle 1, day 15

Table 3: Schedule of Assessments (Cohort D)

Test		Cycle 1		Cycle 2		Cycle 3		Cycle 4[x] (and all subsequent cycles)		End of treatment	Long term follow up	
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of dis-continuation or within 7 days after**	**28 day follow up after progression**	**Every 3 months after 28 day follow up**
Inclusion/exclusion criteria	X	X										
Demographic data	X											
Cancer disease history	X											
Prior anticancer drug/ radiotherapy/ procedures	X											
Medical history	X											
Concurrent medications	X											

Vital signs including weight[q] and height (latest height on record acceptable; height is only performed at screening)	X	X		X	X	X	X	X	X	X	X	X
Test		**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4[x] (and all subsequent cycles)**		**End of treatment**	**Long term follow up**	
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of dis-continuation or within 7 days after**	**28 day follow up after progression**	**Every 3 months after 28 day follow up**
Written informed consent	X											
Enrollment (if eligible)[a]	X											
Physical examination[b,q]	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS[q]	X	X	X	X	X	X	X	X	X	X	X	

Toxicity assessment[q]	X	X	X	X	X	X	X	X	X	X[s]	X[s]	
Test		**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4[y] (and all subsequent cycles)**		**End of treatment**	**Long term follow up**	
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of dis-continuation or within 7 days after**	**28 day follow up after progression**	**Every 3 months after 28 day follow up**
Documentation of AEs, concomitant medications, and procedures [q]	X	X	X	X	X	X	X	X	X	X	X	X[s]
12-lead EKG[c,d, q]	X			X			X				X	X
Full serum chemistry[e, q]	X	X	X	X	X	X	X	X	X	X		
Complete blood count[e, q]	X	X	X	X	X	X	X	X	X	X		
Free T4, TSH[e, f, q]	X							X				
ANA, RF[e,]	X											
Urinalysis (dipstick)[e, q]	X	X	X			X		X		X		

β-HCG pregnancy test, FSH [e, t,q]	X	X	X			X		X				
HIV, HBV, HCV testing	X											
Test		**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4[x] (and all subsequent cycles)**		**End of treatment**	**Long term follow up**	
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of dis-continuation or within 7 days after**	**28 day follow up after progression**	**Every 3 months after 28 day follow up**
M7824 Administration [q]		X[u]	X[u]	X	X	X	X	X	X			
Tumor biopsy [g]											X[n]	
Patient-reported outcomes [q]		X	X	X	X	X	X	X	X		X	
MSI testing [h]	X											
Verification of available specimen for mutation profiling [m]	X											
Tumor evaluation by imaging (w/collection of available staging	X							X			X[v]	X[s]

imaging prior to study enrollment) [j,k,q]												
Verification of available specimen for TGFβ 1,2,3 [q]	X	X		X	X	X	X	X[t]			X	
Test		**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4[x] (and all subsequent cycles)**		**End of treatment**	**Long term follow up**	
Measure	**Day -28 to treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day of dis-continuation or within 7 days after**	**28 day follow up after progression**	**Every 3 months after 28 day follow up**
Verification of available specimen for PD-L1 expression [n]	X											
Collection of buccal and fecal swabs for microbiome testing[q]	X			X		X		X				
Verification of available specimen for testing of pharmacokinetics of M7824 [o,q]		X	X	X		X				X		
Blood for collection of ctDNA	X							Xy		X		

[a]Enrollment will be done after the confirmation of fulfilling all screening inclusion criteria without matching any exclusion criterion.
[b]Physical examination should include a dermatological examination. If abnormal skin findings are observed, patient should be referred to a dermatologist for biopsy of suspicious lesions. An ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be conducted at Screening. At subsequent visits, eye signs and symptoms should be checked. If there are any clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days. Starting with C1D15, a focused examination may be performed centered around patient's symptoms at an assigned visit.
[c]12-lead EKGs should be performed as soon after completion of infusion as possible.
[d]EKGs are to be performed every 6 weeks.
[e]Laboratory draws may be performed +/- 7 days of a scheduled treatment.

[f]For women of child-bearing potential. FSH should be drawn if clarification of post-menopausal state is warranted. Refer to Appendix 2 for further details.
[g]An optional tumor biopsy following progression may be offered to the patient.
[h]Performed on archival tissue or fresh biopsy. MSI testing performed in a CLIA-certified laboratory is acceptable and does not need to be repeated (see section 6.4.5)
[i]Blood for ctDNA collection to be drawn after14 days of completion of standard treatment.
[j]Tumor measurements should occur with CT imaging or MRI. Ideally the same methodology would be used over the course of the study for a given patient. Bone scan should be done at screening if clinically indicated. For collection of those prior imaging studies prior to informed consent, readily available imaging studies since the onset of metastatic/unresectable disease are to be prioritized for collection. If the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the screening CT and/or MRI does not need to be performed.
[k]Tumor measurements are to be assessed every 12 weeks (+/- 5 days). For subjects continuing treatment beyond 12 months, tumor evaluations should take place every 12 weeks (+/- 5 days).
[l]To be performed on archival tissue or fresh biopsy either via hotspot next general sequencing panel in CLIA certified molecular diagnostics laboratory at MD Anderson. TGFβR2, ACVR2A, SMAD2 and SMAD4 will need to be performed if not done previously.
[m]Plasma will be sent for markers including, but not limited to, interleukin (IL) IL-1α, IL-1β, IL-2, IL-5, IL-6, IL-8, IL-13, TNF-α, MCP, MIP-1β, G-CSF, GM-CSF, IFN-γ via a cytokine assay ((Meso Scale Discovery (MSD), 40 Plex). Leukocyte subpopulations and

immune activation status will be assessed by flow cytometry (fluorescence-activated cell sorter [FACS]) on PBMC from heparinized blood samples (10 mL, tubes).

[n]PD-L1 expression by immunohistochemistry on archival tumor specimen or fresh tumor tissue (if available).

[o]One 10 mL vial of blood will be drawn prior to M7824 infusion and immediately following completion of M7824 infusion for doses 1 and 3 (cycle 1 day 1 and cycle 2 day 1) for analysis of pharmacokinetics. One 10 mL vial of blood will be drawn prior to M7824 infusion of M7824 infusion for doses 2 (cycle 1 day 15) and dose 6/end of treatment (whichever comes first). Refer to Section 6.4.3 for details on processing of PK samples.

[p]β-hCG (no FSH) at post-progression follow-up visit

[q]Window of +/- 7 days is allowed

[r]Adverse events are recorded and assessed continuously throughout the trial (see Section 6.4.1.3) and are assessed for final outcome at the End of Treatment visit. After the End of Treatment visit only AEs that are deemed attributable to trial drug by the Investigator should be documented until the Safety Follow-up visit.

[s]For up to one year following discontinuation of treatment on study.

[t]Cycle 4, Day 1 collection only.

[u]Patients must remain at the CTRC for two hours of observation following the first two doses of therapy.

[v]Only to be performed if no disease progression was documented previously.

[w]Including confirmation of R0 resection of metastatic disease

[x]At the discretion of the treating provider and patient in the absence of recurrence or progression

[y]Cycle 4 Day 1, and every 12 weeks (+/1 14 days) thereafter as long as the patient continues study treatment.

1 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by:

The University of Texas - MD Anderson Cancer Center.

The trial will be conducted within the Department of Gastrointestinal Medical Oncology at the University of Texas - MD Anderson Cancer Center in Houston, TX. All clinical assessments will be performed in the outpatient clinic setting. Study drug will be administered in the Cancer Therapy and Research Center (CTRC), an outpatient infusion center at MD Anderson.

The Principal Investigator represents all Investigators for decisions and discussions regarding this trial, consistent with the International Conference on Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

The trial will appear in the following clinical trial registry: www.clinicaltrials.gov

2 Background Information

2.1 Investigational Product

The Investigational Medicinal Product (IMP) for the present trial is M7824.

M7824 is a bifunctional fusion protein that combines an anti-programmed death ligand 1 (PD-L1) antibody and the soluble extracellular domain of transforming growth factor beta (TGFβ receptor type II as a TGFβ neutralizing "trap," into a single molecule. This anti-PD-L1 / TGFβ-Trap molecule is designed to target 2 major mechanisms of immunosuppression in the tumor microenvironment. The anti-PD-L1 moiety of M7824 is identical to avelumab, except for three amino acid substitutions in the heavy chain constant regions, which result in a different human IgG1 allotype, and one amino acid substitution in the heavy chain for antibody stability. As of June 2017, FDA has granted accelerated approval to avelumab for metastatic Merkel cell carcinoma (MCC) and locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy.

Combining these pathways, PD-1 / PD-L1 and TGFβ, is attractive as an antitumor approach. A recent report found that blockade of TGFβ signaling in T cells or deletion of TGFβ1 from T cells in a mouse model led to diminished PD-1 expression in tumor-infiltrating CD8+ T cells[1]. Concomitant PD-1 and TGFβ blockade can restore pro-inflammatory cytokines[2]. In a murine model of hepatocellular carcinoma, TGFβ appeared to increase the expression of PD-L1 in dendritic cells, which in turn promoted T-cell apoptosis and increased percentage of CD25+, Foxp3+ T regulatory cells[3]. Higher levels of circulating myeloid-derived suppressor cells (MDSCs), a significant source of TGFβ, are associated with failure to respond to anti-PD-1 therapy[4].

Experiments demonstrate that M7824 strongly enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either the anti-PD-L1 antibody, avelumab, or TGFβRII control alone. Tumor rechallenge experiments in cured mice show durable protective immunity. In vivo studies showed that the antitumor effects were mediated by CD8+ T cells and NK cells. CD8+ T-cell tumor infiltrates were observed and, overall, the CD8+ response was associated with long term protective immunity. Importantly, in the MC38 model, M7824 showed significantly better efficacy than the combination of avelumab plus TGFβ Trap control, supporting the rationale of combining the 2 active moieties in 1 molecule.

M7824, is comprised of an extracellular domain of the human TGFβ receptor TGFβRII covalently joined via a glycine / serine linker to the C terminus of each heavy chain of the fully human IgG1 anti-PD-L1 antibody, avelumab. Given the emerging picture for PD-1 / PD-L1 class, in which responses are apparent but with room for increase in effect size, it is assumed that cotargeting a complementary immune modulation step will improve tumor response. A similar TGF-targeting agent, fresolimumab, which is a monoclonal antibody targeting TGFβ1, 2, and 3, showed initial evidence of tumor response in a Phase I trial in subjects with melanoma. The objective response was observed in 1 of 28 subjects with 6 subjects showing stable disease[5]. Internal data shows that the TGFβRII portion of M7824 has dose dependent antitumor activity in a mouse pharyngeal carcinoma xenograft model, similar to antitumor findings with soluble receptor reported elsewhere[6]. Given the preclinical and clinical evidence of both pathways, it is anticipated that M7824 may have enhanced antitumor activity compared with avelumab.

2.1.1 Safety

A reasonable safety profile is anticipated when targeting these pathways. The safety of the PD-1 / PD-L1 class continues to emerge but appears to be substantially less adverse compared with the CTLA-4 class of T cell checkpoint inhibitors[7,8]. Two TGFβ inhibiting biologics have been administered in clinical trials and showed an acceptable human safety profile in humans. Fresolimumab was studied in Phase I trial in subjects with cancer (28 with melanoma, 1 with renal cell carcinoma). No DLTs were observed and 15 mg/kg, the highest dose tested, was determined to be safe[5]. The major AE was emergent skin tumors and hyperkeratosis. In a small trial of idiopathic pulmonary fibrosis, the most common AE was fatigue[9]. In a study of 16 subjects with focal segmental glomerulosclerosis, the only AE was pustular rash in 2 subjects[10]. TβM1, an antibody inhibiting the TGFβII receptor, was well tolerated when studied at doses as high as 240 mg with diarrhea as the only DLT event[11]. Notably, one event of low hemoglobin (Hgb) was observed in the high dose group. Importantly, the preclinical profile of M7824 is predominantly benign and highly comparable to that of avelumab. Overall, evidence suggests non-overlapping toxicity profiles for anti-PD-L1 and anti-TGFβ agent classes. There is a theoretical potential of immune-related adverse events (irAEs) that would be the consequence of a double blockade of negative regulatory loops of the immune system; however, taken together, the preclinical profile of M7824 and clinical evidence of each pathway suggests a low risk of synergistic toxicity stemming from the dual-functionality of M7824.

An irAE is defined as off target side effects associated with exposure of immunogenic drug and is consistent with an immune mechanism. In the process of identification of irAEs, any possible etiology of neoplastic, infectious, metabolic, toxin, or any other factor should be ruled out. Serological, histological (biopsy), immunological data should be obtained to support immune

mediation of occurrence of adverse event. Immune-related AEs are AESIs for M7824 and important identified risks (adverse reactions) for M7824, and the precautions and management are discussed in Section 5.5.3.3.

Important identified irAE risks for M7824 include colitis, pneumonitis/interstitial lung disease, endocrinopathies, hyperthyroidism, hypothyroidism, autoimmune thryroiditis, adrenal insufficiency, Type 1 diabetes mellitus), nephritis, hepatitis, retinal microvasculitis, uveitis, myositis, and skin reactions like rash (generalized, maculo-papula, erythematous, bullous pemphigoid). Management algorithms include steroids, other immune-suppressants, study drug interruption / discontinuation, and supportive management. Anti-PDL1 has shown an overall rate of infusion reactions of approximately 10% (Grade 3 / 4 approximately 0.4% [fell to 0.2% with mandatory premedication]; no Grade 5.

A brief summary of safety experience with the PD-1 inhibitors nivolumab (Opdivo®) and pembrolizumab (Keytruda®) is given here, based on prescribing information (refer to current label information for updated information). For pembrolizumab the section on Warnings and Precautions includes adverse reactions of immune-mediated pneumonitis (2.9%), immune-mediated colitis (1%), immune-mediated hepatitis (0.5%), immune-mediated hypophysitis (0.5%), renal failure (0.5%) and immune-mediated nephritis (0.7%), immune-mediated hyperthyroidism (1.2%) and hypothyroidism (8.3%), and a variety of other immune-mediated adverse reactions occurring in less than 1% of patients. In addition, a warning for embryofetal toxicity is provided. For nivolumab the section on Warning and Precautions includes adverse reactions of immune-mediated pneumonitis (2.2%) with fatal immune-mediated pneumonitis in 0.9% (5/574), immune-medicated colitis (2.2%), immune-mediated hepatitis (1.1%), immune-mediated nephritis and renal dysfunction (0.7%), immune-mediated hyperthyroidism (3%) and hypothyroidism (8%) and a variety of other immune-mediated adverse reactions occurring in less than 1% of patients. In addition, a warning for embryofetal toxicity is provided.

Safety experience with various TGFβ targeting agents described in the literature suggests no overlapping immune-related profile with compounds of the anti-PD-1 / anti-PD-L1 class. In Phase I trials, the experience with a molecule with a highly similar mechanism to the M7824 TGFβ trap moiety, the anti-TGFβ-1 and 3 antibody fresolimumab, showed no dose limiting toxicity up to 15 mg/kg and no immune related events[5]. There were no DLTs and the only major AEs were skin lesions, mainly keratoacanthomas, some with atypical features, one event of squamous cell carcinoma, plus hyperkeratosis of the skin. Immune events were not reported. A syndrome known as Ferguson-Smith disease is caused by mutations in TGFβ is associated with the formation of keratoacanthomas, similar to the findings described for fresolimumab[12]. Therefore, it is plausible that skin tumors observed during fresolimumab treatment may be related to TGFβ inhibition. A neutralizing antibody against TGFβ-1, TβM1, was well tolerated when studied as high as 240 mg with diarrhea as the only DLT event. Notably, one event of low Hgb was observed in the high dose group. This is notable since the only preclinical finding associated with M7824 was decreased Hgb. Trabedersen, an antisense oligonucelotide that inhibits TGFβ2 expression, was associated with thrombocytopenia that was moderate[13]. Finally, TGFβ is known to play a role in wound repair[14].

In the recently released initial phase I dose escalation cohort of M7824 (MSB0011359C), 19 subjects had enrolled in the dose-escalation part of the study with 3 subjects treated at each dose

level of M7824 (MSB0011359C): 1, 3, 10, and 20 mg/kg, once every 2 weeks. Median age was 56 years (range: 34 to 78). All had ECOG PS 0 or 1, with a median of 4 prior therapies (range: 2 to 7).

As of the data cutoff date (Oct 3rd, 2016), the overview of treatment emergent adverse events (TEAEs) for the M7824 dose escalation cohort is provided in **Table 4**.

Table 4: Overview of TEAEs for the Dose Escalation Cohorts of M7824

	Dose Level 0.3 mg/kg N = 3 (%)	Dose Level 1 mg/kg N = 3 (%)	Dose Level 3 mg/kg N = 3 (%)	Dose Level 10 mg/kg N = 3 (%)	Dose Level 20 mg/kg N = 7 (%)	Overall N = 19 (%)
Any TEAE	2 (66.7)	3 (100.0)	3 (100.0)	3 (100)	7 (100.0)	18 (94.7)
TEAE, Grade ≥ 3	2 (66.7)	3 (100.0)	1 (33.3)	0 (0.0)	4 (57.1)	10 (52.6)
Related TEAE	1 (33.3)	0 (0.0)	2 (66.7)	1 (33.3)	5 (71.4)	9 (47.4)
Related TEAE, Grade ≥ 3	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (28.6)	3 (15.8)
TEAE Leading to Treatment Discontinuation	0 (0.0)	1 (33.3)	1 (33.3)	0 (0.0)	2 (28.6)	4 (21.1)
Any TEAE leading to Infusion Rate Reduction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (5.3)
Serious TEAE	1 (33.3)	2 (66.7)	1 (33.3)	0 (0.0)	5 (71.4)	9 (47.4)
Related Serious TEAE	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	3 (42.9)	4 (21.1)
TEAE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAE of Special Interest: Infusion-Related Reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (5.3)
Any TEAE of Special Interest: Immune-Related	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	2 (28.6)	4 (21.1)

Note: Reporting of infusion-related reactions is being amended at the time this document was being prepared.
TEAE: treatment emergent adverse events.

18 out of 19 subjects experienced at least one TEAE of any grade. The most frequently observed TEAEs in more than 3 subjects were gastrointestinal disorders reported in 14 subjects (nausea in 9 subjects, vomiting in 7 subjects and abdominal pain in 4 subjects), followed by general disorders and administration site conditions in 8 subjects (fatigue in 5 subjects, localized edema in 4 subjects and fever in 4 subjects), skin and subcutaneous tissue disorders in 7 subjects, anemia in 6 subjects, infections and infestations in 5 subjects, metabolism and nutrition disorders in 5 subjects, musculoskeletal and connective tissue disorders in 4 subjects and respiratory, thoracic and mediastinal disorders in 4 subjects.

Most of the TEAEs are of Grade 1 or 2. Ten subjects experienced at least 1 Grade ≥ 3 TEAE, including Grade 4 cerebrovascular accident (CVA) in 1 subject, Grade 4 anemia in 1 subject, Grade 3 anemia in 4 subjects, cerebrovascular accident (CVA) in 1 subject, nausea in 3 subjects, vomiting in 2 subjects, abdominal pain in 2 subjects, colitis in 1 subject, rectal bleeding in 1 subject, hematuria in 1 subject, decreased urine output in 1 subject, skin infection in 1 subject, soft tissue infection in 1 subject, hypertension in 1 subject, dehydration in 1 subject, back pain in 1 subject, skin squamous cell carcinoma in 1 subject. Grade 3 laboratory abnormalities include decreased lymphocyte counts in 2 subjects, prolonged APTT in 1 subject, acidosis in 1 subject, hypokalemia in 1 subject.

9 out of 19 subjects experienced at least one trial drug related TEAE. 3 subjects experienced at least 1 Grade ≥ 3 trial drug related TEAE, including grade 3 anemia in 1 subject, grade 3 colitis in 1 subject, grade 3 skin infection in 1 subject, grade 3 skin squamous cell carcinoma in 1 subject. All of the other trial drug related TEAEs are of Grade 1 or 2, including hyperthyroidism in 2 subjects, hypothyroidism in 2 subjects, maculopapular rashes in 2 subjects, bullous dermatitis in 1 subject, acneiform dermatitis in 1 subject, pruritus in 1 subject, infusion related reaction in 1 subject, nausea in 1 subject, vomiting in 1 subject, dry mouth in 1 subject, exertional dyspnea in 1 subject.

At the 20 mg/kg dose level, 2 subjects experienced TEAE leading to treatment discontinuation. The maximum tolerated dose (MTD) level was not reached at the highest so far at investigated dose of 20 mg/kg. One subject had a dose limiting toxicity (DLT) with colitis with subsequent bleeding and anemia at the 20 mg/kg dose level. Overall, the TEAE profile was similar across different dose escalation cohorts and the incidences of TEAEs by TEAE category did not increase significantly with increasing dose.

The safety summary of the M7824 expansion cohort in colorectal patients is listed as below. As of April 21 2017, 32 patients with a diagnosis of colorectal cancer have received at least one, or more, doses of 1,200mg of M7824. **Table 5** list both drug-related and not-related AEs for items in which > 10% of patients experience the event, or if the events was recurrent Grade 3 or any Grade 4 or higher. Overall, the drug was well tolerated at the 1,200mg dose level with a typical AE profile for an advanced cancer patient cohort. Of note, the grade 3 toxicities occurring in more than 10 percent of study subjects were anemia (4 out of 32, 12.5%), hyponatremia (4 out of 32, 12.5%) and dyspnea (4 out of 32, 12.5%). There were 4 subjects with Grade 3 events listed as related to M7824. These include anemia (1 event), blood bilirubin increased (1 event), enteritis (1 event) and adrenal insufficiency (1 event). No Grade 4 or Grade 5 events have been reported as related to M7824.

Table 5. Adverse Events (AEs) in Dose Expansion cohort of colorectal cancer patients on EMR200647-001 dosed with 1,200mg M7824 (cut-off date 21 April 2017; n=32). Both drug-related and not drug-related AEs for items in which > 10% of patients experience the event, or if the event was recurrent Grade 3 or any Grade 4 or higher, are listed.

Primary System Organ Class	**Any Grade**	**Grade >=3**	**Grade >=4**	**Grade 5**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**

Anemia	8 (25.0)	4 (12.5)	1 (3.1)	0
Abdominal Pain	10 (31.3)	1 (3.1)	0	0
Constipation	12 (37.5)	0	0	0
Diarrhea	8 (25.0)	0	0	0
Nausea	11 (34.4)	3 (9.4)	0	0
Vomiting	7 (19.4)	2 (6.3)	0	0
Fatigue	10 (31.3)	2 (6.3)	0	0
Pyrexia	8 (25.0)	1 (3.1)	0	0
Cholangitis	1 (3.1)	1 (3.1)	1 (3.1)	0
Sepsis	3 (9.4)	3 (9.4)	2 (6.3)	1 (3.1)
UTI	7 (21.9)	1 (3.1)	0	0
Infusion related reaction	5 (15.6)	0	0	0
Blood bilirubin increased	2 (6.3)	2 (6.3)	0	0
GGT increased	3 (9.4)	3 (9.4)	0	0
Weight decreased	4 (12.5)	0	0	0
Decreased Appetite	10 (31.3)	1 (3.1)	0	0
Dehydration	4 (12.5)	0	0	0
Hyperglycemia	3 (9.4)	3 (9.4)	1 (3.1)	0
Hyperkalemia	1 (3.1)	1 (3.1)	1 (3.1)	0
Hyponatremia	6 (18.8)	4 (12.5)	0	0
Back pain	7 (21.9)	0	0	0
Myalgia	5 (15.6)	0	0	0
Headache	4 (12.5)	1 (3.1)	0	0
Anxiety	4 (12.5)	0	0	0
Cough	5 (15.6)	0	0	0
Dyspnea	9 (28.1)	4 (12.5)	1 (3.1)	0
Pleural Effusion	5 (15.6)	0	0	0
Respiratory Failure	1 (3.1)	1 (3.1)	1 (3.1)	0
Hypotension	2 (6.3)	1 (3.1)	1 (3.1)	0

2.2 Non-Clinical Findings for M7824

2.2.1 In Vitro and in Vivo Pharmacology Findings

Avelumab, a fully human anti-PD-L1 IgG1 antibody, recently entered Phase III clinical development by EMD Serono R&D, Billerica, MA. Preclinical pharmacology investigations have shown that avelumab functionally enhances T cell activation in vitro and significantly inhibits the growth of PD-L1 expressing tumors in vivo; thus avelumab serves as a benchmark for the preclinical proof of principle studies of the anti-PD-L1 / TGFβ Trap (M7824). In addition, M7824,

which consists of the TGFβ trap covalently linked to an inactive anti-PD-L1, was generated to evaluate the effect of inhibition of TGFβ only.

M7824 binds recombinant and cell surface expressed PD-L1 with an affinity similar to that of the parental anti-PD-L1 antibody (avelumab), and binds recombinant human TGFβ1 with high affinity. Importantly, M7824 can bind simultaneously to PD-L1 and TGFβ1 as demonstrated by a two-step binding assay. M7824 potently attenuated TGFβ signaling in cell assays and enhanced interleukin-2 production by T cells stimulated with a super antigen, Staphylococcal enterotoxin A. M7824 is capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro, but at a significantly reduced level compared with the parental avelumab antibody. M7824 was shown to be internalized by PD-L1-expressing cells in vitro with kinetics similar to those of the parental avelumab antibody. In summary, the dual functionalities of M7824 were confirmed by in vitro studies: the fusion protein retains the biological activities of the parental anti-PD-L1 avelumab antibody, but possesses the added modality of effective TGFβ binding and neutralization.

M7824 is cross-reactive with murine PD-L1 and TGFβ1; therefore, its in vivo antitumor efficacy and the immunological response during the course of treatment can be evaluated in syngeneic models; however, since this therapeutic agent is a recombinant human protein with two mechanisms of action aimed at blocking immunosuppression, it caused an augmented mouse antibody against human antibody (MAHA) response in immunocompetent mice, which limits the dosing to a 3- or 6-day window, depending on the strain of mice. To avoid a MAHA response, 2 B cell deficient strains of mice were employed in a series of studies designed to assess the optimal antitumor efficacy of M7824 treatment in cancer models. Homozygous Jh mice (Igh-Jtm1Dhu; Balb/C) lack normal B lymphocyte numbers and have no detectable IgM or IgG antibody titers due to the absence of the Jh gene segments responsible for genetic recombination of the Ig heavy chain. Likewise, B6.129S2-Ighmtm1Cgn/J mice (C57BL/6) lack mature B cells due to a targeted Ighmtm1Cgn mutation. The use of Jh and B6.129S mice allowed clinically-relevant repeat dosing schedules of the M7824 treatment in the in vivo pharmacology studies. To ensure the results obtained were not artifacts due to the B cell deficiency, efficacy and associated immunological responses of M7824 in wild type mice were also demonstrated, although to a lesser extent for efficacy due to the limited dosing window and interference by MAHA.

M7824 possesses superior antitumor activities relative to monotherapy with either PD-L1 blockade or TGFβ sequestration, resulting in complete tumor regression and long-term survival in the EMT-6 breast cancer model and MC38 colorectal cancer model. Dose-dependent efficacy was observed in multiple models, and the effective dose range was between 25 to 492 μg per mouse (approximately 1.25 to 25 mg/kg) depending on the model. Importantly, M7824 therapy induced antitumor activities that conferred a durable, protective immunity in those mice eradicated of their primary tumor. Moreover, the antitumor effect of M7824 was associated with modulations in T cell and NK cell phenotypes, increase in dendritic cell maturation, and reduction in MDSCs in the tumor microenvironment. M7824 was also shown to be capable of activating both adaptive and innate immune responses that included favorable changes in tumor immune infiltrates. Furthermore, tumor antigen-specific CD8+ T cell responses were enhanced with M7824 therapy.

In a trial to further elucidate the mechanisms of action, tumor-bearing mice were systemically depleted of CD4+ T cells, CD8+ T cells or NK cells during treatment. The therapeutic efficacy of M7824 was completely abrogated by the depletion of either CD8+ T cells or NK cells, but not by the depletion of CD4+ T cells. Consistent with the reduced ADCC in vitro, the effector function of M7824 did not play an important role in the antitumor effect in vivo. Furthermore, the dominant role of CD8+ T cells in maintaining long-term protective immunity following M7824 induced tumor eradication has been demonstrated.

The therapeutic potential of M7824 was explored in combination with various standard-of-care therapies. In combination with the core components of the FOLFOX chemotherapy regimen (oxaliplatin, 5-fluorouracil and oxaliplatin), an additive enhancement in efficacy was demonstrated against MC38 colorectal carcinoma. In combination with fractionated, localized radiotherapy, a highly synergistic antitumor effect was achieved with only a single low dose of M7824 in the MC38 tumor model. An augmented antitumor effect was also observed when M7824 was combined with pazopanib in a mouse renal cell carcinoma model, and with anti-CTLA-4 in a B16 melanoma model. Immunological readouts from these combination studies consistently showed additive immunomodulatory effects that correlated with antitumor response. These data suggest that M7824 can be explored as a combination partner in different clinical settings for the treatment of cancer patients.

Refer to the Investigator's Brochure for full details of the preclinical pharmacology of M7824.

2.2.2 Pharmacokinetics / Immunogenicity Findings

Preclinical PK data and PK / PharmDyn analysis for M7824 is available from mice and cynomolgus monkeys. The single-dose data in monkey shows non-linearity between the low doses of 0.8 and 4 mg/kg versus the high dose of 20 mg/kg, which had reduced clearance, suggesting a saturable component. The TGFβ1 binding was assessed and showed suppression for prolonged periods beyond drug exposure at all dose levels; however, baseline data contained data below lower limit of quantification and therefore these data were not considered relevant for PK/PharmDyn projections. The fusion protein appeared stable since there was no evidence of intralinker cleavage. Mouse PK / PharmDyn models for tumor and peripheral blood (CD3+ splenic) PD-L1 occupancy were also generated.

A brief summary of PK and PK / PharmDyn is as follows:

- The predicted human terminal half-life ($t_{1/2}$) for M7824 is approximately 6 days
- Simulations predict that a 1 mg/kg dose will provide an average exposure of approximately 7 μg/mL in humans
- Based on PK / PharmDyn modeling and human projections:
  - At a human dose of 0.1 mg/kg, 95% PD-L1 total occupancy at maximum serum concentration observed post-dose (C_{max}) is expected in PBMCs, providing approximately 60% total occupancy in tumor
  - At a human dose of 1.0 mg/kg, more than 95% of PD-L1 total occupancy at C_{max} is expected in PBMCs and tumor

- At a human dose of 1.0 mg/kg, 20% effect is projected in tumor regression in the PK / PharmDyn model compared with 95% at 7.5 mg/kg

- Human projections indicate a dose of 7.5 mg/kg and higher (range 4 to 20 mg/kg), on a biweekly schedule is needed to achieve full efficacy based on a mouse tumor model in which complete tumor regressions were observed.

Anti-drug antibodies were observed in some animals; however, the impact on PK or PK / PharmDyn is not known. Preclinical antidrug antibody formation is not predictive of human antibodies.

2.2.3 Toxicology

The toxicological profile of M7824 was investigated in vivo in mice and cynomolgus monkeys. In addition, an optimized in vitro cytokine release assay in human PBMCs as well as tissue cross-reactivity studies in normal human and cynomolgus monkey tissues were performed.

Investigations of local tolerance were integrated in the repeat-dose toxicity studies. The investigation of safety pharmacology relevant parameters (CNS, respiratory, cardiovascular) was included in the pivotal 4-week intravenous (IV) repeat-dose toxicity study in cynomolgus monkeys. Please refer to the investigator brochure for M7824 for further details.

2.2.4 Brief Summary of the Clinical Findings for M7824

As of October 2016, 19 subjects had enrolled in the dose-escalation part of the dose escalation study with M7824. Please see Table 4 for further details.

No subject experienced a DLT and no subject was discontinued from treatment for drug-related TEAEs. No subject was reported with a TEAE with a Preferred Term of infusion-related reaction; however using a post-reporting analysis according to criteria outlined in the Statistical Analysis Plan, 3 subjects were reported with TEAEs that were classified as “infusion-related reactions,” with the Preferred Terms of abdominal pain, pyrexia, and back pain (Note: these events are undergoing further review).

The safety summary of the M7824 expansion cohort in colorectal patients is listed in **Table 5**. As of April 21 2017, 32 patients with a diagnosis have received at least one, or more, doses of 1,200mg of M7824. **Table 5** list both drug-related and not-related AEs for items in which > 10% of patients experience the event, or if the events was recurrent Grade 3 or any Grade 4 or higher. Overall, the drug was well tolerated at the 1,200mg dose level with a typical AE profile for an advanced cancer patient cohort. Of note, the grade 3 toxicities occurring in more than 10 percent of study subjects were anemia (4 out of 32, 12.5%), hyponatremia (4 out of 32, 12.5%) and dyspnea (4 out of 32, 12.5%). There were 4 subjects with Grade 3 events listed as related to M7824. These include anemia (1 event), blood bilirubin increased (1 event), enteritis (1 event) and adrenal insufficiency (1 event). No Grade 4 and Grade 5 events have been reported as related to M7824. Please see **Table 5** for further details.

2.2.5 Rationale for Cohorts

The programmed death 1 (PD-1) protein/ PD ligand-1 (PD-L1) interaction is important for immune evasion. PD-L1 is expressed on many cells including tumor cells. The PD-1/PD-L1 interaction results in peripheral T effector cell exhaustion and promotes conversion of T cells towards a T-regulatory (T_{reg}) phenotype. Other cell types express PD-L1 such as natural killer (NK) cells, myeloid cells and dendritic cells. These cells all contribute to the tumor microenvironment (TME) and have the potential to upregulate PD-L1. Evidence for disrupting this interaction via checkpoint inhibitors has been shown in melanoma and non-small cell lung cancer. PD1 antibodies, nivolumab and pembrolizumab tested in phase III trials versus standard of care chemotherapy have demonstrated better clinical outcomes in melanoma[4,15,16], non-small cell lung cancer[17-19]. Initial data suggests anti-PD-1 therapy may have efficacy in MSI-H mCRC[20].

TGFβ is a cytokine with multiple functions[21]. It is produced by various cell types including platelets[22], various myeloid populations, fibroblasts and T regulatory (T_{reg}) cells[23]. TGFβ has dual roles in cancer[24]. In early stage disease, TGFβ promotes differentiation and apoptosis acting as a tumor suppressor**.** In late stage cancer, TGFβ has a tumor promoter function. TGFβ enhances epithelial mesenchymal transition (EMT) by the control of genes like ZEB1,2, TWIST, SNAIL and SLUG that control expression of cell surface markers that mediate epithelial cell-cell contacts such as E-cadherin[25]. TGFβ has autocrine and paracrine functions in fibroblasts, macrophages and myeloid derived suppressor cells (MDSC)[26]. These cells have direct and indirect effects on the overall inflammatory/immune state of the tumor microenvironment (TME).

TGFβ also contributes to an immunosuppression within the TME. Cancers secrete various cytokines and chemokines that stimulate myelopoiesis and attract immature myeloid cells towards the tumor. Granulocyte (PMN-MDSC) and monocyte (M-MDSC) can be recruited and under TME specific conditions such as hypoxia, cause differentiation of these precursors into tumor associated macrophages and neutrophils (TAMs and TANs)[26-28]. TGFβ forms one of the many cytokines that forms autocrine feedback to sustain immunosuppressive signaling at the TME level[29]. In addition, these immature precursors are highly immunosuppressive while the TAMs are polarized towards alternatively activated forms such as the immunosuppressive M2 phenotype. Together, MDSC and M2 macrophages promote downregulation of tumor immunity through direct mechanisms on cytotoxic T cells. These include substrate metabolism (arginine) or sequestration (L-cystine), direct effects of reactive oxygen species (ROS) or reactive nitrogen species on T-cell receptor subunits and through the secretion of cytokines that promote Treg differentiation. TGFβ has downregulatory effects on cytotoxic T cells and natural killer (NK) cells[26]. In the bloodstream, TGFβ released from platelets after contact with circulating tumor cells downregulates NK tumorilytic activity in vitro[30,31] and downregulates NKG2D receptors on NK cells[32], providing another immune escape mechanism.

TGFβ has pleotropic effects extend beyond the immune regulation. Through effects on local innate immune cells, endothelial cells and activated fibroblasts, TGFβ is a central component of the cytokine milieu that also promotes angiogenesis[25]. TGFβ also mediates an environment of matrix remodeling via cancer associated fibroblasts (CAFs) and immune cells. The induction of these cells results secretion of matricellular proteins.

Modulation of the extracellular matrix (ECM) is a dynamic process. The ECM forms the structural components holding cells together in a tissue architecture but it has several functions beyond the cytoskeletal capacity. It serves as a reservoir for growth factors such as TGFβ, provides survival signals and inhibition signals via cell surface molecules such as integrins. TGFβ is secreted and bound to latent factors that are bound to the ECM until activated and liberated[33]. Integrins may also modulate TGFβ release[34]. Active signaling in this way is crucial in embryonic development, morphogenesis and wound healing[35].

In cancer, the extracellular signals that result in apoptosis or growth suppression from the ECM are perturbed. Growing tumors resist inhibitory growth signals and the local ECM is disrupted. Liberated factors and danger signals now available for recognition by innate immune cells cause a cascade of events analogous to wound healing[23]. Inflammation via activated macrophages set off a cascade inflammatory molecules that recruit further infiltration of neutrophils and immature myeloid cells to the area. Fibroblasts are also activated in this process and secrete TGFβ through autocrine and paracrine pathways. TGFβ induces production of ECM related genes including metalloproteinases (MMPs)[36]. Chronic remodeling without removal of the cancer trigger results in a perpetual cycle of remodeling. TGFβ secretion begets further TGFβ production and as a result, the TME is primed for angiogenesis, invasion, ECM breakdown and immune escape.

The relationship between immune infiltrates and MSI-H in CRC is well established[37]. Immunotherapy with anti-PD1 therapy may have efficacy in this population[38]. Nivolumab and ipilumumab was well tolerated with a response rate of 33% in metastatic MSI-H CRC[39]. TGFβ, being a central determinant of an immune suppressive TME may be a key resistance mechanism in PDL1 therapy strategies[40]. It does so both directly on T cells to differentiate into T_{regs} or indirectly via attraction of immunosuppressive immature myeloid and MDSCs into the TME. Upregulation of TGF-β signaling has been associated with de novo resistance to anti-PD-1 treatment in patients with metastatic melanoma and following development of acquired resistance to these agents following an initial response to therapy. Given the ability of M7824 to sequester TGF-β in the circulation away from the TME, we hypothesize that M7824 may promote T cell effector function via disruption of PD-1/PD-L1 axis to enhance anti-tumor response following resistance to anti-PD-1/PD-L1 therapy in patients with MSI-H mCRC.

The consensus molecular subtypes (CMS) are the best representation of the variation seen within CRC on the basis of gene expression[41]. Briefly, CMS1 is characterized by hypermutated tumors with immune infiltrates and often associated with MSI-H. Notably, MSI-H is a subset of CMS1 and there is a proportion within this group that current biomarkers do not capture. CMS4 is a mesenchymal phenotype and is associated with a number of features associated with poor prognosis. Hallmark features of CMS4 include TGFβ activation, immune infiltration, EMT, matrix remodeling, and angiogenesis[41]. In contrast to CMS1, the immune infiltration displays a relative absence of cytotoxic T cells but a high proportion of tumor associated macrophages (TAMs)[42]. TGFβ signaling and immune suppression in the microenvironment are contributory factors to the aggressive biology that is reflected in the poor overall survival within this group. TGFβ activation conditions stroma at other sites to form metastatic niches that promote a receptive environment for circulating tumor cells or increases tumor initiating cell capacity in conjunction with fibroblast activation[43]. TGFβ inhibition with LY215299 in the TME prevented metastasis formation in patient derived tumor organoids[44]. Blocking TGFβ signaling may help reverse a number of key processes in the CMS4 poor prognosis group which include: reversing fibroblast activation,

removing tumor initiating capacity, reversing immature myeloid and MDSC infiltration and downregulating EMT. Given the role of inflammatory cells and TGFβ, M7824 may reprogram an inflammatory response that is immune suppressive to an immunogenic response.

In a recent pilot study of patients with mCRC treated with M7824 monotherapy[45], there were 22 patients with adequate tumor tissue available for CMS subtyping. Patients here had been permitted to enroll without prior knowledge of CMS status. In this cohort, there were 10 patients with CMS4 mCRC. Only one of these ten patients demonstrated a radiographic response, which remained > 6 months in duration. Conclusions from this CMS4 cohort however were limited by the lack of available fresh paired tissue biopsies in order to understand better the intratumoral pharmacodynamics activity of M7824.

Given the lack of activity noted with single-agent M7824 in the CMS4 CRC setting, additional interventions may boost the immunogenicity of these tumors in order to improve the anti-tumor responses. Radiotherapy has been shown to induce tumor cell damage through apoptosis- and necrosis-induced mechanisms[46-48], and augment exposure of more tumor-associated antigens for recognition by antigen-presenting cells and tumor attack by effector T cells[49]. Radiated tumor cells promote release of danger-associated molecular patterns[50], which likewise recruit more activated T cells to the tumor microenvironment. In preclinical MC38 and CT26 models of colorectal cancer using immunocompetent mice, concomitant stimulation by immune checkpoint blockade agents may render these tumors more susceptible to disrupting the PD-1:PD-L1 axis in combination with radiotherapy[51-54].

TGF-β activation within the tumor microenvironment by cancer-associated fibroblasts promotes T cell exclusion in preclinical models of CRC akin to the CMS4 subtype[55]. This may render immunotherapy agents ineffective in certain patients with MSS CRC if activated T cells are unable to penetrate intratumorally. Indeed, knockdown of TGF-β activity microscopically in these preclinical models did not eradicate established MSS tumors, although T cells reflexively increased PD-L1 expression on the surface in response to TGF-β inhibition. However, treatment with anti- TGF-β agents in the pre-metastatic setting (i.e., prior to development of exclusionary TGF-β activated stroma) decreased the onset of metastatic tumors for these models. Recently, identification of micrometastases in patients with CRC has become more feasible due to the advent of circulating tumor DNA (ctDNA) technology. Series of patients with non-metastatic and metastatic CRC alike have demonstrated resoundingly the strong association between CRC recurrence and the presence of ctDNA following curative resection[56-58], with (+) ctDNA bearing a 90-100% positive predictive value for the event of recurrent CRC, a surrogate for the presence of micrometastatic disease. Applying these findings, it is possible then to treat patients with (+) ctDNA following resection of oligometastatic CRC and completion of standard-of-care chemotherapy in the absence of clinically/radiographically macroscopic disease elsewhere, who may have remnant microscopic disease that can be eradicated by dual PD-L1: TGF-β targeted therapies.

Following on from the high response rates seen with PD-1 blockade in MSI-H mCRC, subsequent phase 2 studies have demonstrated impressive response rates in MSI-H tumors, irrespective of site of origin. A tumor agnostic phase 2 study enrolling patients with MSI-H metastatic tumors demonstrated an ORR of 53% and disease control rate of 77% with median PFS and OS not yet reached[59]. The cohort of 86 patients included CRC, neuroendocrine, ampulla of Vater, gastric,

pancreatic, prostate and cholangiocarcinomas. Predictive analysis using NGS from known databases across 32 different tumors suggests that the most common adenocarcinomas with a MSI-H signature include endometrial, gastric, small intestinal, colon, rectum, cervical, prostate and neuroendocrine tumors. Ovarian and uterine sarcomas are the non-epithelial tumors expected to contain subsets of MSI-H. While only 4% of these tumors are stage IV, the number of tumors that display the MSI-H phenotype has led to an estimation of 20,000 patients in the US who would derive benefit in the advanced setting with PD-1 and immunotherapy treatments[59].

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP and any additional applicable regulatory requirements. Based on the available nonclinical and clinical data to date, the conduct of the trial specified in this protocol is considered justifiable.

2.2.6 Summary of the Overall Benefit and Risk

The risk-benefit ratio has been carefully considered in the planning of the trial. Based on the preclinical data available to date, the conduct of the trial is considered justifiable using the dose and schedule of M7824 as specified in this protocol. The trial will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit ratio and would render continuation of the trial unjustifiable. The following are considered potential risks of exposure to M7824:

- Infusion-related reactions including hypersensitivity
- irAEs / autoimmune disorders
- Anemia
- Rash with hyperkeratosis, keratoacanthoma, and squamous cell carcinoma of the skin
- Alterations in wound healing or repair of tissue damage
- Embryofetal toxicities

Respective safety measures that comprise inclusion / exclusion criteria for participation in clinical trials with M7824, guidance for prevention, monitoring, and medical management of potential risks, as well as guidance on study treatment interruption or discontinuation. See Section 2.2.4 for a summary of clinical safety findings.

2.2.6.1 Infusion-related Reactions / Hypersensitivity

Infusion-related reactions hypersensitivity are a risk inherent to the administration of any recombinant protein to humans. Incidence of immunogenicity and character or severity of immunogenicity-induced side effects cannot be predicted by animal models because humanized or fully human proteins usually provoke a much stronger immune-response in rodents or non-human primates than in humans. The parent antibody (avelumab) caused lethal immune-mediated anaphylactic hypersensitivity reactions in mice after repeated application, while a control antibody lacking pharmacological activity only triggered a moderate immune reaction. However, in primates (cynomolgus monkeys), as a species closer to human, neither in the pilot 4-week IV repeat-dose toxicity trial nor in the pivotal 13-week IV infusion repeat-dose toxicity trial, clinical signs of hypersensitivity have been seen at dose levels of 20, 60, and 140 mg/kg, respectively.

As of 05 November 2014, from the EMR100070-001 trial with the parent avelumab antibody, 1 subject (2.0%) in the dose-escalation cohort reported an infusion-related reaction event (Grade 2) and 49 (10.2%) of the 480 subjects in the expansion cohorts experienced at least 1 episode of an infusion-related reaction when receiving avelumab monotherapy. Most of the events were Grade 1 (8 subjects, 1.7%) or Grade 2 (36 subjects, 7.5%) in intensity, and Grade 3 (3 subjects, 0.6%) or Grade 4 events (2 subjects, 0.4%) were less frequent. No Grade 5 events have been reported. Most of the infusion-related reaction events had an onset after the first (30 subjects, 6.3%) or second (16 subjects, 3.3%) avelumab infusion. In 8 subjects (1.7%), avelumab treatment was discontinued because of infusion-related reaction events.

2.2.6.2 Immune-related Adverse Events / Autoimmune Disorders

Since inhibition of PD-L1 and TGFβ signaling stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Treatment of irAEs should follow guidelines set forth in Section 5.5.3.3:

- Instructions for trial treatment discontinuation or interruption in case of irAEs / autoimmune disorders (see Section 5.5.3.3).
- Guidance for the medical management of irAEs / autoimmune disorders including specific guidance with regard to the affected organ / body system (see Section 5.5.3.3).
- irAEs / autoimmune disorders (any grade) are considered as AESIs requiring expedited reporting from the Investigator to Merck/EMD Serono. For non-serious AESIs, an AESI Report Form has to be completed; for serious events, an SAE Report Form has to be used.
- Regular laboratory tests on parameters indicative for autoimmune disorders will be performed as detailed in the Schedules of Assessments (see **Tables 1-3**).
- To help monitor for autoimmune effects, baseline ophthalmology examination including slit lamp inclusive of the anterior segment and including visual acuity. If clinically relevant eye signs or symptoms during the study, appropriate ophthalmology examination within 2 days including slit lamp inclusive of the anterior segment and including visual acuity.

2.2.6.3 Anemia

As the 4-week toxicology studies in cynomolgus monkeys demonstrated reversible decreases in red blood cell counts, as well as corresponding Hgb and hematocrit, anemia is considered a potential risk. Inclusion criteria for the study will require adequate entry Hgb value. Risk management measures are provided in Section 5.5.3.4. The amount of blood drawn during the study for non-essential biomarkers will be carefully considered, especially given the preclinical finding of reduced Hgb levels.

2.2.6.4 Alterations in Wound Healing or Repair of Tissue Damage

Alternations of wound healing and tissue damage repair are considered a potential risk given the TGFβ mechanism. Management should be discussed with the principal investigator on a case-by-case basis.

2.2.6.5 Rash with Hyperkeratosis / Keratoacanthoma / Squamous Cell Carcinoma of the Skin

Phase I information from a TGF antibody showed excess acanthomas, some with atypical features, and one confirmed squamous cell carcinoma[5]. A genetic disorder in the TGF pathway is also known to be associated with skin tumors[12]. Based on this information, skin tumors are considered a potential risk. Monitoring will include skin assessments as defined in the schedule of assessments (see **Tables 1-3**). Management should be discussed with the on a case-by-case basis. Dermatological consults should be requested as needed. Rash with hyperkeratosis / keratoacanthoma / squamous cell carcinoma of the skin are considered as AESIs requiring expedited reporting from the Investigator to the Merck/EMD Serono. Any suspicious lesion should be biopsied. For non-serious AESIs, an AESI Report Form has to be completed; for serious events, an SAE Report Form has to be used (see Section 6.4.1.2).

2.2.6.6 Embryofetal Toxicity

Embryofetal toxicities are a known risk of the PD-1 / PD-L1 targeting class. Animal models link the PD-1 / PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Based on its mechanism of action (MoA), M7824 may cause fetal harm when administered to a pregnant female. An appropriate contraception warning is provided in this clinical protocol. Subjects with pregnancy or in lactation period are prohibited from being enrolled in clinical trials.

2.2.6.7 Potential Benefit

In cohort A-C, patients will be selected based on MSI-H status and progression on prior immune checkpoint therapy on trial entry. Single agent responses to nivolumab in MSI-H mCRC have been updated in early key studies and range from 31%[60] and 50%[38]. In a population in whom the anticipated response rate is high but who have progressed on therapy, M7824, which targets a possible immunotherapy resistance mechanism in the form of TGFβ upregulation, appears promising. Beyond CRC, patients with MSI-H tumors who have progressed on prior immunotherapy will be enrolled. ORR and DCR to single agent pembrolizumab was 52% and 77% respectively in a population that contained ampulla of Vater, duodenal, pancreatic, neuroendocrine, cholangiocarcinoma, gastric, ovarian cancers and uterine sarcomas[59]. Many of the these tumors lack effective salvage treatments and when considered in context of the response rates to single agent PD-1 blockade, targeting a potential resistance mechanism for potential durable responses with M7824 is a promising option.

In cohort B, patients with treatment-refractory CMS4 mCRC who have progressed on at least two standard-of-care options will be studied. M7824 has limited benefit as monotherapy in this setting. SBRT will be administered after a one dose lead-in of M7824. Given the paucity of effective available therapies for patients with mCRC who have progressed on prior oxaliplatin-based and irinotecan-based chemotherapy, the risk-benefit ratio in this population for M7824 is also favorable given the prognosis in this population and studies showing that SBRT to metastatic tumors have demonstrated ability to increase tumor-associated antigens and augment immunogenicity. While SBRT is preferred, IMRT or 3D conformal techniques may be utilized at the discretion of the treating radiation oncologist depending on the dose to surrounding normal tissues. Patient will receive a total dose of 24Gy over three days with one of the following modalities, at the discretion of the treating radiation oncologist: SBRT, IMRT and 3D conformal.

In Cohort D, patients with MSS mCRC who have completed therapy following R0 resection with or without chemotherapy for removal of all clinically and radiographically evident macroscopic disease will be tested for the presence of ctDNA. Given the correlation between detectable ctDNA and the presence of minimal residual disease, patients in this cohort are at high risk for recurrence.

This clinical trial will be conducted in compliance with the clinical trial protocol, GCP (ICH Topic E6), and the applicable national regulatory requirements.

3 Trial Objectives

3.1 Primary Objective

The primary objectives of this study are to estimate efficacy of M7824 with:

- Objective response rate (ORR) in microsatellite instability-high (MSI-H) patients who have progressed on immune checkpoint blockade therapy (Cohort A-C).

  OR

- ORR in patients with treatment-refractory, consensus molecular subtype 4 (CMS4) mCRC patients coadmnistered SBRT (Cohort B). While SBRT is preferred, IMRT or 3D conformal techniques may be utilized at the discretion of the treating radiation oncologist depending on the dose to surrounding normal tissues. Patient will receive a total dose of 24Gy over three days with one of the following modalities, at the discretion of the treating radiation oncologist: SBRT, IMRT and 3D conformal.

  OR

- Clearance of ctDNA in ctDNA(+) patients with resected mCRC following completion of standard-of-care therapy (Cohort D).

3.2 Secondary Objectives

To estimate progression-free survival (PFS) for M7824 in patients with:

- MSI-H solid tumors whose disease has progressed on prior immune checkpoint blockade therapy (Cohort A-C).

  OR

- Treatment-refractory, CMS4 mCRC coadministered SBRT (Cohort B). While SBRT is preferred, IMRT or 3D conformal techniques may be utilized at the discretion of the treating radiation oncologist depending on the dose to surrounding normal tissues. Patient will receive a total dose of 24Gy over three days with one of the following modalities, at the discretion of the treating radiation oncologist: SBRT, IMRT and 3D conformal.

To estimate overall survival (OS) for M7824 in patients with:

- MSI-H solid tumors who are refractory to prior immune checkpoint blockade therapy (Cohort A-C).

  OR

- Treatment-refractory, CMS4 mCRC coadministered SBRT (Cohort B). While SBRT is preferred, IMRT or 3D conformal techniques may be utilized at the discretion of the treating radiation oncologist depending on the dose to surrounding normal tissues. Patient will receive a total dose of 24Gy over three days with one of the following modalities, at the discretion of the treating radiation oncologist: SBRT, IMRT and 3D conformal.

  OR

- ctDNA(+) resected mCRC following completion of standard-of-care therapy (Cohort D).

To estimate disease-free survival (DFS) in patients with resected mCRC following standard-of-care treatment (cohort D).

To evaluate safety and tolerability of treatment with M7824 in patients with:

- MSI-H mCRC who are refractory to prior immune checkpoint blockade therapy (Cohort A-C).

  OR

- Treatment-refractory, CMS4 mCRC (Cohort B)

  OR

- ctDNA(+) resected mCRC following completion of standard-of-care therapy (Cohort D).

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3.3 Exploratory Objectives

1. To evaluate intratumoral pharmacodynamic changes in immune populations using paired biopsies from patients with MSI-H solid tumors (Cohort A-C) or CMS4 mCRC treated with

M7824 and SBRT (Cohort B). While SBRT is preferred, IMRT or 3D conformal techniques may be utilized at the discretion of the treating radiation oncologist depending on the dose to surrounding normal tissues. Patient will receive a total dose of 24Gy over three days with one of the following modalities, at the discretion of the treating radiation oncologist: SBRT, IMRT and 3D conformal.

2. To characterize circulating immune cell populations and cytokine profiles in tumor and circulation following treatment with M7824.

3. To describe changes in levels of TGF-β following treatment with M7824.

4. To correlate the presence of microsatellite instability with CMS1 profile.

5. To correlate MSI-H and CMS4 to CpG island methylator phenotype (CIMP) status, KRAS and BRAF mutation status.

6. To quantify correlation with CMS4 and immune populations within tumor infiltrate.

7. To correlate anti-tumor response to M7824 with PD-L1 expression.

8. To conduct RNAseq, RNA Scope, WES targeted sequencing and tissue IO gene expression by Nanostring.

9. To evaluate novel markers in blood by liquid biopsy including, but not limited to, circulating-free DNA (cfDNA), exosomes, and circulating tumor cells (CTC).

10. To describe changes in microbiome profiling upon treatment with M7824 (with or without radiation).

4 Investigational Plan

4.1 Overall Trial Design and Plan

4.1.1.1 Cohort A-C – MSI-H solid tumors

This is a phase Ib expansion study to assess efficacy of M7824 in patients with MSI-H solid tumors who have progressed on prior anti-PD-1/PD-L1 therapy. The hypothesis is that these patients will demonstrate anti-tumor response upon treatment with M7824. Patients successfully enrolled will have had at least two doses of prior immune checkpoint therapy (anti-PD1, anti-PDL1 or anti-CTLA4) with documented progression on CT or MRI imaging.

M7824 will be administered intravenously at a dose of 1200mg every 14 days (-3/+1 day). M7824 will be administered until documented PD, unacceptable toxicity, or withdrawal of informed consent. Tumor assessments will be performed every 8 weeks. Progressive disease, stable disease, partial response, and complete response will be defined by iRECIST 1.1. Patients who discontinue due to toxicity will continue to be assessed via imaging until documented PD.

4.1.1.2 Cohort B – CMS4 mCRC

This is a phase 2, single arm, Simon's optimal two-stage design to assess ORR in treatment-refractory CMS4 mCRC receiving M7824 with SBRT. The hypothesis is that efficacy of M7824 coadministered with SBRT will be demonstrated in patients with CMS4 mCRC

Patients successfully enrolled will have had CMS4 classification after characterization of their pre-treatment primary tissue biopsy. M7824 will be administered intravenously at a dose of 1200mg every 14 days (+/- 7 days). The first dose of M7824 will be administered alone. After the second dose of M7824, patients will receive SBRT for a total dose of 24Gy over three days, with first treatment of radiotherapy administered within 7 days of completion of the second dose of M7824 (cycle 1, day 15). Radiotherapy must be completed prior to the third dose of M7824. While SBRT is preferred, IMRT or 3D conformal techniques may be utilized at the discretion of the treating radiation oncologist depending on the dose to surrounding normal tissues. Patient will receive a total dose of 24Gy over three days with one of the following modalities, at the discretion of the treating radiation oncologist: SBRT, IMRT and 3D conformal.

M7824 will be continued until documented PD or unacceptable toxicity. Tumor assessments will be performed every 8 weeks. Progressive disease, stable disease, partial response, and complete response will be defined by iRECIST 1.1. Patients who discontinue due to toxicity will continue to be assessed via imaging until documented PD.

4.1.1.3 Cohort D – ctDNA(+) MSS mCRC following resection of metastatic disease

This is a pilot study to assess the clearance of ctDNA with M7824 following R0 resection of metastatic disease in patients with MSS mCRC. Patients with oligometastatic colorectal cancer must have undergone an R0 resection with no remnant clinically or radiographically evident disease. The primary tumor must have also been resected, and patients must have completed all standard-of-care treatment for the primary tumor (e.g., chemoradiation for primary rectal cancer, adjuvant chemotherapy, etc) at the discretion of the treating physician.

Following at least 14 days of completion of standard therapy, patients will be tested for the presence or absence of ctDNA. Patients with a confirmed (+) ctDNA result will be allowed to proceed with M7824 treatment.

M7824 will be administered intravenously at a dose of 1200 mg every 14 days (+/- 7 days). ctDNA and CT scans will be repeated at 12 weeks. Patients without evidence of clinical or radiographic progression will have the option to continue on treatment every 2 weeks with M7824, until the time of disease recurrence and/or progression, either radiographically or clinically. Radiographic assessments will occur every 12 weeks thereafter, until disease progression or patient discontinuation on study.

4.1.2 Planned number of subjects

4.1.2.1 Cohort A-C – MSI-H solid tumors

The planned number of subjects for this trial is 15 patients with MSI-H metastatic solid tumors.

4.1.2.2 Cohort B – CMS4 mCRC

In this Simon two-stage design, the planned number of subjects is 15 in the first stage. Should at least 2 patients demonstrate radiographic response (i.e. CR + PR), then 14 additional patients will be treated in the second stage, for a total of 29 patients. If there is an anti-tumor signal in the 29 patients with CMS4 metastatic CRC who are treated with this combination, then the study may be amended to expand patient selection across all CMS subgroups.

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4.1.2.3 Cohort D -- ctDNA(+) MSS mCRC following resection of metastatic disease

The planned number of subjects for this cohort is 15 patients.

4.1.3 Planned treatment duration

The trial duration for a subject is estimated to be up to 2 years. This includes an 28-day screening period (decision will be made in this period for subject's trial inclusion if all eligibility criteria are met), a treatment duration until confirmed PD, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 4.5) and an 28-Day Safety Follow-up visit 4 weeks after the last dose of M7824 administration.

Subjects who have experienced a durable, confirmed PR or CR may continue treatment for a maximum of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the principal investigator. In the case of pseudoprogression, subjects should continue treatment through one additional tumor assessment, if they meet the criteria described in Section 4.5.1.

Adverse events (AEs) and adverse drug reactions (ADRs) should be followed until they resolve, return to baseline, or are irreversible (see Section 6.1.4 for details).

In both cohorts, it is anticipated to enroll the first planned subject by October 2017, and the final subject enrolled by October 2018.

4.1.4 Dose Modification and ADRs Requiring Treatment Discontinuation

4.1.4.1 Dose Modification

The dose of M7824 is 1200mg. Further details about discontinuation, withholding and restarting M7824 based on ADRs and AEs are presented in further detail in Section 5.5.3.

4.1.4.2 Adverse Drug Reactions Requiring Treatment Discontinuation

The following ADRs, defined as any AE assessed as related to M7824 by the Investigator and / or Merck/EMD Serono, require permanent treatment discontinuation:

Any Grade 4 ADRs require treatment discontinuation except for single laboratory values out of normal range that do not have any clinical correlate, and resolve to Grade ≤ 1 or Baseline grade within 14 days with adequate medical management.

Any Grade 3 ADRs require treatment discontinuation <u>except</u> for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1 or Baseline grade.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis. The study principal investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities. If the amylase or lipase abnormality not associated with symptoms or clinical manifestations of pancreatitis has not resolved to Grade ≤ 1 within the subsequent 2 doses (28 days), the subject should permanently discontinue treatment with M7824.
- Grade 3 Hgb decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use does not require treatment discontinuation.
- Increases in Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3 that resolves to ≤ 2 by Day 1 of the next cycle (infusions should not be given if the ECOG PS is ≥ 3 on the day of IMP administration and should be delayed until ECOG PS ≤ 2).

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle but it is manageable and / or not clinically relevant, the ADR should be discussed with the principal investigator and based upon discussion it is possible the infusion will be given on the following cycle. If at the end of the following cycle, the event has not resolved to Grade 1, discussion should be had with the principal investigator about permanently discontinuing treatment with M7824.

- Upon the second occurrence of the same Grade 2 ADR in the same subject (except for fatigue and hormone insufficiencies that can be managed by replacement therapy), continuation of treatment with M7824 has to be discussed with the principal investigator and might be permanently discontinued.

- Infusion-related reactions and hypersensitivity reactions (Grades 1 to 4) should be handled according to the guidelines provided in Sections **5.5.3.1 and 5.5.3.2**, respectively.

- Anemia should be handled according to the guidelines provided in Section **5.5.3.4**.

4.1.5 Analysis Cut-Off Dates

4.1.5.1 Cohort A-C

The primary data cut-off for the analysis will be after 24 weeks after the last subject received M7824.

The final data cut-off will be 1 year after the last subject has received the last dose of M7824.

4.1.5.2 Cohort B

The first data cut-off for the interim analysis will be 12 weeks after the 15th subject enrolled has received study treatment. A decision to continue on to the target 29 patients will be based on the number of responses observed. If 2 or more confirmed responses are observed, the primary data cut-off for the analysis will be 24 weeks after the last subject (n=29) received study treatment.

The final data cut-off will be 1 year after the last subject has received the last dose of M7824.

4.1.5.3 Cohort D

The primary data cut-off for the analysis will be after 24 weeks after the last subject received M7824.

The final data cut-off will be 1 year after the last subject has received the last dose of M7824.

4.2 Discussion of Trial Design

4.2.1.1 Cohort A-C

This is a Phase Ib, open-label trial in patients with MSI-H metastatic solid tumors who have progressed on prior checkpoint inhibitor treatment.

The study focuses on the subset of patients with metastatic solid tumors that has displayed higher responses rates to immune checkpoint blockade. Microsatellite instability is associated with higher immune infiltration[61-63] . One early study demonstrated that responders to the anti-PD-1 antibody, pembrolizumab, were restricted to MSI-H mCRC patients in comparison to non-MSI-H CRC[38]. Updated results from this study demonstrated RR of 50% and disease-control rate (DCR) of 89%

seen in MSI-H, compared to 0% and 16% in non-MSI-H mCRC patients, respectively[59]. Pembrolizumab has since received breakthrough designation by the FDA for approval in MSI-H solid tumors (including mCRC). In addition, PD-L1 expression was not associated with OS in this study and preliminary results from the Checkmate-142 trial, in which patients with mCRC were treated with the anti-PD-1 antibody nivolumab[60]. Therefore, using MSI-H as the current selection biomarker for this study is appropriate.

MSI-H non-CRC tumors have demonstrated impressive ORR of 53% with PD-1 blockade in a variety of tumors was 53% and DCR of 77% with median PFS and OS not being met[59]. Given the mechanism of M7824, use of MSI-H as a biomarker as already demonstrated is appropriate to enrich for likely responders while selection based on prior progression following checkpoint immunotherapy approaches ensures targeting of a potential resistance mechanism.

4.2.1.2 Cohort B

This is a phase II, single arm, Simon two-stage design to assess efficacy of M7824 as an abscopal phenomenon with radiation to a single metastatic lesion in patients with treatment-refractory, CMS4 mCRC receiving M7824. Tumors ≥ 7.0 cm in largest diameter should be excluded from receiving radiation as part of this study. As previously described, TGFβ represents an immune resistance mechanism via recruitment of immunosuppressive cells and downregulation of existing anti-tumoral responses within the TME. TGF-β signaling may also promote resistance to an abscopal phenomenon in patients with mCRC administered immunotherapy with radiation. The trial design is also justified based on pre-clinical evidence that CMS4 mCRC demonstrate an intrinsically inflamed, immunosuppressive phenotype mediated by upregulation of TGF-β signaling.

Restriction in this study to CMS4 comes from a number of preclinical studies implicating it with upregulation of TGF-β activation[43,64,65]. Several of the hallmark features including EMT, stromal infiltration, angiogenesis and matrix remodeling are explained by some of the pleotropic effects of TGF-β. TGFβ represents an immune resistance mechanism via recruitment of immunosuppressive cells and downregulation of existing anti-tumoral responses within the TME[26,66]. CMS4 is associated with poorer cancer specific outcomes and non-benefit to current adjuvant chemotherapy strategies[3], and therefore novel effective therapies ae needed for this subpopulation of mCRC.

4.2.1.3 Cohort D

This is a pilot study of M7824 in patients with MSS mCRC who have detectable ctDNA following R0 resection of metastatic disease. The inevitability of disease recurrence for patients with colorectal cancer, as seen in the presence of ctDNA following resection of CRC,suggests existence of micrometastatic minimal residual disease in these cases. Given that macroscopic metastases may use TGF-β signaling to exclude anti-tumor immune cells from the microenvironment, limiting selection of patients with micrometastatic disease may identify a subpopulation of mCRC patients that selectively benefit from immunotherapy.

4.2.2 Inclusion of Special Populations

Not applicable.

4.3 Selection of Trial Population

4.3.1 Inclusion criteria

1. Histologically or cytologically confirmed adenocarcinoma of the colon or the rectum that is metastatic or unresectable (cohort B); or histologically or cytologically confirmed adenocarcinoma of the colon or the rectum following resection of the primary tumor and metastatic disease, following completion of standard-of-care perioperative therapy at the discretion of the treating provider (cohort D).
2. Confirmation of:
    a. Cohort A-C: microsatellite instability
    b. Cohort B: CMS4 CRC classification on pretreatment primary tumor.
    c. Cohort D: microsatellite stability
3. Age >18 years at time of study entry.
4. Ability to provide written informed consent.
5. Documented progression to prior therapies (Cohorts A-C and B):
    a. Cohort A-C: Disease progression following prior immune checkpoint blockade therapy
    b. Cohort B: Progression or intolerance to at least 2 prior lines of standard therapy for unresectable or metastatic CRC
6. Available primary tumor tissue for CMS4 biomarker assessment (cohort B)
7. Life expectancy ≥12 weeks as judged by the treating physician.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
9. Measurable disease according to iRECIST v1.1 (Cohorts A-C and B). For cohort B, measureable lesions must be identified apart from the irradiated tumor lesion. Patients in cohort D must have no evidence of radiographically evident disease at the time of study entry.
10. Adequate hematological function, defined by ANC ≥ 1.0×10^9/L, lymphocyte count ≥ 0.5×10^9/L, platelet count ≥100×10^9/L, and Hgb ≥ 9 g/dL (in absence of blood transfusion).
11. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal (ULN), an AST level ≤ 2.5 × ULN, and an ALT level ≤ 2.5 × ULN. If liver metastases are present, then it is acceptable for AST level ≤ 5.0 × ULN, and an ALT level ≤ 5.0 × ULN.
12. International normalized ratio (INR) < 1.5
13. Adequate renal function defined by an estimated creatinine clearance >30 mL/min according to the Cockcroft-Gault formula or be measure for creatinine clearance from 24 hour urine collection.

14. **Highly** effective contraception for both male and female subjects if the risk of conception exists. **Highly** effective contraception must be used 30 days prior to first trial administration, for the duration of trial treatment, and at least for 4 months after stopping trial treatment (see Appendix 2 for further details). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately.
15. Ability to tolerate receipt of radiotherapy to a metastasis not adjacent to a normal dose-limiting structure, at the discretion of the treating radiation oncologist (cohort B).
16. Presence of detectable ctDNA following completion of R0 resection with or without perioperative therapy (cohort D only).
17. Completion of all standard-of-care adjuvant therapy (cohort D).

4.3.2 Exclusion criteria

1. Concurrent treatment with non-permitted drugs and other interventions.
2. Anticancer treatment within 14 days before the start of trial treatment [e.g., cytoreductive therapy, radiotherapy (with the exception of palliative radiotherapy delivered in a normal organ-sparing technique), immune therapy, or cytokine therapy].
3. Major surgery as determined by the investigator within 28 days before the start of trial treatment (prior diagnostic biopsy is permitted).
4. Systemic therapy with immunosuppressive agents within 7 days before the start of treatment; or use of any investigational drug within 28 days before the start of trial treatment.
5. Cohort A-C only: Intolerance or serious adverse immune related adverse events (irAEs) [refer to section 5.5.3.3] that were symptomatic or required or continues to require ongoing immunosuppression to previous immune checkpoint therapy.
6. Cohorts B and D: prior exposure to any immune checkpoint blockade agent or any other immunomodulatory agent used for antineoplastic therapy for mCRC.
7. Previous malignant disease (other than the target malignancy to be investigated in this trial) within 3 years prior to study treatment initiation. Other Lynch syndrome cancers do not exclude patients from participating on study, at the discretion of the Principal Investigator. Subjects with a history of cervical carcinoma in situ, superficial or non-invasive bladder cancer, or basal cell or squamous cell carcinoma in situ, previously treated with curative intent are NOT excluded. Subjects with other localized malignancies treated with curative intent need to be discussed with the Principal investigator.
8. Subjects with active central nervous system (CNS) metastases are excluded. Subjects with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 2 months, and do not require continued steroid therapy.
9. Receipt of any organ transplantation, including allogeneic stem-cell transplantation, but with the exception of transplants that do not require immunosuppression (e.g., corneal transplant, hair transplant).
10. Significant acute or chronic infections including, among others:

a. Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.
b. HBV or HCV infection (HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA or HBV core antibody positive alone with reflex to positive HBV DNA or positive HCV antibody with reflex to positive HCV RNA).
c. Subjects with active tuberculosis (history of exposure or history of positive tuberculosis test plus presence of clinical symptoms, physical or radiographic findings).

11. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:
    a. Subjects with type I diabetes, vitiligo, alopecia, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
    b. Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10mg of prednisone or equivalent per day.
    c. Administration of steroids for other conditions through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) is acceptable.
12. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v4.03), any history of anaphylaxis, or recent (within 5 months) history of uncontrolled asthma.
13. Persisting toxicity (except alopecia and vitiligo) related to prior oncologic therapy Grade >1 NCI-CTCAE v4.03, however, sensory neuropathy Grade ≤ 2 is acceptable.
14. Clinically significant cardiovascular/ cerebrovascular disease as follows: cerebral vascular accident / stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class >II), or serious cardiac arrhythmia.
15. Clinically relevant diseases (for example, inflammatory bowel disease) and / or uncontrolled medical conditions, which, in the opinion of the Investigator, might impair the subject's tolerance or ability to participate in the trial.
16. Vaccine administration within 4 weeks of M7824 administration. Vaccination with live vaccines while on trial is prohibited. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines).
17. Cohort D: peritoneal carcinomatosis.

4.3.3 Screening Eligibility (cohort B)

Patients are eligible for screening for CMS subtyping prior to enrollment on cohort B provided that the following elibility criteria are met:

- Histologically or cytologically confirmed adenocarcinoma of the colon or the rectum that is metastatic or unresectable.

- Progression on at least one prior line of systemic therapy for metastatic disease.
- Prior tissue sampling of primary tumor with core biopsy, endoscopic biopsy, or surgical resection to be used for CMS subtype testing.

4.4 Criteria for Initiation of Trial Treatment

The inclusion and exclusion criteria will be checked at the Screening visit. Eligible subjects will be enrolled before treatment start after verification of fulfilling all inclusion criteria and satisfy no exclusion criteria. Documentation of satisfaction of eligibility criteria for each patient will be performed within CORe.

4.5 Criteria for Subject Withdrawal

4.5.1 Withdrawal from Trial Treatment

Subjects will be withdrawn from trial treatment for any of the following reasons:

- PD as defined by iRECIST 1.1
  - Patients may continue on M7824 until immune confirmed PD (iCPD) provided they meet the criteria for pseudoprogression (see 5.5.1.1 below)
- Therapeutic failure requiring urgent additional cancer therapy
- Occurrence of any Grade ≥ 3 ADRs or repetitive Grade 2 ADRs as defined in Section 5.5.3.3.
- Occurrence of AEs, at the Investigator's discretion
- Pregnancy
- Use of prohibited concomitant drug, as defined in Section 5.5.2, where the predefined consequence is withdrawal from the IMP
- Non-adherence / non-compliance to the trial protocol or trial requirements (see Section 5.9)
- Withdrawal of consent
- Participation in any other trial

4.5.1.1 Pseudoprogression

Pseudoprogression is defined as an initial disease flare followed by a delayed disease response. At the time of progression, there is no definitive way to distinguish this from true progressive disease without a confirmatory scan.

To account for pseudoprogression, patients will have PD, SD, PR or CR recorded as defined by iRECIST 1.1. However, PD will require a subsequent scan at the next planned tumor assessment in 8 weeks or earlier if clinically indicated. Patients will be allowed to continue on M7824 despite first documentation of PD if:

- No new Grade 2 or greater severity of symptoms or significant worsening of existing symptoms
- No decrease in ECOG PS
- In the opinion of the Investigator, the subject does not require new anticancer therapy.

Failure to satisfy **all** of these conditions results in discontinuation of M7824.

Confirmed PD on the subsequent scan also results in study discontinuation.

The time point for PD will be taken from the first noted date and not the time of the confirmation scan.

4.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial. If a subject withdraws participation while on study, survival information may still be collected via phone calls, electronic communication, letters or publically available records.

A subject must be withdrawn if any of the following occur during the trial:

- Withdrawal of the subject's consent
- Participation in any other therapeutic trial during the treatment duration of this trial; however, subjects will continue to be followed for survival

If a subject fails to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of withdrawal from the trial, the assessments scheduled for the last visit (28-Day Safety Follow-up visit) should be performed (see Section 6.1.3), if possible, with focus on the most relevant assessments. In any case, the appropriate 28-Day Safety Follow-up electronic case report form (eCRF) in the Prometheus database visit must be completed. In case of withdrawal, subjects will be asked to continue safety and survival follow-up, which includes the collection of data on survival and subsequent anticancer therapy. After completion of the Follow-up period or after the End of Treatment visit, whatever is applicable, the appropriate eCRF section for Trial Termination must be completed in the Prometheus database.

If a subject is withdrawn prior to PD for any reason the subject will not be replaced.

4.6 Premature Termination of the Trial

For either cohort, the trial may be discontinued prematurely in the event of any of the following:

New information leading to unfavorable risk-benefit judgment of the IMP, for example, due to

1. Evidence of inefficacy of the IMP,
2. Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
3. Other unfavorable safety findings.

(Note: Evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or non-clinical examinations, for example, toxicology.)

- Merck/EMD Serono or the IND Office's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the Merck/EMD Serono's IMP.

Health Authorities and Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of Health Authorities.

4.7 Definition of End of Trial

If the trial is not terminated for a reason given in Section 4.6, the end of the trial is defined as 1 year after the last subject receives the last dose of M7824.

5 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" (IMP) refers to an active substance or a placebo being tested or used as a reference therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form. The only IMP used in this trial is M7824.

5.1 Description of the Investigational Medicinal Product

M7824 drug product is a sterile, freeze-dried formulation presented at a concentration of 600 mg/vial in United States Pharmacopeia (USP) type I glass vial closed with a rubber stopper and sealed with an aluminum plastic crimping cap.

Each vial contains 600 mg of M7824 as a preservative-free histidine-buffered solution (pH=5.5) containing trehalose dihydrate, sodium chloride, L-methionine and polysorbate 20 (Tween 20). Only excipients that conform to the current USP are used for M7824 drug product.

5.2 Dosage and Administration

5.2.1 M7824 Administration

Subjects will receive IV infusion of M7824 over 1 hour (-10 minutes / +20 minutes) once every 2 weeks as detailed in the Schedules of Assessments (see **Tables 1-3**). Modifications of the infusion rate due to infusion-related reactions are described in Section 5.5.3.1.

The dose for M7824 is 1200mg. In cohorts A-C and B, subjects will receive M7824 once every 2 weeks until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 4.5). Subjects who have experienced a persistent, confirmed PR

or CR may continue treatment through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the principal investigator. In cohort D, patients will receive M7824 for 6 doses. After 6 doses, the patient will have blood checked for ctDNA clearance. If there is no evidence of radiographic or clinical progression, then the patient may continue on study at the discretion of the investigator.

For subjects who achieve a PR or CR on M7824 therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, a re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial principal investigator. Subjects re-initiating treatment should be assessed according to the Schedules of Assessment of the trial starting at Week 1, Day 1 (see **Tables 1-3**).

5.2.2 Radiotherapy (cohort B only)

Radiation therapy will be delivered to a single metastatic lesion, with total dose of 24 Gy in 3 daily fractions of 8 Gy each. Radiation therapy will be delivered on consecutive business days. All 3 fractions will be administered after the second dose of M7824 and prior to the administration of the third dose of M7824.

Patients will undergo CT simulation, with or without IV contrast. The gross tumor volume (GTV) will include a single metastatic lesion. The metastatic lesion to be irradiated must not be adjacent to a dose-limiting normal structure (e.g., heart, bowel) at the discretion of the treating radiation oncologist. The planning target volume (PTV) will include the GTV with a 5-7 mm margin in all directions. For lesions affected by respiratory motion, appropriate motion management techniques should be used, such as inspiratory breathhold. Daily volumetric imaging with cone beam CT (CBCT) or CT on rails (CTOR) will be used for image guidance.

5.3 Assignment to Treatment Groups

Not applicable

5.4 Noninvestigational Medicinal Products to be Used

In order to mitigate potential infusion-related reactions, premedication with an antihistamine (e.g., 25-50 mg PO at the discretion of the investigator) and with acetaminophen (e.g., 325-650 mg PO at the discretion of the investigator) approximately 30 to 60 minutes prior to each dose of M7824 is mandatory for the first 2 infusions and is optional and at the discretion of the Investigator starting with the third infusion. If Grade $\geq$ 2 infusion reactions are seen during the first two infusions, then premedications should not be stopped. **Steroids as premedication are not permitted**. Special precautions for monitoring of subjects and management of infusion-related reactions / hypersensitivity including modifications of the infusion rate and stopping of trial drug are described in Section 5.5.3 and subsections. As with all monoclonal antibody therapies, there is a risk of allergic reaction including anaphylactic shock. M7824 should be administered in a setting

that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg IV), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access in the event of an anaphylactic reaction. Infusion of M7824 will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactic reactions. Following M7824 infusions, subjects must be observed for a minimum of 2 hours post end of infusion for potential infusion-related reactions. Please see the guidelines for handling of infusion-related reaction in Section 5.5.3.1.

If an allergic reaction occurs, the subject must be treated according to the best available medical practice. Guidelines for management of infusion-related reactions and severe hypersensitivity reaction according to the National Cancer Institute are found in Section 5.5.3.

Further precautions are provided in Section 5.5.3.2. For prophylaxis of flu-like symptoms, a non-steroidal anti-inflammatory drug (NSAID) for example, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each dose of M7824 IV infusion.

5.5 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF (Prometheus) and medical record, noting the name, dose, duration and indication of each drug. Nondrug interventions (other than vitamins) and any changes to a concomitant medication or other intervention should also be recorded in the eCRF (Prometheus) and medical record.

5.5.1 Permitted Medicines

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary to protect subject welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

Other drugs to be used for prophylaxis, treatment of anaphylactic reactions, infusion-related reactions, and severe hypersensitivity reactions / flu-like symptoms and irAEs are described in Section 5.5.3.

Palliative radiotherapy delivered in a normal organ-sparing technique may be administered during the trial. The assessment of PD will not be based on the necessity for palliative radiotherapy.

5.5.2 Prohibited Medicines

As stated for the exclusion criteria in Section 4.3.2, subjects must not have had chemotherapy, radiotherapy (other than palliative radiotherapy delivered in a normal organ-spearing technique as described in Section 5.5.1), major surgery, or received another investigational agent within 28 days before the start of trial treatment.

The following treatments must not be administered during the trial:

- Immunotherapy including interferon, immunosuppressive drugs (for example, chemotherapy or systemic corticosteroids except for short term treatment of allergic reactions, endocrine replacement therapy at low dose prednisone [≤ 10 mg daily] or equivalent, or for the treatment of irAEs or other appropriate short term steroid use), or other experimental pharmaceutical products. Short term administration of systemic steroid or other immunosuppressant such as infliximab or mycophenolate (that is, for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed. Note: for subjects with glioblastoma, steroid use is allowed.

- Adefovir.

- Prophylactic use of corticosteroids for infusion related reactions is prohibited.

- Any live vaccine therapies for the prevention of infectious disease. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines).

- Blood transfusions and erythroid growth factors are permitted for Hgb ≤ less 7 g/dL and/or for life threatening bleeding

If the administration of a non-permitted concomitant drug becomes necessary during the trial, the subject will be withdrawn from trial treatment (the Principal investigator may be contacted to discuss whether the IMP must be discontinued).

Medications other than those specifically excluded in this trial (as outlined in this section) may be administered for the management of symptoms associated with the administration of M7824 as required. These might include analgesics, anti-emetics, antihistamines, diuretics, anti-anxiety medications, and medication for pain management, including narcotic agents.

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF (Prometheus) and medical record, noting the name, dose, duration, and indication of each drug.

The following non-drug therapies must not be administered during the trial (and within 28 days before the start of trial treatment):

- Major surgery (excluding prior diagnostic biopsy).

- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known

- to potentially interfere with major organ function (for example, hypericin)

- Subjects should not abuse alcohol or other illicit drugs during the trial

5.5.3 Special Precautions

As a routine precaution, subjects all enrolled in this trial must be observed for 2 hours in the CTRC post end of infusion, in an area with resuscitation equipment and emergency agents at least for the first two doses of treatment with M7824. If no medical problems arise during the first two treatments, then the 2 hour observation period does not need to continue starting with the third dose of treatment. At all times during M7824 treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

Infusion of M7824 will be stopped in case of Grade ≥ 2 hypersensitivity, inflammatory response, or anaphylactic reaction. The treatment recommendations for infusion-related reactions and severe hypersensitivity reactions according to the NCI are outlined in Sections 5.5.3.1 and 5.5.3.2, respectively.

Investigators should also monitor subjects closely for potential irAEs (described in Section 5.5.3.3), which may become manifest after several weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.

5.5.3.1 Infusion-related reactions

IRRs are defined as any signs or symptoms experienced by participants during the infusion of pharmacologic or biologic agents or any event occurring during or within 1 day of drug administration. IRRs are common ADRs with monoclonal antibodies timely related to drug administration and have been reported as anaphylaxis, anaphylactoid reactions, and cytokine release syndrome, among other terms used. IRRs are important identified risks (adverse reactions) for M7824, and the precautions and management are provided in Table 46

A. Signs and symptoms of infusion related reactions (IRRs) including hypersensitivity include but not limited to pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria, were reclassified as important identified risks (adverse reactions).

B. Management

Table 6: Treatment Modification for Symptoms of Infusion-related Reactions Caused by M7824

NCI-CTCAE Grade	Treatment Modification for M7824
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated intervention not indicated.	• Decrease the M7824 infusion rate by 50% and monitor closely for any worsening.

	• The total infusion time for M7824 should not exceed 120 minutes
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• Stop M7824 infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and / or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the M7824 infusion immediately and disconnect infusion tubing from the subject. • Subjects have to be withdrawn immediately form M7824 treatment and must not receive any further M7824 treatment

IV = intravenous; NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs

Additional Modifications for Subjects with Grade 2 Infusion-related Reactions

If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in **Table 7** (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion of IMP should be stopped for that day. At the next infusion, the Investigator may consider the addition of H2-blocker antihistamines (for example, famotidine or ranitidine), in addition to premedication, for select subjects. However, prophylactic steroids are NOT permitted. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, with or without the addition of further medication to premedication, the infusion should be stopped and the subject removed from M7824 treatment.

5.5.3.2 Severe Hypersensitivity Reactions and Flu-like Symptoms

If a hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) and can be found at https://www.resus.org.uk/pages/reaction.pdf. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

A. Symptoms

- Impaired airway
- Decreased oxygen saturation (< 92%)

- Confusion
- Lethargy
- Hypotension
- Pale / clammy skin
- Cyanosis

B. Management

1. Epinephrine injection and IV dexamethasone
2. Patient should be placed on cardiac, blood pressure, heart rate, and oxygen saturation monitor immediately
3. Alert intensive care unit for possible transfer if required

For prophylaxis of flu-like symptoms, a NSAID, for example, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each dose of M7824 IV infusion.

5.5.3.3 Immune-Related Adverse Events

For reporting irAE severity/toxicity grading, refer to CTCAE v4.03 toxicity grading system.

For treatment management of irAE per CTCAE v4.03 criteria, refer to American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines and National Comprehensive Cancer Network irAE Management Guidelines.

Treatment of irAEs is mainly dependent upon severity as defined by NCI-CTCAE v4.03. In general, management by CTCAE v4.03 grading, as per ASCO, is listed below:

- Grade 1: study treatment should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Grade 2: study treatment may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent).
- Grade 3: study treatment is generally suspended and the high-dose corticosteroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) treatment should be initiated. Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy.
- Grade 4: in general, permanent discontinuation of study treatment is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Treatment of irAEs should follow guidelines set forth in the ASCO/NCCN Management of Immunotherapy-Related Toxicities (https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf).

5.5.3.4 Anemia

Anemia is considered a potential risk based on toxicological findings with M7824 in cynomolgus monkey indicating a decrease in Hgb, RBCs, and hematocrit that was fully reversible or showed a substantial trend toward recovery. Notably, there are many reasons for anemia in patients with advanced cancer, which is why a thorough investigation of new anemia cases of unspecified etiology is requested.

Risk management measures in addition to routine laboratory tests will include:

- Subjects must enter the study with Hgb values at least 9 g/dL, independent of recent (≤ 28 days) packed red blood cell transfusion and/or use of an erythropoietin-stimulating agent.
- Routine monitoring of Hgb will be performed every 2 weeks (prior to treatment).
    - Instructions for study treatment discontinuation or modification in case of anemia will be provided, briefly described here: In case of any Hgb < 8 g/dL, the Investigator should use discretion to initiate anemia work up, including Coombs, haptoglobin, indirect bilirubin and peripheral smear, and prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR); Hgb and hematocrit are to be closely monitored.
- For new anemia events assessed as treatment-related, items queried may include but are not limited to detailed relevant past medical and treatment history, bruising tendency, history of blood transfusions and/or dependency, and a request for an updated eCRF including details such as concomitant medications, all laboratory data, updated dosing information and recent tumor evaluation scans.
- If a subject experiences significant anemia, then the amount of blood to be drawn may be reduced by not taking blood at selected time points for PD-L1 target occupancy, immunomonitoring, soluble factors, and TGFβ. The decision to reduce the time points for these biomarkers will be taken by the Investigator in consultation with the principal investigator.

- **Evaluation Guidance of baseline anemia and Suspected Treatment-related Anemia AEs**

Baseline anemia evaluation (prior to transfusion, if feasible)	
Hb and CBC with differential (e.g. MCV, RDW, ANC, hematocrit, reticulocytes counts) Peripheral blood smear for cell morphological assessment Complete metabolic panel including liver panel-LFTs, bilirubin, LDH, renal function, and serum folate, B12 values and other chemistries Coagulation factors (PT, PTT, INR) Urinalysis including culture Iron panel (TIBC, ferritin, Fe) TSH/hormonal panel Fecal-occult blood testing Peripheral blood smear haptoglobin	
Further recommendation based on suspected etiology (in addition to baseline anemia testing)	
Unknown etiology, suspect possible hemolysis	Coombs test, fibrinogen, d-dimer Consider hematology consultation. Consider blood transfusion at clinical discretion.
Unknown etiology, suspect possible bleeding	Consider blood transfusion at clinical discretion. Consider surgical/interventional radiology consultation. Consider imaging, as clinically indicated (e.g. FAST scan, CT scan, MRI, angiography). Consider endoscopy (upper/lower)
Unknown etiology despite above work-up	Hematology consultation Consider bone marrow aspiration/morphologic evaluation

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5.5.3.5 Rash with Hyperkeratosis / Keratoacanthoma / Squamous Cell Carcinoma of the Skin

Treatment-related skin lesions with hyperkeratosis, keratoacanthoma, cutaneous squamous cell carcinoma possibly due to TGFβ inhibition as important identified risks (adverse reactions) for M7824. They have been manageable and did not lead to permanent discontinuations in M7824 studies. Patients with known Lynch Syndrome who develop keratoacanthomas on study are encouraged to be evaluated for Muir Torre syndrome. Monitoring will include skin assessments as defined in the Schedules of Assessments (**Tables 1-3**), with biopsy of suspicious lesions. Management should be discussed with the principal investigator on a case-by-case basis. Dermatological consults should be requested as needed in the event that possible drug-related skin toxicity is suspected by the investigator.

5.5.3.6 Alterations in Wound Healing or Tissue Damage Repair

Due to the involvement of TGFβ in repair of skin and other tissue injuries, alterations in wound healing or repair of tissue damage is considered a potential risk. No AEs have been reported in

Phase I studies. For any surgeries conducted post-treatment initiation, surgical wound healing will be closely monitored. Management should be discussed with the principal investigator on a case-by-case basis. Dermatological consults should be requested as needed.

5.5.3.7 Dose Interruptions for Adverse Events not related to Study Drug

In case of Grade 3 and Grade 4 AEs not study drug-related, the study treatment may be interrupted based on the Investigator assessment and the subject will be medically treated for the event.

If the AE reduces to a lower tolerable grade the study treatment might be resumed in the subsequent cycle. If the AE remains the same in spite of medical treatment until the next treatment (second cycle after the AE occurred) a discussion with the principal investigator should occur and consideration of a possible extension of the dose interruption for up to 1 additional cycle or a permanent withdrawal from the study treatment should be considered.

If upon the resumed study treatment the subject experiences the same AE this should be re-discussed with the principal investigator to assess permanent withdrawal from the study treatment.

Grade 3 and 4 laboratory abnormalities that do not have clinical significance do not require dose interruption.

5.6 Packaging and Labeling of the Investigational Medicinal Product

M7824 drug product is a sterile freeze-dried formulation presented at a concentration of 600 mg/vial in USP type I glass vial closed with a rubber stopper and sealed with an aluminum plastic crimping cap.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice guidelines. M7824 will be packed in boxes containing a suitable number of vials. The information on the medication will be in accordance with approved submission documents.

M7824 will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

5.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

M7824 drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long term stability studies with M7824.

M7824 drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. M7824 must not be frozen. Rough shaking of the reconstituted solution must be avoided.

For application in clinical trials, M7824 drug product must be reconstituted with 4.5 mL of Water for Injection and diluted with 0.9% saline solution (sodium chloride injection). The chemical and physical in-use stability for the infusion solution of M7824 in 0.9% saline solution has been demonstrated for a total of 72 hours at room temperature; however, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user. No other drugs should be added to the infusion containers containing M7824.

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation.

M7824 must not be used for any purpose other than the study. The administration of IMPs to subjects who have not been enrolled into the study is not covered by the study insurance.

The contents of the M7824 vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

5.8 Investigational Medicinal Product Accountability

The Investigational Pharmacy is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- IMP accountability records will include the following:
    - Confirmation of IMP receipt, in good condition and in the defined temperature range.
    - The inventory of IMP provided for the clinical trial and prepared at the site.
    - The use of each dose by each subject.
    - The disposition (including return, if applicable) of any unused IMP.

-
- Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMP prepared at the site), and the individual subject trial numbers.

The Investigator site should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMP must not be used for any purpose other than the present trial. No IMP that is dispensed to a subject may be redispensed to a different subject.

The clinical trial monitor will periodically collect and review the IMP accountability forms and where applicable, will check all returns (both unused and used containers) before arranging for their return or authorizing their destruction by the trial site.

At the conclusion or termination of this trial, trial site personnel and the IND Office will conduct a final product supply inventory on the Investigational Drug Accountability Forms and all unused containers will be destroyed. Instructions for destruction of product will be provided to the site. The Clinical Trial Monitor will be supplied with a copy for filing of the Investigational Drug Accountability Forms. This documentation must contain a record of clinical supplies used, unused, and destroyed and shall include information on

- all administered units,
- all unused units,
- all destroyed units (during the trial),
- all destroyed units at the end of the trial,
- date of destruction(s),
- name and signature of the Investigator / pharmacist.

It must be ensured at each trial site that the IMP is not used

- after the expiration date, and
- after the retest date unless the IMP is reanalyzed and its retest date extended.

This is to be closely monitored by the Clinical Trial Monitor.

5.9 Assessment of Investigational Medicinal Product Compliance

In this trial, subjects will receive M7824 IV infusions at the investigational site. Well-trained medical staff will monitor and perform the IMP administration. The information of each IMP administration including the date, time, and dose of IMP will be recorded in Prometheus. The

Investigator will make sure that the information entered into Prometheus regarding IMP administration is accurate for each subject. Any reason for noncompliance should be documented.

Noncompliance is defined as a subject missing > 1 administration of trial treatment for nonmedical reasons. If 1 treatment administration was missed and the interval between the subsequent treatment and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well. Continuation of treatment should be discussed with the principal investigator.

5.10 Medical Care of Subjects after End of Trial

After a subject has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice and depending on the subject's individual medical needs.

Upon withdrawal from the trial, subjects may receive whatever care they and their physicians agree upon. Subjects will be followed for survival and AEs as specified in Section 6.1.4.

6 Trial Procedures and Assessments

6.1 Schedule of Assessments

A complete schedule of assessments is provided in **Tables 1-3**, including sample collection for tumor biopsies and plasma samples.

Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent according to the procedure described in Section 7.2.

6.1.1 Screening and Baseline Procedures and Assessments

There is a 28-day washout / recovery period for prior anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative radiotherapy delivered in a normal organ-spearing technique], immune therapy, or cytokine therapy except for erythropoietin) and major surgery before the start of trial treatment (Section 4.3.2). Hematology and chemistry laboratory samples must be drawn and reviewed within 72 hours prior to dose administration.

During the screening period and before any trial related investigations and assessments are started, the subjects will be asked to sign the relevant ICFs. The subjects' information that will be documented during screening includes the demographic information (birth date, sex, ethnicity, and race) and the complete medical history, including the history of the tumor disease and prior anticancer therapies, previous medications (prior 30 days to signing of ICF), concomitant medications, and baseline medical condition (the information of concomitant medications and AEs will be monitored throughout the trial treatment period).

During screening, subjects will undergo a complete physical examination, dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions), recording

vital signs, including body weight and height (height only at screening), 12-lead electrocardiogram (EKG), and a determination of the ECOG PS (Appendix 1).The screening laboratory examination includes hematology, full serum chemistry and full urinalysis. Antinuclear antibody (ANAs), rheumatoid factor (RF), free thyroxine (T4), and TSH will also be assessed at screening.

During screening, a serum β-human chorionic gonadotropin (β-HCG) pregnancy test will be performed for females of child bearing potential and blood. HIV, HBV, and HCV testing will be performed for all screening subjects as these conditions are trial entry exclusion criteria. A female is considered of childbearing potential (that is fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level (> 40 mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in females not using hormonal contraception or hormonal replacement therapy.

For Cohort D, patients will be screened for the presence or absence of ctDNA in the screening period prior to treatment initiation.

Additional blood will be collected during screening for exploratory blood biomarkers including circulating cytokines and leukocyte subpopulations (Section 6.4.5).

The tumor evaluation (type / staging, etc.) will be performed using CT scan or MRI (if MRI is used, CT of chest is mandatory.

Collection of tumor biopsies or archived surgical specimen will also be done during this period, if applicable and at 4 weeks into the study (prior to dose 3) for cohort A-C. For cohort B, tumor biopsies will be collected pretreatment, prior to dose 2, and prior to dose 4.]Pretreatment and/or post-treatment biopsies will be subjected to assessment of immune infiltration, expression of PD-L1, and CMS classification by FFPE RNA analysis.

6.1.2 Treatment period

For this protocol, a cycle is defined as 28 days. M7824 will be given until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 4.5). Subjects who have experienced a PR or CR should continue treatment through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the principal investigator. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in Section 4.5.1.

For subjects who achieve a PR or CR on M7824 therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, a re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial principal investigator. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial M7824 therapy. Prior to re-initiation of the study treatment, malignant

disease needs to be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory samples must be drawn and results available and verified prior to re-initiating of treatment.

Subjects will be asked to visit the investigational site according to the Schedules of Assessments (see **Tables 1-3**). In addition, the tumor evaluation (see Section 6.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days). Furthermore, if any Screening procedures are conducted within 3 days prior to Day 1 of trial treatment (Cycle 1, Day 1), the assessments scheduled on Cycle 1, Day 1 do not need to be repeated except for the evaluation of AEs and concomitant medications.

During the treatment period, the following assessments will be performed (see **Tables 1-3** for the detailed schedule):

- AEs and concomitant medications will be documented in each study visit
- ECOG PS will be assessed prior to trial treatment on Day 1 (unless the Screening ECOG PS was performed within 3 days prior to Day 1)
- Physical examination will be performed prior to trial treatment on Day 1 (Cycle 1) and then prior to trial treatment according to **Tables 1-3**
- Eye signs and symptoms should be checked. If clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days
- Dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions according to **Tables 1-3**)
- Vital signs, including body weight, will be assessed prior to trial treatment according to **Tables 1-3**.
- The 12-lead EKG will be assessed according to **Tables 1-3**.
- The laboratory hematology tests will be assessed prior to trial treatment according to **Tables 1-3**. Complete blood count results must be drawn and reviewed within 72 hours prior to dose administration.
- Full serum chemistry will be assessed prior to trial treatment according to **Tables 1-3**. Samples for full chemistry results must be drawn and reviewed within 72 hours prior to dose administration.
- A basic urinalysis will be performed prior to trial treatment every according to **Tables 1-3**.
- Samples for ANAs and RF according to **Tables 1-3**.

- A serum HCG pregnancy test will be required at Screening, urine or serum β-HCG pregnancy test will be performed prior to each administration of the study drug (if applicable).

- The tumor evaluation (see Section 6.3) will be performed prior to treatment at week 8, and then once every 8 weeks, with a tumor assessment visiting time window of 5 days prior to dosing. For subjects continuing treatment beyond 12 months (in consultation with the principal investigator), tumor evaluations should take place every 12 weeks.

- Tumor biopsies at Week 4, prior to the third treatment dose (-7 day window permitted). Archival tissue may be used in place of a fresh pretreatment biopsy if adequate tumor is available for analysis. If insufficient tissue is available for analysis for pretreatment tumor, then a mandatory fresh biopsy must be obtained. In cohort A, the site of tumor tissue for the pretreatment sample, whether archival or fresh, may be from the primary tumor or the metastasis. In cohort B, the site of tumor for the pretreatment sample, in order to classify the CMS subtype, must come from the primary tumor. The week 4, on-treatment biopsy for both cohorts may come from the primary tumor or from a metastatic site.

- Free T4, and TSH will be measured prior to trial treatment according to **Tables 1-3**.

- The exploratory blood biomarkers including circulating cytokines and leukocyte subpopulations will be performed as detailed in **Tables 1-3** as described in Section 6.4.5.2

- Samples for TGFβ determination will be drawn as detailed in **Tables 1-3**.

6.1.3 End of Treatment

6.1.3.1 End of Treatment Visit

All subjects must undergo an End-of-Treatment visit after discontinuation of M7824 for any reason. This visit should be performed on the day of or within 7 days after the decision to discontinue trial treatment but before any new antineoplastic therapy is started (if possible), whichever occurs earlier (see **Tables 1-3**). If it is known to the Investigator at the time of the End of- Treatment visit that the subject will start new treatment within 28 days of last treatment or they will be unable to return within 28 days of last treatment, assessments associated with the 28-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit. For all these subjects, the discontinuation visit consists of:

- Documentation of AEs and concomitant medication.

- Physical examination including vital signs and body weight.

- Eye signs and symptoms should be checked. If clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days.

- Dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions).
- Laboratory hematology, full serum chemistry, and basic urinalysis.
- ECOG performance status will be assessed.

6.1.4 Post Treatment Follow Up

6.1.4.1 28-Day Safety Follow Up

A Safety Follow-up visit is scheduled 4 weeks (28 ± 5 days) after the last administration of M7824 but before any new therapy is started, if possible, whichever occurs earlier. If it is known to the Investigator at the time of the End of-Treatment visit that the subject will start new treatment within 28 days of last treatment or they will be unable to return within 28 days of last treatment, assessments associated with the 28-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit. The 28-Day Safety Follow-up visit will comprise a full assessment for safety, immunogenicity, and tumor response as appropriate, which will include the following (refer to **Tables 1-3**):

- AEs, concomitant medications.
- Vital signs and body weight.
- Physical examinations.
- Eye signs and symptoms should be checked by the treating investigator. If clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days.
- Dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions) by the treating investigator.
- The 12-lead EKG.
- Complete blood count, full serum chemistry.
- Full urinalysis.
- ECOG performance status will be assessed.
- The β-HCG pregnancy test (in females of childbearing potential).
- The tumor evaluation (only to be performed, if no disease progression was documented previously).

- Free T4, and TSH.
- Samples for ANAs and RF.
- The exploratory blood biomarkers including circulating cytokines and leukocyte subpopulations will be performed as detailed in **Tables 1-3** as described in Section 6.4.5.2.
- Samples for TGFβ determination.
- Blood samples for gene expression evaluation for subjects with PD.
- An optional tumor biopsy following progression may be offered to the patient.

6.1.4.2 Long-term Follow-up / Trial Termination

All SAEs ongoing at the 28-Day Safety Follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up." In addition, all trial drug-related SAEs occurring after 28-Day Safety Follow-up visit and ongoing at the Safety Follow-up visit have to be followed up in the same manner.

Subjects without PD at the 28-Day Safety Follow-up visit will be followed up for disease progression (CT / MRI scans every 12 weeks) until PD.

After the 28-Day Safety Follow-up visit, subjects will be followed quarterly (± 14 days) for survival (including assessment of any further anticancer therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of M7824.

6.1.5 Blood Consumption for Clinical Assessments

The overall amount of blood to be drawn from a single subject must not exceed 120 mL/day and 550 mL in an 8-week period for safety laboratory testing, pregnancy testing, exploratory biomarker investigation, and antibody evaluation.

6.2 Demographic and Other Baseline Characteristics

The assessments and procedures described in this section must be performed during the Screening period.

6.2.1 Demographic Data

The following demographic data will be recorded:

- Subject identifier
- Date of birth
- Sex

- Ethnicity
- Race

6.2.2 Diagnosis of Tumor

The tumor disease information that will be documented and verified at the Screening visit for each subject includes:

- Detailed history of the tumor, including histopathological diagnosis, grading and staging in accordance with the American Joint Cancer Committee (7th Edition) Tumor Node Metastasis Classification at diagnosis (AJCC TNM).
    - The M category (M0 or M1) of the tumor at the time of study entry, based on screening assessments.
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy and chemotherapy, immunotherapy, etc.).
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy.
- Current cancer signs and symptoms and side effects from current and / or previous anticancer treatments.
- Current cancer disease status.

6.2.3 Medical History

In order to determine the subject's eligibility to the trial, a complete medical history of each subject will be collected and documented during Screening, which will include, but may not be limited to, the following:

- Past and concomitant non-malignant diseases and treatments.
- All medications taken and procedures carried out within 30 days prior to Screening.

For the trial entry, all the subjects must fulfill all inclusion criteria described in Section 4.3.1, and none of the subjects should have any exclusion criterion from the list described in Section 4.3.2.

6.2.4 Vital Signs and Physical Examination

Vital signs including body temperature, respiratory rate, heart rate (after 5-minute rest), and arterial blood pressure (after 5-minute rest), body weight and height will be recorded at study entry.

Physical examinations will be performed according to **Tables 1-3**. An ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be conducted.

The ECOG PS will be documented during the Screening phase.

6.2.5 CT or MRI Scans for Tumor Assessment at Baseline

A CT scan or MRI (if MRI is used, CT of chest is mandatory) of the chest, abdomen, and pelvis will be performed within 28 days prior to trial treatment start in order to document the baseline status of the tumor disease using iRECIST 1.1 target and non-target lesions. However, if the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the Screening CT / MRI does not need to be performed.

A bone scan should be done at Screening as clinically indicated.

6.2.6 Cardiac Assessments

A 12-lead EKG will be recorded at Screening. The EKG will be recorded after the subject has been in a supine position breathing quietly for 5 minutes. The EKG results will be used to evaluate the heart rate, atrial-ventricular conduction, QR, QT, and corrected QT intervals, and possible arrhythmias.

The EKGs will be documented by recording date and time of collection. All EKG results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the subject. EKGs are to be performed according to local procedures and will NOT be digitally uploaded.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided if the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF (Prometheus). Abnormal values will not be recorded as AEs unless they are the reason for discontinuation of the trial IMP due to AEs or are SAEs.

6.2.7 Clinical Laboratory Tests

Blood samples will be collected at screening for clinical laboratory parameter evaluations. These clinical laboratory test results will serve not only as the baseline values for subsequent safety clinical laboratory evaluations during the trial, but also help to make sure that each enrolled subject fulfills all the trial entry criteria as listed in Section 4.3.1 and does not meet any of the trial exclusion criteria for laboratory parameters as listed in Section 4.3.2. Detailed description of laboratory assessments is provided in Section 4.4.3.

6.2.8 ctDNA testing

Guardant360 is a next-generation sequencing (NGS) panel of 70 clinically actionable onco- and tumor suppressor genes utilizing digital sequencing of cell-free circulating tumor DNA (cfDNA) isolated from a simple, non-invasive blood draw. It is medically indicated for the prevention of a repeat invasive biopsy in advanced cancer patients when the initial biopsy is insufficient (QNS) or unavailable/unobtainable as well as when cancer has progressed or recurred despite treatment. The test detects single nucleotide variants via complete exon sequencing in 70 genes, copy number

amplifications in 16 genes, small indels in EGFR, ERBB2 and MET exon 14 skipping, and fusions in ALK, FGFR2, FGFR3, RET, ROS1 and NTRK1. The genes are selected because mutations in these genes have FDA-approved matched therapies or are eligible for late phase clinical trials, as well as non-druggable genes with high prevalence alterations that may be helpful in monitoring for molecular response/non-response such as TP53.

Guardant360 is an advanced diagnostic laboratory test (ADLT) offered by a sole source laboratory certified by the Clinical Laboratory Improvement Amendments (CLIA) for high complexity (molecular pathology) testing and accredited by the College of American Pathology (CAP). Due to high rates of false positives with traditional NGS assays when tumor DNA is in low concentrations, the majority of "liquid biopsy" methods interrogating cell-free DNA have been limited to hotspot analyses. In contrast, the ultra-high specificity (> 99.9999%) of the digital sequencing method enables the sequencing of long, targeted regions (146,000 base pairs) without false positives. Complete exons are sequenced for all exons in 30 genes and the critical exons (those reported as having a somatic mutation in COSMIC) in 40 additional genes. Thus, its key differentiating characteristic from other "liquid biopsy" methods is the ability to sequence complete exons in many genes, in contrast to gene hotspot testing.

Advantages of the Guardant360 cell-free DNA NGS methodology versus solid tumor tissue-based NGS are:

1. An invasive needle or surgical biopsy is avoided with ctDNA, reducing costs and complications.

2. CtDNA provides a quantitative measure (concentration or mutant allele frequency) of mutations present whereas solid tumor biopsy typically provides a qualitative result (mutation either present or not detected). The quantitative cfDNA result may be followed over time to monitor response to treatment and evolution of acquired resistance.

3. CtDNA sequencing identifies both germline and somatic mutations in the same sample.

4. The assay failure rate is for ctDNA is less than 0.5% (in the first 9,000+ samples) compared to 15%-25% failure rates of tissue-based NGS related to insufficient quantity of tissue (QNS).

Guardant360 utilizes algorithmic methods to encode and ultimately decode inputs and outputs from massively parallel deep sequencing analysis. By leveraging signal transduction processing technology where voice or image data is digitally encoded before transmission and then decoded post-transmission, this NGS method, known as Digital SequencingTM, enables signal interference to be reduced by two orders of magnitude or more [88]. Four validation studies have been published with concordance to tissue biopsy-based genomic testing [88-91]. With high enough sensitivity and specificity to robustly quantitate ctDNA from blood, this approach has the potential to evaluate the multiple genomic targets required in NCCN guidelines, to act as a "summary" of the different tumor clones in patients with intra-tumor and inter-tumor heterogeneity, and to prevent the time

delays, costs and complications inherent in invasive biopsies. The analytical and clinical validation of Guardant360 is conducted in conformance with evidentiary standards established by the Standards for Reporting of Diagnostic Accuracy (STARD), REporting of tumor MARKer Studies (REMARK), Evaluation of Genomic Applications in Practice and Prevention (EGAPP), and the recent Next-generation Sequencing: Standardization of Clinical Testing (Nex-StoCT) biomarker guidelines [92-95].

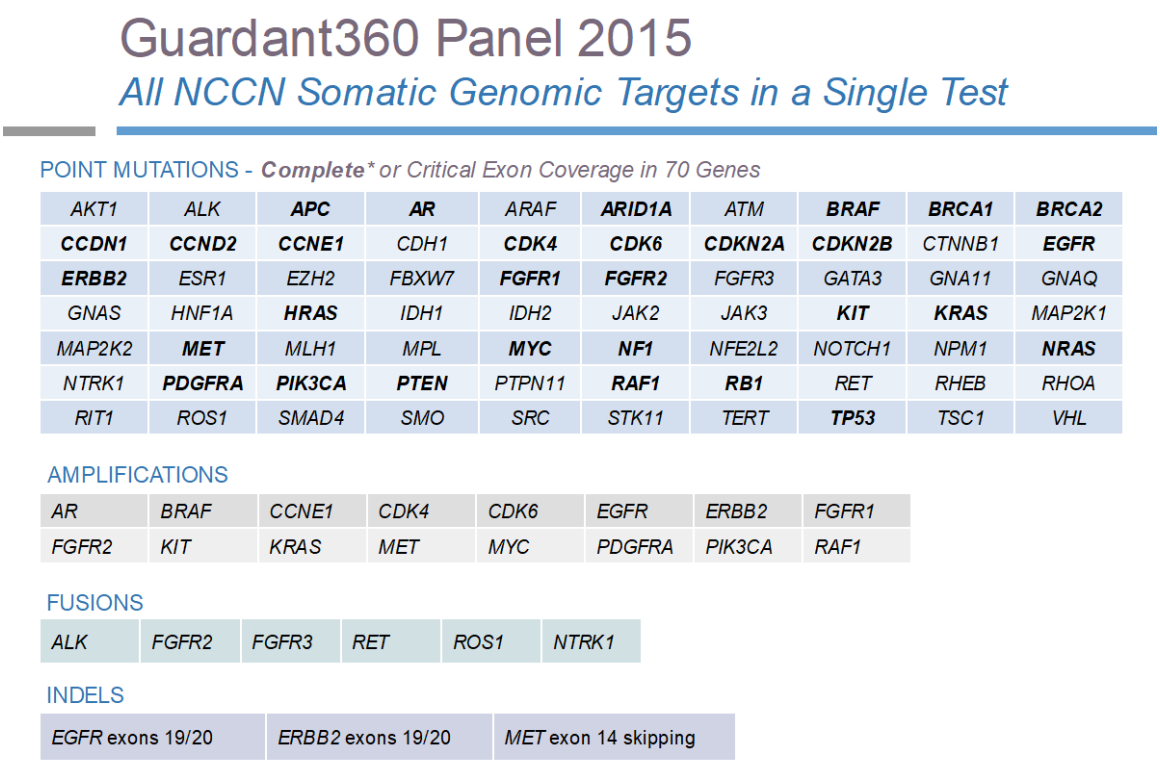
Methodology

The gene panel was selected to focus on those genomic alterations that are currently actionable defined as being targets of sensitivity or resistance to an FDA-approved matched therapy and/or a targeted therapy in clinical trials. The test simultaneously sequences the 70 cancer-related genes to an average depth of coverage of greater than 8,000X. To summarize, cell-free DNA is extracted from plasma and genomic alterations are analyzed by massively parallel paired end synthesis-by-sequencing of amplified target genes utilizing an Illumina Next-Seq platform complemented by systematic end-to-end process optimization including conversion of cell-free DNA fragments into digital sequences, improvements in the Illumina next generation sequencing process itself, followed by bioinformatics algorithms which enable ctDNA to be measured as a quantitative percentage of total cell-free DNA.

Two 10mls of whole blood are collected in Streck Cell-Free DNA Blood Collection (Streck) tubes, which contain a proprietary formaldehyde-free preservative in that stabilizes white blood cells, preventing the release of genomic DNA and allowing shipping and stability for seven days without need for refrigeration, cold bricks or preliminary centrifugation prior to shipping.

After digital libraries are produced, the sample is sequenced and post-sequencing data is processed using bioinformatics algorithms to quantify the absolute number of unique DNA fragments at a given nucleotide position. This proprietary process is referred to as Digital SequencingTM and enables reporting of the fractional concentration (mutant allele frequency) of a given SNV. Circulating cell-free DNA is mostly derived from leukocyte lysis (germline) and generally a much smaller amount of tumor DNA is derived from cancer cell apoptosis/necrosis. All of the cell-free DNA fragments, including leukocyte-derived and tumor-derived, are simultaneously sequenced with up to single molecule sensitivity. In other words, both tumor DNA and “normal”/germline DNA are sequenced and measured in the same sequencing assay. The fractional concentration or mutant allele frequency for a given mutation is calculated as the fraction of circulating tumor DNA harboring that mutation in a background of wild-type cell-free DNA fragments. The analytic sensitivity reaches detection of 1-2 single mutant cell-free DNA molecules from a 10 ml blood sample.

Gene list and genomic alterations in the Guardant360 Panel



6.3 Efficacy Assessments

For all subjects, tumor response assessment will be performed by CT scan or MRI (if MRI is used, CT of chest is mandatory. All the scans performed at baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. In general, lesions detected at baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

Skin metastasis can be used as target lesions according to iRECIST 1.1 using measurements by caliper, if they fulfill iRECIST 1.1 for target lesions as described below. The presence of new cutaneous lesions will be considered diagnostic of progression for iRECIST 1.1, even if not imaged. For each subject, the Investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and / or metastatic tumor masses, physical examination findings, and the results of other assessments. All available images collected during the trial period will be considered. The most appropriate measures to evaluate the tumor status of a subject should be used. The measure(s) to be chosen for sequential evaluation during the trial have to correspond to the measures used to document the progressive tumor status that qualifies the subject for enrollment. The tumor response assessment will be assessed and listed according to the Schedule of Assessments (refer to **Tables 1-3**).

The foreseen treatment duration is until documentation of PD, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 4.5).

The treatment should be stopped immediately, if the subject does not tolerate M7824 anymore or if therapeutic failure occurs, which requires urgent treatment with an additional drug or results in clinically significant progression / deterioration.

Tumor responses to treatment will be assigned based on the evaluation of the response of target, non-target, and new lesions according to iRECIST 1.1 (all measurements should be recorded in metric notation).

- To assess objective response, the tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and non-target lesions according to iRECIST 1.1

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

Any CR or PR should be confirmed according to iRECIST 1.1.

The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD.

As outlined in Section 4.1, treatment should continue with M7824 if the patient has PD provided:

- There are no new Grade 2 or greater symptoms or significant worsening of existing symptoms.
- There is no decrease in ECOG PS.
- In the opinion of the Investigator, the subject does not require new anticancer therapy.

PD and any of the above conditions not satisfied results in study discontinuation.

Subjects who have experienced a confirmed PR or CR should continue treatment through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the principal investigator.

6.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings including vital signs and eyes signs and symptoms, and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 6.4.1.2). Given the intended MoA, particular attention will be given to AEs that may follow the enhanced T-cell activation such as persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, uveitis and other inflammatory eye conditions, or other immune-related reactions. Ophthalmologic examinations should be considered, when clinically indicated, for signs or symptoms of uveitis. Furthermore, due to the anti-TGFβ activity, particular

attention will also be given to events associated with, anemia, and rash with hyperkeratosis / keratoacanthoma and squamous cell carcinoma of the skin.

The reporting period for AEs is described in Section 6.4.1.3.

The safety assessments will be performed according to the Schedules of Assessments (see **Tables 1-3**).

6.4.1 Adverse Events

6.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition / illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as an AE, and the death is considered as its OUTCOME.

The investigator (or physician designee) is responsible for verifying and providing source documentation, grading the severity and assigning the attribution for all adverse events.

Investigators will reference the NCI-CTCAE v4.03 (publication date: 17 November 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity / intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event Grades are also provided.

If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Life-threatening

Grade 5: Death

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I	Phase I	Phase I
			Phase II	Phase II	Phase II
				Phase III	Phase III
Unlikely	Phase I	Phase I	Phase I	Phase I	Phase I
			Phase II	Phase II	Phase II
				Phase III	Phase III
Possible	Phase I	Phase I	Phase I	Phase I	Phase I
	Phase II	Phase II	Phase II	Phase II	Phase II
		Phase III	Phase III	Phase III	Phase III
Probable	Phase I	Phase I	Phase I	Phase I	Phase I
	Phase II	Phase II	Phase II	Phase II	Phase II
		Phase III	Phase III	Phase III	Phase III
Definitive	Phase I	Phase I	Phase I	Phase I	Phase I
	Phase II	Phase II	Phase II	Phase II	Phase II
		Phase III	Phase III	Phase III	Phase III

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE as per Section 6.4.1.4; however, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. “Fatal” will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the IMP using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the

M7824 include, but may not be limited to, temporal relationship between the AE and the M7824, the known safety profile of M7824, medical history, concomitant medication, course of the underlying disease, trial procedures.

Unrelated: Not reasonably related to the IMP. The AE could not medically (pharmacologically / clinically) be attributed to the IMP under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP. The AE could medically (pharmacologically / clinically) be attributed to the IMP under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an EKG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

6.4.1.1.1 Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Merck/EMD Serono, it results in any of the following outcomes:

- Death

- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 90 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Office (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, Merck/EMD Serono**'s guidelines, and Institutional Review Board policy.**

6.4.1.1.2 Events Not to Be Considered as AEs / SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are not to be considered AEs.

AE / SAEs Observed in Association with Disease Progression

Progression of the disease / disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an AE / SAE, unless the subject's general condition is more severe than expected and / or unless the outcome is fatal within the AE reporting period (as defined in Section 6.4.1.3).

6.4.1.1.3 Pre-defined AEs of Special Interest (AESI) for Safety Monitoring

Any AE that is suspicious to be a potential irAE (see Section 5.5.3.3), including ophthalmologic findings, has to be reported in an expeditious manner and will be considered an AE of special interest (AESI).

Infusion-related reactions / hypersensitivity, regardless of grade, must be reported as AESIs.

In addition, rash with hyperkeratosis / keratoacanthoma / squamous cell cancer of the skin are regarded as AESIs. Please note that squamous cell cancer of the skin should be considered as medically important condition and thus as a serious AESI, which has to be reported in an expedited manner as a SAE.

Anemia when considered related to M7824 will be reported as AESI regardless of grade.

The reporting of AESI is defined in Section 6.4.1.4.

6.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF (Prometheus). All SAEs and all non-serious AEs of special interest must be additionally documented and reported using the eSAE database.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times to be completed when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

6.4.1.2.1 Investigator Communications with Merck/EMD Serono

- In addition to the regular reporting obligations, the following reportable events must be submitted to EMD Serono within 48 hours for fatal/life-threatening SAEs and 5 business days for all other SAEs.

- Exposure during pregnancy or breastfeeding (even if not associated with an adverse event) and occupational exposure (even if not associated with an adverse event) shall also be reported.

Contact information for submission of reportable events and monthly extracts to EMD Serono:

E-mail: GlobalDrugSafety@merckgroup.com or **Fax:** +49 6151 72 6914

Specifying:

- PROTOCOL Number
- SUBJECT Number
- SITE Number/PI Name
- SAE/ONSET DATE

6.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance from the first protocol intervention to 90 days after last study drug administration and continues through the trial's 28-Day Safety Follow-up visit, defined as 28 days (± 5 days) after last trial drug administration. After the 28-Day Safety Follow-up visit only AEs that are deemed attributable to trial drug by the Investigator should be documented until the Safety Follow-up visit, defined as 28 days (+/- 7 days) after the last trial drug administration.

Any SAE assessed as related to M7824 must be reported whenever it occurs, irrespective of the time elapsed since the last administration of M7824.

6.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum 24 hours after becoming aware of the event) inform the IND Office and/or Merck/EMD Serono using the SAE Report Form following specific completion instructions.

In exceptional circumstances, a SAE (or follow-up information) may be reported by telephone; in these cases SAE Report Form must be provided immediately thereafter.

Reporting procedures and timelines are the same for any new information on a previously reported SAE (= follow-up).

Relevant pages from the eCRF (Prometheus) may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, and autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF (Prometheus).

The Investigator must respond to any request for follow-up information (for example, additional information, outcome final evaluation, other records where needed) or to any question the IND Office and/or Merck/EMD Serono may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure a prompt assessment of the event by the IND Office and/or Merck/EMD Serono and (as applicable) to allow the IND Office to meet strict regulatory timelines associated with expedited safety reporting obligations.

Adverse Events of Special Interest

In the event of a non-serious Grade ≥ 3 AESI, the Investigator must report the AESI using the eSAE database within 5 days, and the logs should be provided to Merck/EMD Serono every 3 months. Serious AESIs have to be reported in an expedited manner as SAEs within 24 hours as outlined above, and reported to EMD Safety. For Grade 1 and Grade 2 non-serious AESIs, results from the eSAE database should be forwarded to Merck/EMD Serono every 3 months.

Safety Report to Health Authorities, Independent Ethics Committees / Institutional Review Boards and Investigators

The IND Office will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC / IRB that approved the trial.

In accordance with ICH GCP guidelines, Merck/EMD Serono will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IEC's / IRB's approval / favorable opinion to continue the trial." In particular and in line with respective regulations, Merck/EMD Serono will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reactions [SUSARs]). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, Merck/EMD Serono will provide appropriate Safety Reports directly to the concerned lead IEC / IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC / IRB of any Safety Reports provided by Merck/EMD Serono and of filing copies of all related correspondence in the Investigator Site File.

6.4.1.5 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the trial (see Section 6.4.1.3) and are assessed for final outcome at the End of Treatment visit. After the End of Treatment visit only AEs that are deemed attributable to trial drug by the Investigator should be documented until the Safety Follow-up visit.

All SAEs ongoing at the 28-Day Safety Follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". In addition, all trial drug related SAEs occurring after 28-Day Safety Follow-up visit and ongoing at the Safety Follow-up visit must be followed up in the same manner.

Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

6.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs; however, all pregnancies with an estimated conception date during the period defined in Section 6.4.1.3 must be recorded by convention in the AE page / section of the eCRF (Prometheus). The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must also notify the IND Office in an expedited manner of any pregnancy using the Paper Pregnancy Report Form, which must be transmitted according to the same timelines as described for SAE reporting in Section 6.4.1.4.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the IND Office of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child / Fetus Adverse Event Report Form if the child / fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 6.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The IND Office must be notified without delay and the subject must be followed as mentioned above.

6.4.3 Clinical Laboratory Assessments

It is essential that the IND Office be provided with a list of laboratory normal ranges before shipment of IMP. Any change in laboratory normal ranges during the trial will additionally be forwarded to the IND Office.

Blood samples will be taken from non-fasted subjects. All routine laboratory analyses will be performed at a laboratory facility local to the investigational site and relevant results must be drawn and checked before administration of M7824. The report of the results must be retained as a part of the subject's medical record or source documents. Complete blood count and full serum chemistry must be checked within 72 hours prior to each dose administration.

ANA, RF, T4, TSH, and urinalysis will be assessed at the time points defined in the Schedules of Assessments (**Tables 1-3**).

If confirmation of a subject's postmenopausal status is necessary, a FSH level will also be performed at Screening, see Section 6.1.1.

Table 7: Required Laboratory Panel Tests

Full Chemistry	**Hematology**
Albumin	Absolute lymphocyte count
Alkaline phosphatase	Absolute neutrophil count
Alanine aminotransferase	Hematocrit
Amylase+	Hemoglobin
Aspartate aminotransferase	Platelet count
Bicarbonate	RBC count
Blood urea nitrogen / total urea	White blood cell count and differential count
Calcium	Red blood cell morphology**
Chloride	Reticulocytes
	Mean corpuscular hemoglobin
Creatine kinase	Mean corpuscular volume
Creatinine	Mean corpuscular hemoglobin concentration
C-reactive protein	
Glucose	
Lactate dehydrogenase	
Lipase+	
Phosphorus / phosphates	
Magnesium	**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening and 28-Day Safety Follow-up visits and a basic urinalysis prior to Day 1 of every cycle.
Potassium	
Sodium	
Total bilirubin / direct bilirubin/ indirect bilirubin*	
Total protein	
Uric acid	
	ANA*, RF***, TSH, and T4**

	Hepatitis Screening[a] Hepatitis B surface antigen, hepatitis B core antibody Hepatitis C Antibody

ACTH=adrenocorticotropic hormone; ANA=antinuclear antibody; IMP=Investigational Medicinal Product; PCR = polymerase chain reaction; RF=rheumatoid factor; TSH=thyroid-stimulating hormone; T4=free thyroxine.

** Only in case of anemia onset assessed as related to study treatment

+Only day 1 of every cycle

***Only at pre-screening evaluation (see schedule of assessments)

a If hepatitis B surface antigen positive and hepatitis B core antibody positive, then reflex to quantitative HBV DNA (PCR); if hepatitis B core antibody positive alone, then reflex to quantitative hepatitis B DNA (PCR); if hepatitis C antibody positive, then reflex to quantitative hepatitis C RNA (PCR).

If a subject has a clinically significant abnormal laboratory test value that is not present at Baseline, the test will be repeated weekly and the subject will be followed until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable.

For **pharmacokinetic assessment of M7824**, a blood sample should be collected prior to infusion of M7824 and following completion (within 30 minutes) of infusion of M7824 (doses 1 and 3), prior to dose 2, and prior to dose 6/end of treatment visit (whichever of these two comes first). Samples should be processed as follows:

1. Collect 3.5 mL of blood in an SST tube with silica clot activator and polymer gel.
2. Gently invert the tube 5 times to mix the clot activator with the blood.
3. Allow blood to clot for 30 minutes at room temperature in a vertical position.
4. After allowing clot to form, centrifuge the tube for 15 minutes at 1100-1300x g at 25°C. If refrigerated centrifuge is available, set the temperature at 25°C in order to prevent heating during centrifugation and to optimize flow of the barrier material. Flow may be impeded if chilled before or during centrifugation.
5. Carefully collect and aliquot the serum equally into 2 separate Micronics tubes.
6. Place the tubes immediately into the freezer in an upright position at -80°C.
7. Samples will be analyzed as a batch with EMD Serono at a later date.

6.4.4 Vital Signs, Physical Examinations, and Other Assessments

The ECOG PS will be assessed at Screening and at subsequent visits as indicated in the Schedules of Assessments (**Tables 1-3**) and documented in the eCRF (Prometheus).

Body weight will be measured at Screening and at subsequent visits as indicated in the Schedules of Assessments (**Tables 1-3**) and documented in the eCRF (Prometheus). Body height will be measured at screening only.

A physical examination will be conducted at Screening and at subsequent visits as indicated in the Schedules of Assessments (**Tables 1-3**) and documented in the eCRF (detailed description in Section 6.1). Any abnormalities arising or worsening after the signing of the ICF should be

documented in the eCRF (Prometheus) Adverse Event section (see Section 6.4.1). Abnormal findings are to be reassessed at subsequent visits.

Physical examination should include a dermatological examination. If abnormal skin findings are observed, the patient should be referred to a dermatologist for biopsy of suspicious lesions.

An ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be conducted at Screening. At subsequent visits, eye signs and symptoms should be checked. If there are any clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days.

Digital 12-lead EKGs will be recorded as a single recording at the screening visit. Subsequent EKGs will likewise be obtained as single recordings.

All newly diagnosed or worsening conditions, signs and symptoms observed since Screening, whether related to trial treatment or not, are to be reported as AEs.

For female subjects of childbearing potential, serum β-HCG pregnancy test will be carried out during the Screening phase. A urine β-HCG test may be performed prior to schedule on treatment assessments. Results of the most recent pregnancy test should be available prior to the next dosing of IMP. Subjects who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and if needed FSH > 40 mIU/mL [in the postmenopausal range] as outlined in Section 6.1.1), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.

6.4.5 Biomarkers

Due to limited understanding of the biological activities induced by M7824 in cancer subjects, there can be no certainty that the doses examined will be associated with relevant antitumor immune activities. Further details regarding translational studies are listed in Appendix 3. As the consequence, the trial will serve to

1. Evaluate MSI-H status with CMS subtype
    a. MSI will be assessed by MSI-H CRC either by IHC for loss of protein expression in one of 4 mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) or by detection of microsatellites within the tumor DNA (as per institutional practices)
    b. External MSI testing in a CLIA certified laboratory with a documentation of MSI-H status performed prior to screening is acceptable for inclusion in cohort A- C.
2. Evaluate PD-L1 expression as a predictor of response
    a. Primary tumor will be stained for PD-L1 expression by IHC
    b. PD-L1 staining will be semi-quantitatively scored by absence, weak, moderate, strong by a pathologist

c. The above will be performed on the mandatory fresh on-treatment biopsy.

3. Evaluate the effect on TGFβ concentrations in plasma.

4. Evaluate potential predictive / prognostic biomarker candidates related to the drug and / or the cancer (such as the CMS, immune infiltrating populations, systemic cytokine profiles)

    a. CMS will be assessed using a 75 gene FFPE based assay using the Nanostring technology in a CLIA-certified laboratory at MD Anderson.

        i. Current discovery of 74 samples run in 18 batches with random duplicate samples to assess technical validity demonstrate accuracies compared to gold standard gene expression by Affymetrix hybridization:

            1. A 75 gene model had 4 group CMS accuracy of 87.1% with very high accuracies (>90%) in CMS1 and CMS2 groups which were over-represented in this small cohort

            2. The CMS4 versus other subgroups demonstrated accuracy of 90.6%

            3. The Nanostring technology on FFPE has been successfully applied to breast cancer[67] and lymphoma[68] cohorts

            4. The Nanostring codesets utilized for the CMS classification are now being assessed for technical validity in MDA's CLIA molecular pathology laboratory

    b. Immune infiltrating populations will be analyzed by immunohistochemistry (IHC), and Multiplex IF analyses.

            1. IHC markers will include, but are not limited to, PD-L1, CD3, Foxp3, CD25, CD8, CD68, CD56, CD20, CD45RO and granzyme B. We may also include PD-L2, B7-H3, B7-x/H4, galectin 9, HVEM and CD48 to measure in tumors and PD-1, 2B4, LAG-3, Tim-3 and BTLA in TILs. These studies will be conducted at TMP-IL.

            2. Multiplex IF Analysis. Up to 10 immune markers, 2 panels may be utilized. Currently, there are 2 Vectra panels optimized: Panel#1, CD3, CD8, CD68, PD-L1, PD-1 pan-cytokeratin and DAPI; Panel #2, CD20, CD45RO, FOXP3, Granzyme B, CD57, pan-cytokeratin and DAPI. A third myeloid panel will be developed. For multiplex IF analysis, we will use the Opal chemistry and multispectral microscopy Vectra system (Perkin-Elmer) which includes the Nuance software; analysis will be performed using the InForm software. Additional markers will be selected according the results of the gene expression analysis and may include other

immunotherapy targets (e.g., OX-40, Vista, GITR, TIM-3, LAG-3, NKp46/CD16, etc.) and proliferation markers (e.g., Ki67).

3. RNAscope. TGF-β and other additional markers may be analyzed by RNA scope.

c. Immune infiltrating populations and systemic cytokine profiles

i. Blood collections and biopsies prior to week 8 treatment will be collected for immune studies under the supervision of the Translational Molecular Pathology Immunoprofiling Lab (TMP-IL) at MD Anderson.

ii. In tumor tissue, IHC studies will be performed to evaluate $CD3^+$, $CD4^+$ and $CD8^+$ T cells, T_{reg}, NK cells, macrophage [M1/2 profile] infiltrating populations. Fresh tissue will be available for flow cytometry analysis on larger tumor samples only. We will assess the proportion of MDSC, macrophage, DC and NK cell subsets within the Live CD45+ cells in panel 3. The expression of checkpoint ligands will be explored using panel 4. Live cells will be sub-gated as CD45-negative to exclude immune cells. EPCAM will be used as a marker of tumor cells and CD90 as a fibroblast marker. The expression of CD80, CD86, GITR-L, ICOS-L, MIC A/B, B7-H3, B7-H4, CD73, PD-L2, OX40L and other relevant immune cells will be assessed.

iii. In peripheral blood, evaluation by circulating immune populations will include, but not be limited to, $CD4^+$, $CD8^+$, NK, T_{reg}, monocytes and neutrophils as outlined by the Schedules of Assessments (**Tables 1-3**). High order flow cytometry panels will be designed. The panels will focus on 1) delineation of major immune cell types (T cells, B cells, NK cells, DC), 2) determination of T cell differentiation status and limited functionality (IFNγ, TNFα, GB) and 3) defining the expression level of costimulatory and coinhibitory molecules on T cells. The proposed studies will be conducted retrospectively on cryopreserved PBMCs.

iv. Serum Cytokine Analyses. Cytokines (IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, and TNF-α) will be measured in the serum using the Meso Scale Discovery Platform (Rockville, MD). This technology allows for the detection of up to 40 analytes per well and uses a very low sample volume. This method has a sensitivity up to 1000 fold higher than traditional ELISA assays with a large linear range of 3-4 logs. The instrument performs immunoassays utilizing electrochemiluminescense to detect the signal in a 96 well plate format. This technology can be utilized for either single agent detection or in multiplex format. A wide menu of validated single or multiplex kits for the detection of 1 to 40 analytes are available from the manufacturer and can be customized.

d. Mutational profiling

i. KRAS, NRAS and BRAF will be assessed via next generation sequencing in a panel of 409 genes that sequences known hotspots to a coverage of at least x250 coverage depth performed in the Molecular Diagnostic Laboratory (MDL) at MD Anderson. The lab is CAP accredited and CLIA certified to perform high complexity molecular testing for clinical purposes.

ii. Tumor DNA analysis for KRAS, NRAS and BRAF performed in another CLIA certified molecular diagnostics laboratory do not need to be tested again

iii. TGFβ signaling pathway mutations will also be assessed via this panel which will include, but not limited to, TGFβR2, ACVR2A, SMAD2 and SMAD4.

iv. RNA-seq and WES. This analysis will be performed using fresh frozen tissue specimens from CNB at MD Anderson Sequencing Facilities.

v. Optionally, using plasma specimens, genotyping analysis of circulating free DNA (cfDNA), circulating tumor cells (CTCs), and exosome (exo)-DNA may be performed to monitor tumor response and progression.

5. Microbiome analyses of buccal and fecal biospecimens

i. Buccal and fecal specimens may be collected at defined time points for microbiome studies. Buccal swab (buccal smear or cheek swab) will be collected firmly rubbing the entire inner surface of both cheeks for 10 sec each side using a sterile polyester swab using standard SOPs. Stools for enteric microbiome analysis will be collected using the OMNIgene kit (DNA Genotek, Ottawa, Ontario, Canada). The collection will allow obtaining high quality DNA suitable for microbiome profiling and sequencing.

ii. Analysis: Bacterial identification and classification is achieved by profiling the 16S rRNA gene, which is present in all bacteria but has sufficient sequence level diversity for classification purposes. 16S deep sequencing is cost-effective and technically and computationally robust, and can be utilized as a primary assay to initially characterize fecal samples. Briefly, the bacterial 16S rRNA V3-V4 region from each sample will be amplified and amplicons sequenced using a MiSeq 2x250 bps protocol. An internal pipeline will be utilized for read processing and analysis. Operational taxonomic unit (OTU) classification will be achieved by mapping the UPARSE OTU table to an optimized version of the SILVA database. Abundances will be recovered by mapping the de-multiplexed reads to the UPARSE OTUs and a custom script will construct an OTU table from the output files generated in the previous two steps. This OTU table will be used to calculate diversity, 2-dimensional visualization, and taxonomic summaries.

Details of time points and sampling are provided in the Schedules of Assessments (**Tables 1-3**).

All proposed biomarker analyses are exploratory and dependent on the quality and availability of sufficient materials. The panel of biomarkers might be adjusted based on results from ongoing research related to anti-PD-1 / PD-L1 therapies and / or safety, therefore, each subject will also be asked whether any remaining tumor tissue and blood-derived samples can be stored at a central repository (until such time as these samples cannot support any further analysis) and can be used for future exploratory research on the drug and / or disease-related aspects. A subject's consent to the use of any remaining samples for such future exploratory research shall be optional and shall not affect the subject's participation in the current trial.

6.4.5.1 Target-related Biomarkers

Blood will be collected to analyze PD-L1 target occupancy, TGFβ 1, 2, 3 concentrations, and circulating cytokine levels according to the Schedule of Assessments (**Tables 1-3**).

6.4.5.2 Immunomonitoring

As biomarker research is constantly evolving, the selection of markers with the highest specificity and relevance to treatment effect may change.

Leukocyte subpopulations and immune activation status will be assessed by flow cytometry (fluorescence-activated cell sorter [FACS]) on PBMC from heparinized blood samples (10 mL, tubes) drawn at the time points outlined in the Schedule of Assessments (**Tables 1-3**).

Soluble factors (for example, cytokines profile, soluble PD-1, and soluble PD-L1) will be assessed on blood (plasma / serum) samples collected as outlined in the Schedule of Assessments (**Tables 1-3**).

Plasma will be stored at -80 degrees and sent for immunoprofiling for interleukin (IL) IL-1α, IL-1β, IL-2, IL-5, IL-6, IL-8, IL-13, TNF-α, MCP, MIP-1β, G-CSF, GM-CSF, IFN-γ via a cytokine assay.

6.4.5.3 Predictive and Prognostic Biomarkers

It is important to identify biomarkers that help to predict and / or evaluate the efficacy of the therapy, in order to achieve the optimal benefit from targeted therapies. No thoroughly validated biomarkers are available to date for anti-PD-1 / PD-L1 and anti-TGFβ therapies; therefore, this trial plans to evaluate biomarkers from pre-treatment and post-treatment tumor biopsies of primary tissue and blood samples that might be predictive of therapy outcome for all indications. Of note, availability of a tumor sample will be a prerequisite for all subjects.

The following requirements apply to the tissue samples collected during the trial:

Tissue collection: Endoscopic biopsies, core needle biopsies, excisional biopsies and surgical specimens are acceptable. Fine needle aspiration biopsies are not acceptable.

Additionally, a mandatory on-treatment biopsy will be performed in cohort A-C prior to cycle 2, day 1 of M7824 administration. A mandatory on-treatment biopsy prior to cycle 1, day 11 and cycle 2, day 1 for cohort B will also be performed. Resected tissue from metastatic resection will serve as the baseline, pretreatment specimen for Cohort D.

Microbiome sample collection: Collection of stool samples for microbiome analyses can be done using OMNIgene-Gut kits. OMNIgene-Gut is an all-in-one system for easy self-collections and stabilization of microbial DNA from feces. It allows easily self-collection at home. Samples are rapidly homogenized and stabilized at the point-of-collection and shipped to the laboratory for aliquoting and freezing at -80C prior DNA extraction. This kit allows the collection of high-quality DNA suitable for 16 rRNA microbiome profiling, sequencing and other assays. Buccal swab (buccal smear or cheek swab) will be collected firmly rubbing the entire inner surface of both cheeks for 10 sec each cheek side using a sterile polyester swab and storing in Eppendorf tube at -80°C until DNA extraction and analyses. **Tissue processing**: The cancer tissues should be fixed in 10% neutral buffered formalin (NBF), paraffin-embedded and routinely processed for histological evaluation. Formalin substitutes are not suited as fixative.

Tissue storage: Fresh tumor tissue obtained from subjects for the evaluation of efficacy should be stored in defined cryopreservation medium containing 10% dimethyl sulfoxide [CryoStor® CS10].

Provision of samples: 1. priority: tumor-containing formalin fixed, paraffin embedded (FFPE) tissue block; 2. Priority: if the tumor containing FFPE tissue block cannot be provided in total, sections from this block should be provided which are freshly cut, 4 µm thick and mounted on positively-charged microscope slides. SuperFrost Plus glass slides are recommended. Preferably, 25 slides should be provided; if not possible a minimum of 10 slides is required. Tumor tissues suitable for biomarker analysis are required. Suitable means that the central laboratory can confirm that the tissue is evaluable (enough viable tumor cells are present).

Sample storage: At the central laboratory the FFPE tissue blocks shall be stored at room temperature and the fresh-frozen tumor slides shall be frozen in sealed containers at -20°C.

A panel of putative markers including molecular, soluble and cellular markers will be analyzed at baseline from archived tumor tissue (or fresh tumor biopsy, preferred when available), and from serum / plasma samples/microbiome to investigate a possible correlation between clinical efficacy and analyzed markers.

The following assessment will be considered:

- CMS classification based on FFPE based RNA expression.
- Level of PD-L1 expression in fresh biopsy by IHC staining. Of note, further techniques to evaluate the expression of PD-L1 and / or marker candidates impacting the targeting or contributing to improve its expression may be also investigated if needed.
- Level of circulating TGFβ.
- Frequency and localization of tumor-infiltrated leukocytes (for example, CD3, CD8, CD4 T-cells, Treg, NK cells, macrophage [M1/2 profile]) by IHC.

- If quantity of tissue permits, genomic characterization of TGFβ signaling components (for example, SMAD4)
- Further exploratory markers related to the MoA) of the drug such as soluble PD-L1 sera level, intratumoral cytokine profile, and auto-antigen proteomic arrays may be explored.
- Further cellular and / or molecular markers specific to the cancer may be also investigated according to the indication.
- Microbiome sequencing analyses of buccal and fecal samples will be conducted.

7 Statistics

7.1 Sample Size Calculations

7.1.1 Cohort A-C

7.1.2 The total sample size of this cohort is 15 patients. With this sample size, the half-width of the 95% confidence interval for the estimated response rate will be at most 0.253. Cohort B

For this cohort, the Simon's Optimum two-stage design will be implemented. A historical response rate of 5% and a target response rate of 25% are assumed under the null and the alternative hypotheses, respectively. In the first stage, we will enroll 15 patients; if 1 or fewer achieves a best response of CR/PR, we will stop enrolling patients. Otherwise, we will continue to enroll all 29 patients and the treatment is deemed as promising if there are 4 or more responders out of these 29 patients. The design has a type I error rate of 0.042, a 90% power and a probability of early termination of 82.9% under the null hypothesis. Patient enrollment will be temporarily suspended when the enrollment for the first stage patients has been completed yet not enough responders have been observed to trigger the start of second stage.

7.1.3 Cohort D

The total sample size of this cohort is 15 patients. With this sample size, the half-width of the 95% confidence interval for the estimated response rate will be at most 0.253.

7.2 Randomization

Not applicable.

7.3 Endpoints

7.3.1 Primary Endpoints

The primary endpoints are objective response (i.e. CR+PR) according to iRECIST 1.1 criteria for cohorts A-C and B, and clearance of ctDNA for cohort D.

7.3.2 Secondary Endpoints

The secondary endpoints to this study are:

- PFS according to iRECIST 1.1 criteria.
- DFS (cohort D)
- OS
- Number, severity, and duration of treatment related AEs according to NCI-CTCAE v4.03

7.3.3 Exploratory Endpoints

The exploratory endpoints for this study are:

- Changes in intratumoral immune populations, gene expression and proteomic profiles pre and post-treatment with M7824 where paired biopsies are available
- Changes in circulating immune cell populations and cytokine profiles pre and post-treatment with M7824
- Circulating levels of TGF-β collected from serial plasma samples.

7.4 Analysis sets

The following analysis sets will be defined:

Safety Analysis Set: All subjects who receive at least 1 dose of trial treatment.

7.5 Description of Statistical Analyses

7.5.1 General Considerations

All data recorded during the study will be presented in individual data listings performed on the Safety Analysis Set. All data will be evaluated as observed, and no imputation method for missing values will be used. All data will be presented in a descriptive manner. Each cohort will be analyzed separately, and no multiplicity adjustment across cohorts will be performed.

Descriptive statistics will be used to summarize the trial results, that is, statistics for continuous variables may include means, medians, ranges, and appropriate measures of variability. Categorical variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals. Unless otherwise specified, the calculation of proportions

will be based on the sample size of the analysis set of interest. Counts of missing observations will be included in the denominator and presented as a separate category.

All other statistical analyses will be performed using SAS® Version 9.1.3 or higher, or R, Version 2.10.1 or higher.

7.5.2 Analysis of Primary Endpoint

7.5.2.1 Response Rate

7.5.2.1.1 Cohorts A-C and B

Patient response will be determined using iRECIST 1.1. Unconfirmed responses will not be used in the final analysis. ORR is defined by the number of (PR + CR)/ (total number of treated patients) in the safety analysis set. For all cohorts, we will estimate the response rate along with the two-sided exact 95% confidence interval. Also for Cohort B, if the trial continues to the full enrollment of 29 patients, we will declare M7824 with radiation promising and worthy of further investigation if there are at least 4 responders out of these 29 patients.

7.5.2.1.2 Cohort D

Identification of somatic mutations in the blood will be confirmed by sequencing of the resected tumor using a CLIA-certified next-generation sequencing panel at MD Anderson. Clearance of ctDNA will be characterized by the disappearance of all somatic mutations identified in the blood, as well as no appearance of any additional new somatic mutations following 6 doses of M7824. For this cohort, we will estimate the response rate as the percentage of patients whose ctDNA status converts from “positive” to “negative” after twelve weeks of therapy with M7824 relative to the total number of patients treated.

7.5.3 Analysis of Endpoints

7.5.3.1 Secondary Endpoints

The secondary endpoints of PFS (cohorts A-C and B) and DFS (cohort D) according to iRECIST 1.1 and OS time will be presented using the Kaplan-Meier method. PFS will be measured in months from the date of first administration of M7824 to the date of documented progression by RECIST 1.1 or death by any cause, whichever is earlier. For Cohort D, DFS will be measured in months from the date of documented recurrence or development of distant metastasis by iRECIST 1.1 criteria. Median PFS and DFS and 95% confidence intervals will be estimated using the Kaplan-Meier method.

OS will be measured in months from the date of first administration of M7824 to the date of death by any cause. Median OS with 95% confidence interval will be estimated using the Kaplan-Meier method. Severity of AEs will be graded using the NCI-CTCAE v4.03 toxicity grading scale. Safety will be assessed by descriptive statistics and summarized in tabular format. This data will be separated based on organ class, immune-relation, severity and relation to M7824.

Adverse events (serious and non-serious) will be considered treatment emergent adverse events when emerging during the on-treatment period defined as the time from first trial drug administration to the last drug administration date + 30 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated. All premature terminations will be summarized by primary reason for treatment withdrawal.

7.5.3.2 Exploratory Endpoints

Summary statistics will be tabulated for microsatellite instability, CMS1, CIMP, KRAS and BRAF status. Paired t-test or Wilcoxon signed rank test will be used to assess the changes in biomarkers pre- and post-treatment. The differences in biomarker levels between responders and non-responders will be assessed using X^2 or Fisher's exact test as appropriate. Similar analysis will be used to assess the correlation between biomarker mutation statuses.

Statistical analyses will be conducted by MDACC statisticians. Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals, unless otherwise stated. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

7.5.3.3 Adverse Events

Severity of AEs will be graded using the NCI-CTCAE v4.03 toxicity grading scale. Safety will be assessed by descriptive statistics and summarized in tabular format. This data will be separated based on organ class, immune-relation, severity and relation to M7824.

Adverse events (serious and non-serious) will be considered treatment emergent adverse events when emerging in the on-treatment period defined as the time from the first trial drug administration to the last drug administration date + 30 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated. All premature terminations will be summarized by primary reason for treatment withdrawal.

7.5.3.4 Laboratory Variables

Laboratory results will be classified by grade according to NCI-CTCAE v4.03. The worst on-trial grades after the first trial treatment will be summarized. Shifts in toxicity grading from first treatment to highest grade will be displayed. Results for variables that are not part of NCI-CTCAE will be presented as within or above normal limits. Only subjects with post-Baseline laboratory values will be included in these analyses.

7.5.3.5 Physical Examination, Including Vital Signs and 12-Lead Electrocardiogram

Vital signs (body temperature, respiratory rate, heart rate, and blood pressure), eye signs and symptoms based on System Organ Class of "eye disorders", and 12-lead EKG recorded according to the Schedules of Assessments (refer to **Tables 1-3**) will be presented.

7.6 Interim safety monitoring

For each cohort, we will implement Bayesian toxicity monitoring[69] such that we will all stop patient enrollment into a cohort if there is a high probability that the AE rate of M7824 is greater than 20%. For each cohort separately, we will apply the toxicity monitoring rule in cohort size of 5, starting from the 5th patient. For cohort A-C, the toxicity stopping rule to be applied is as follows: Stop patient enrollment in a cohort if Prob(p>0.20 |data) > .75, where p denotes the probability of toxicity.

Assuming a beta(.4, 1.6) priori for p, the above decision criterion implies that we will stop cohort A or cohort C according to **table 8** below.

Table 8: Toxicity stopping boundaries for Cohort A-C and D

Number of evaluable patients	Number of patients with toxicities is **at least**
5	2
10	4
15	5

The operating characteristics for toxicity monitoring in cohort A-C are illustrated in **Table 9.**

Table 9: Operating Characteristics for Toxicity Monitoring in Cohort A-C and D

True toxicity rate	Prob (stop early)	Average Sample Size
0.10	0.086	14.2
0.20	0.284	12.3
0.30	0.532	10.0
0.40	0.750	8.0
0.50	0.894	6.5

Similarly for cohort B, the toxicity stopping rule to be applied is as follows: Stop patient enrollment if Prob(p>0.20 |data) > .85, where p denotes the probability of toxicity. Assuming a beta(.4, 1,6) priori for p, the above decision criterion implies that we will stop cohort B according to **table 10** below.

Table 10: Toxicity stopping boundaries for Cohort B

Number of evaluable patients	Number of patients with toxicities is **at least**
5	3
10	4
15	5
20	7
25	8
29	9

The operating characteristics for toxicity monitoring in cohort B are illustrated in **Table 11**.

Table 11: Operating Characteristics for Toxicity Monitoring in Cohort B

True toxicity rate	Prob (stop early)	Average Sample Size
0.10	0.25	28.5
0.20	0.238	24.9
0.30	0.623	18.4
0.40	0.900	12.3
0.50	0.989	8.7

The stopping boundaries and the operating characteristics for cohorts A-C and B were generated using Shiny application for Bayesian toxicity monitoring (http://qctrlshiny/postprobtoxicity).

AEs of 3 or greater and deemed related to M7824 (section 6.4.1.1.1) will count towards toxicity calculations with respect to interim safety monitoring. AEs of 3 or greater deemed unrelated to M7824 are not included towards safety decision making. These include AEs attributable to disease progression (section 6.4.1.1.2) and abnormal laboratory or investigational values that are asymptomatic or do not result in treatment discontinuation (section 6.4.1.1.1).

The time period that grade 3 AEs attributable to M7824 are counted towards interim safety monitoring decisions is defined from their onset to 90 days after the last dose of study drug (section 6.4.1.1.3).

Any grade 5 event on-study will require suspension of the study pending review of the safety data regarding the death.

The Investigator is responsible for completing an efficacy/safety summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 5 evaluable patients per cohort, complete 1 cycle of study treatment, and every 5 evaluable patients per cohort, thereafter. On every report submission, the information from previous reported patients will need to be updated.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "IND Office correspondence".

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