Abbreviated Title: M7824 in Small Cell Cancers
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Title: Safety Run-In and Phase II Trial of M7824 and Topotecan or Temozolomide in Relapsed Small Cell Cancers

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Drug Name:	**M7824**	**Topotecan**	**Temozolomide**
IND Number:	136852		
Sponsor:	Center for Cancer Research, National Cancer Institute		
Manufacturer:	EMD Serono	Generic	Generic
Supplier:	EMD Serono	NIH CC Pharmacy	NIH CC Pharmacy

PRÉCIS

Background

- Small cell lung cancer (SCLC) is an aggressive cancer with a poor prognosis. Although highly responsive to chemotherapy initially, SCLC relapses quickly and becomes refractory to treatment within a few months.
- Extrapulmonary small cell cancers are extremely rare and management of systemic disease with chemotherapy is patterned after the approach used in SCLC.
- The inability to destroy residual SCLC cells despite initial chemosensitivity suggests the existence of a highly effective DNA damage response network. SCLC is also characterized by high DNA replication stress (RB1 inactivation, MYC and CCNE1 activation). Similarly, extrapulmonary small cell cancers have no standard treatments and it appears that although these cancers can arise by different mechanisms, they have in common high replication stress, that may be susceptible to DNA damage and immune checkpoint blockade.
- There is only one FDA approved treatment for patients with relapsed SCLC after first-line chemotherapy: topotecan, which inhibits religation of topoisomerase I-mediated single-strand DNA breaks leading to lethal double-strand DNA breaks. Temozolomide, an oral alkylating agent, which causes DNA damage by alkylating guanine at position O6 also has activity in relapsed SCLC, particularly for brain metastases.
- Preliminary evidence indicates that disruption of the immune checkpoint PD-1/PD-L1 pathway can yield responses in a subset of SCLC patients, but response rates (~10%) are lower than NSCLC and other tumors with comparable tumor mutational burden indicating additional immunosuppressive mechanisms at play in the SCLC tumor microenvironment.
- M7824 is a bifunctional fusion protein consisting of an anti-programmed death ligand 1 (PD-L1) antibody and the extracellular domain of transforming growth factor beta (TGF-β) receptor type 2, a TGF-β trap.
- Safety data from the dose-escalation study in solid tumors as well as preliminary data from expansion cohorts show that M7824 has a safety profile similar to other checkpoint inhibiting compounds.
- Combining immunotherapy, and chemotherapy could synergistically improve the anticancer activity of immunotherapy. Combination of chemotherapy with immunotherapy have improved outcomes in NSCLC and melanoma leading to FDA approvals of such combinations.
- We hypothesize that increased DNA damage induced by topotecan and temozolomide will complement the anti-tumor activity of M7824, in recurrent SCLC.

Objective

- The primary objective of the trial is to determine the efficacy (using objective response rate) of M7824 plus topotecan or temozolomide in relapsed SCLC.

Eligibility

- Subjects with histological or cytological confirmation of SCLC or extrapulmonary small cell cancers.
- Subjects must be ≥ 18 years of age and have a performance status (ECOG) ≤ 2.
- Subjects must not have received chemotherapy, or undergone major surgery within 2 weeks and radiotherapy within 24 hours prior to enrollment.
- Subjects must have adequate organ function and measurable disease.

Design

- Arm A (M7824 monotherapy): Up to 10 patients may be treated with M7824 monotherapy to obtain safety and PK data, and a preliminary estimate of clinical responses to M7824 in SCLC. Patients with progressive disease on Arm A may then receive M7824 plus temozolomide as per description of treatment for Arm C.
- Arm B (M7824 plus topotecan) and Arm C (M7824 plus temozolomide) will be administered in 3 and 4-week cycles respectively; these arms will have a safety run-in followed by efficacy analysis. Up to 10 patients with extrapulmonary small cell cancer will be enrolled in arm C to receive the combination of M7824 and temozolomide.
- Optional tumor biopsies will be obtained at pre-treatment on C1D1 and C1D15 for Arm C; pre-treatment on C1D1 and C2D1 for arms A and B.
- Every subject of each arm of the safety run-in will be observed for at least 7 days after first dose of M7824 before the subsequent subject can be treated. Subjects who are not evaluable for DLT will be replaced and not included into evaluation

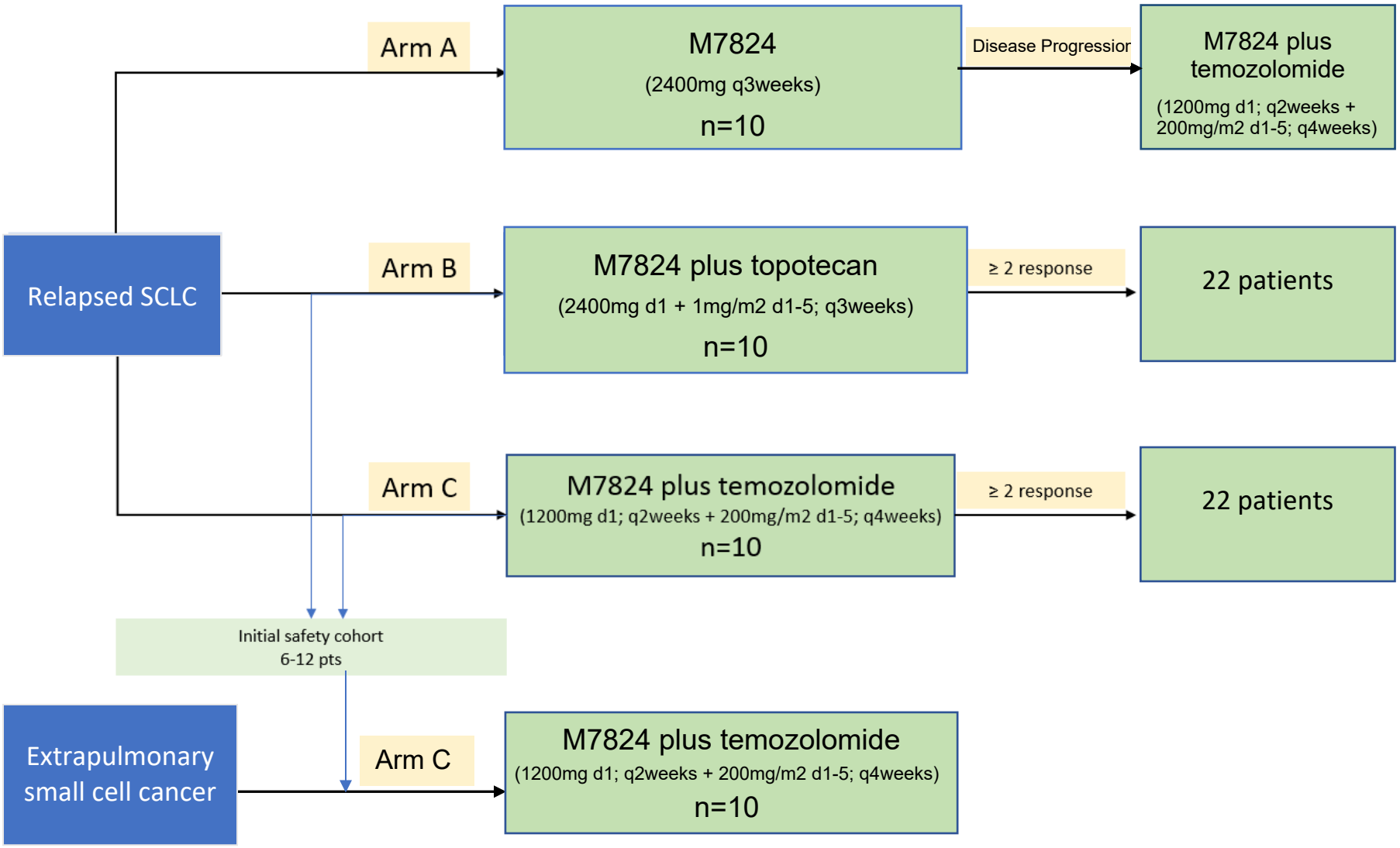
ARMS

- Arm A (3-week cycles): M7824 monotherapy 2400 mg every 3 weeks until disease progression or a criterion in section **3.8.1** is met. Patients with progressive disease on Arm A may then receive 1200 mg M7824 every 2 weeks plus temozolomide 200 mg/m^2/day on days 1-5 every 4 weeks.
- Arm B (3-week cycles): M7824 2400 mg plus topotecan 1 mg/m2 on days 1-5 every 3 weeks until disease progression or a criterion in section **3.8.1** is met.
- Arm C (4-week cycles): M7824 1200 mg every 2 weeks plus temozolomide 200 mg/m^2/day on days 1-5 every 4 weeks until disease progression or a criterion in section **3.8.1** is met.

Dose de-escalation Schedule Arm B		
Dose Level	M7824	Topotecan
Level 1	2400 mg every 3 weeks	1 mg/m2 on days 1-5 every 3 weeks
Level -1	2400 mg every 3 weeks	0.75 mg/m2 on days 1-5 every 3 weeks

Dose de-escalation Schedule Arm C		
Dose Level	M7824	Temozolomide
Level 1	1200 mg every 2 weeks	200 mg/m^2/day on days 1-5 every 4 weeks
Level -1	1200 mg every 2 weeks	150 mg/m^2/day on days 1-5 every 4 weeks

SCHEMA


Relapsed SCLC
Arm A
M7824
(2400mg q3weeks)
n=10
Disease Progressior
M7824 plus temozolomide
(1200mg d1; q2weeks + 200mg/m2 d1-5; q4weeks)
Arm B
M7824 plus topotecan
(2400mg d1 + 1mg/m2 d1-5; q3weeks)
n=10
≥ 2 response
22 patients
Arm C
M7824 plus temozolomide
(1200mg d1; q2weeks + 200mg/m2 d1-5; q4weeks)
n=10
≥ 2 response
22 patients
Initial safety cohort
6-12 pts
Extrapulmonary small cell cancer
Arm C
M7824 plus temozolomide
(1200mg d1; q2weeks + 200mg/m2 d1-5; q4weeks)
n=10

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To determine the efficacy (using objective response rate) of M7824 plus topotecan or temozolomide in relapsed SCLC.

1.1.2 Secondary Objectives

- To assess the safety and tolerability of M7824 plus topotecan or temozolomide relapsed SCLC.
- To determine the progression-free survival (PFS), duration of response (DOR) and overall survival (OS) of a combination of M7824 plus topotecan or temozolomide in relapsed SCLC.

1.1.3 Exploratory Objectives

- To characterize the immunomodulatory effects of DNA damage-inducing cytotoxic therapy.
- To characterize gene expression and mutations which predict response and changes associated with response and resistance.
- To evaluate the pharmacokinetic profile of M7824 in serum, and of Topotecan and Temozolomide in plasma.
- To evaluate ORR, PFS and OS of patients with extrapulmonary small cell cancer receiving M7824 and Temozolomide.
- To evaluate the ORR and PFS for patients who are on Arm A but receive combination treatment after progression, beginning with the date the second treatment commences.

1.2 BACKGROUND AND RATIONALE

Small cell lung cancer (SCLC) is an aggressive cancer with a poor prognosis. Annually there are approximately 34,000 new cases of SCLC in the United States. SCLC is characterized by rapid doubling time, high growth fraction and early and widespread metastatic involvement. Approximately two thirds of patients present with extensive-stage disease with tumor involvement of contralateral lung, liver, adrenal glands, brain, bones and/or bone marrow.

The primary treatment modality for patients with extensive-stage SCLC (ES-SCLC) is systemic chemotherapy consisting of platinum and etoposide followed by prophylactic cranial irradiation in patients with a response [1]. Although initial response rates to chemotherapy are very high, the tumor usually relapses within months, and nearly all cases relapse within one year, becoming generally unresponsive to additional chemotherapy, with fewer than 5% of patients surviving two years. The only approved drug for relapsed disease is topotecan, which inhibits religation of topoisomerase I-mediated single-strand DNA breaks leading to lethal double-strand DNA breaks. Other drugs with more modest activity include amrubicin, doxorubicin, paclitaxel, and

temozolomide. The median survival for patients with ES-SCLC ranges from 8 to 13 months. Less than 5% of patients survive two years and less than 2% are alive five years after diagnosis.

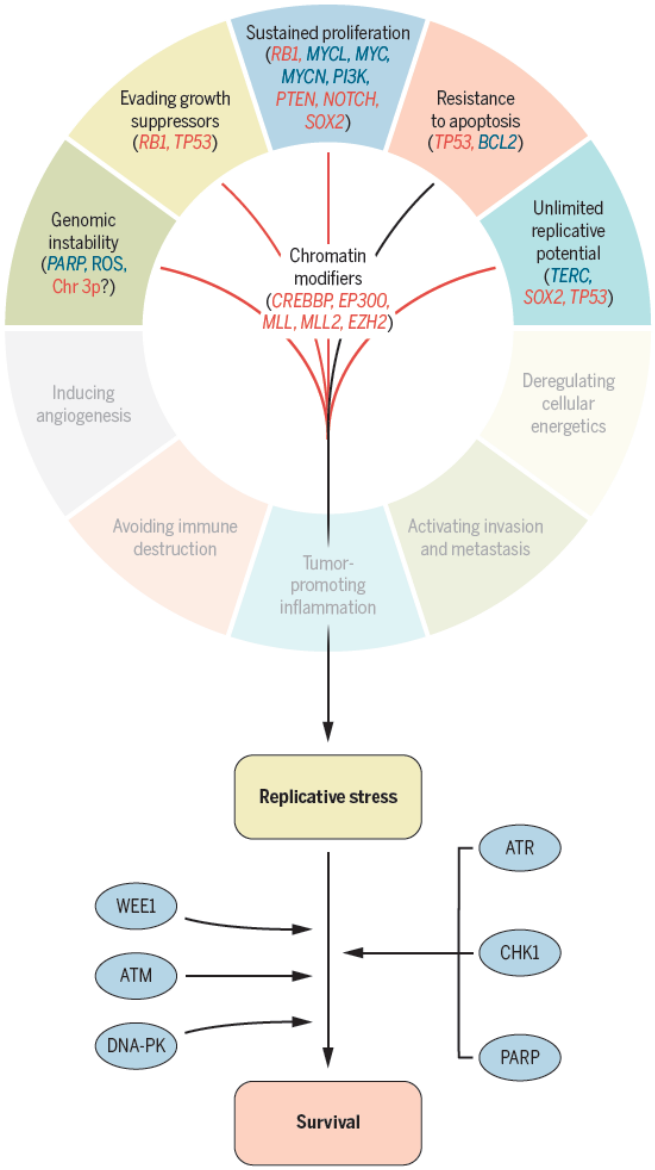

Figure 1. *Replicative Stress in SCLC: Causes, Consequences and Therapeutic Opportunities (adapted from: Thomas & Pommier, Sci Trans Med 2016).*

In patients with disease that is refractory to or relapsed after first-line chemotherapy, the median survival ranges from 2 to 6 months.

Active chemotherapeutic agents in SCLC have one thing in common: almost all of them interfere with DNA replication, except paclitaxel which disrupts microtubule function. Cisplatin and carboplatin form crosslinks between DNA bases creating DNA replication barriers. Temozolomide is a nonclassic oral alkylating agent, which causes DNA damage by alkylating guanine at position O6. Topotecan, irinotecan, etoposide, doxorubicin, and amrubicin trap topoisomerases, stalling replication forks and causing toxic double-stranded DNA breaks.

The standard treatment of ES-SCLC today reflects the prevailing state-of-the-art from the early 1980s. Among the many strategies that have been evaluated unsuccessfully over the last three decades are dose-dense chemotherapy regimens, addition of a third drug to standard two drug chemotherapies, alternating non-cross resistant chemotherapy regimens, maintenance therapy and more recently targeted therapies. Not unexpectedly, the outcomes for these patients have also largely remained poor. Clearly there is a critical need for newer therapeutic approaches for patients with SCLC and patients with extrapulmonary small cell carcinomas.

We recently postulated that replicative stress is a SCLC hallmark (**Figure 1**) [2]. DNA damaging agents are the cornerstone of SCLC treatment, yet they provide only transient benefit. The inability to destroy residual SCLC cells despite initial chemosensitivity suggests the existence of a highly effective DNA damage response (DDR) network. Cellular responses to replicative stress-referred to as the DDR-is critical for repair of the damage and normal cell cycle progression and may have a role in chemotherapy resistance in SCLC.

The DNA damage response pathway is depicted in **Figure 2**[3]. Apical kinases ataxia-telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) are recruited via DNA damage sensors. In addition to single-stranded DNA breaks, ATR responds to genotoxic stress that is caused by DNA replication stress, caused by oncogenes. Eventually via phosphorylation of a number of mediators, DNA damage response signaling converges on downstream effectors such as p53 and the cell division cycle 25 (CDC25) phosphatases.

Despite the importance of the DNA damage response for cell survival following DNA damage, defects in this pathway are common in cancer. For example, loss of ATM signaling capacity is frequently observed, either through loss of expression of ATM itself, or through defects in upstream regulators and downstream effectors such as p53. Although they appear to confer a growth advantage, defects in ATM signaling cause an excessive reliance on remaining DNA damage response components, such as ATR, and thus provide an 'Achilles' heel' that could be targeted by drugs.

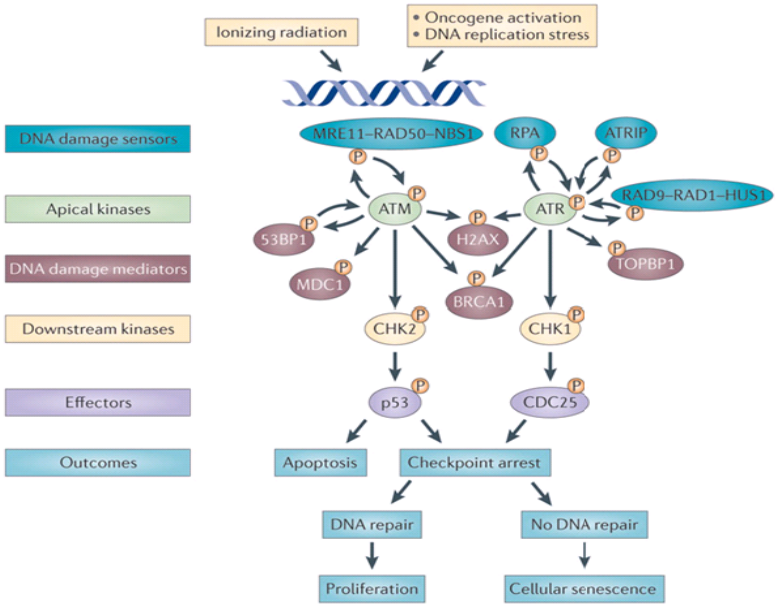

Figure 2. *DNA damage response pathway.*

The most frequently mutated genes in SCLC are shown in **Figure 3** [4]. SCLC is characterized by high frequency of alterations in p53, a key downstream effector of the ATM pathway. Furthermore, SCLC is also characterized by the widespread expression of oncogenes that drive replication stress. This combination of high replication stress and a defective ATM-p53 signaling pathway may provide a strong reliance on ATR for survival following DNA damage in SCLC.

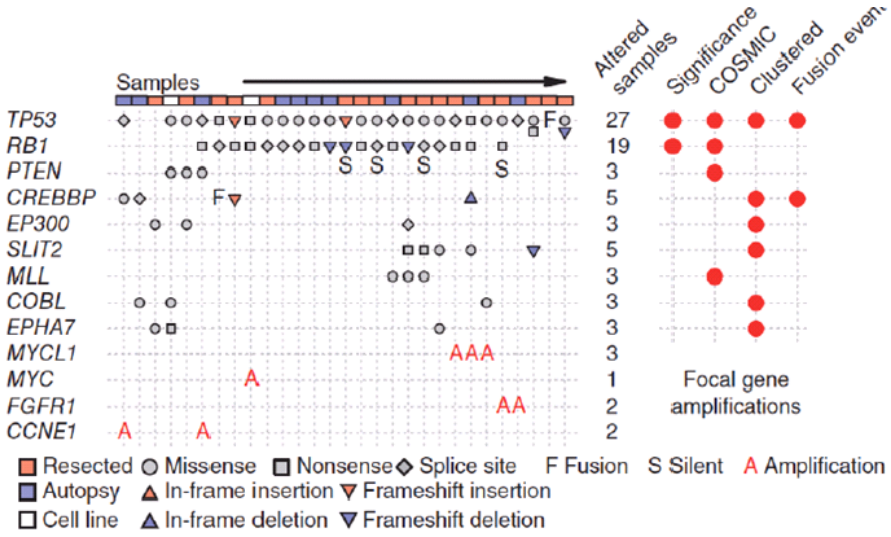

Figure 3. *Most frequently mutated genes in SCLC.*

1.2.1 Immune checkpoint inhibitors in SCLC

Emerging data from PD-1 and PD-L1 indicate a clinical benefit in terms of response rates in patients with SCLC. The safety and efficacy of pembrolizumab, was assessed in patients with PD-L1-expressing relapsed extensive-stage SCLC in the multicohort, phase Ib open-label KEYNOTE-028 study[5]. PD-L1 expression was assessed by immunohistochemistry. PD-L1-positive patients had membranous PD-L1 expression in ≥ 1% of tumor and associated inflammatory cells or positive staining in stroma. 163 patients were screened to identify 24 patients who eventually received treatment. One of 24 patients had a complete response, and seven patients had partial responses, resulting in an ORR of 33%. Nivolumab with or without ipilimumab was assessed in unselected SCLC patients with disease progression after at least one prior platinum containing regimen in the multi-cohort, phase 1/2 CheckMate 032 study[6]. An objective response was achieved in ten (10%) of 98 patients receiving nivolumab 3 mg/kg, 14 (23%) of 61 receiving nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and ten (19%) of 54 receiving nivolumab 3 mg/kg plus ipilimumab 1 mg/kg.

Although promising, there are quite a few challenges with immunotherapy in relapsed SCLC, in particular, in platinum resistant and or refractory relapsed SCLC. First, due to the high burden of disease and the rapidity of progression, the time that it takes to mount an effective anti-tumor response may exceed the overall survival of the patient. Second, contrary to what one would expect for a smoking-related tumor with a high mutational load, response rates to monotherapy with immune checkpoint inhibitors in SCLC is low in comparison to other immune checkpoint inhibitor-responsive tumors such as NSCLC and melanoma. Third, the frequency of adverse events with combination immunotherapy is high: 16% of patients in the CheckMate 032 study discontinued due to treatment-related adverse events and 3 immune-related deaths occurred (from pneumonitis, myasthenia gravis, and renal failure). Any grade treatment-related adverse events occurred in 82% of the combination vs. 60% for nivolumab alone; Grade 3/4 serious adverse events occurred in 33% for the combination vs. 14% for nivolumab alone. Finally, there are no known predictive biomarkers of response to immunotherapy in SCLC. PD-L1 expression,

unlike in non-small cell lung cancer, is absent in SCLC tumor cells and presented in about 20% of stroma and immune infiltrates[7].

The limited activity of immune checkpoint inhibitors in SCLC patients suggests that immunosuppressive mechanisms beyond PD-1/L1 and CTLA4 checkpoints may be involved in SCLC tumor microenvironemt and targeting these alternate pathways could be of clinical relevance. Constitutive expression and secretion of biologically active TGF β1 has been described in SCLC[8, 9]. In SCLC cell lines, IL-2-dependent T-cell growth was severely suppressed by TGF β1. A specific anti-TGF beta 1 antibody blocked the immunosuppressive activity induced by TGF β1. High levels of TGF-β are also detected in the serum of patients with lung cancer compared with normal individuals[10].

1.2.2 Topotecan

Topotecan has been approved by the FDA for the treatment of metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy, small cell lung cancer sensitive disease after failure of first-line chemotherapy, and as a combination therapy with cisplatin for Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy. Topotecan is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single-strand breaks. The cytotoxicity of topotecan is thought to be due to double-strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double strand breaks. Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan at the approved doses (refer topotecan FDA package insert).

The NCI SCLC program recently completed a phase I trial of VX-970 (referred to now as M6620), a selective inhibitor of ATR, a key DDR mediator, in combination with topotecan. This trial showed preliminary pharmacodynamic evidence of ATR inhibition and enhanced DNA DSBs to the combination. Immunophenotyping of PBMCs in this trial showed preliminary evidence of a favorable immunomodulatory effect after topotecan (manuscript in print JCO).

A significant decrease was observed in the frequency of myeloid-derived suppressor cells (MDSC) after the combination relative to baseline. Total CD14+ monocytes increased significantly after topotecan, but markedly decreased after the combination. There was a marked redistribution among the monocyte subsets. The more immunosuppressive classical monocytes were the major population at baseline, whereas intermediate and nonclassical monocytes, which tend to promote antitumor activity were the minor populations. Following the combination, classical monocytes significantly decreased whereas intermediate and nonclassical monocytes significantly increased. Both monocytes and MDSCs returned to near-baseline-levels in most patients 3 weeks after treatment. No significant changes in T cell subsets including Tregs, conventional CD4+ T-cells and CD8+ T-cells were observed. The study also demonstrated interesting clinical activity signals in refractory SCLC patients, who tend not to respond to topotecan alone, and several patients achieving prolonged SD (manuscript under review).

TOP1-induced DNA damage at ribonucleotide sites leads to replication stress and genome instability[11]. Such damage has been known to cause an unchecked inflammatory response and has been described in syndromes associated with mutations in genes that encode for proteins that are involved in various aspects of nucleic acid repair. Aicardi–Goutieres syndrome (AGS) is a

rare, genetic neurological disorder characterized by unchecked inflammatory response in the absence of exogenous stimuli[12]. Mutations in the TREX1, RNASEH2A, RNASEH2B, RNASEH2C, and SAMHD1 genes have been identified in people with Aicardi-Goutieres syndrome. It is thought that in patients with these mutations, there is a high level of aberrant nucleic acid because proper DNA and/or RNA processing is compromised. This leads to an interferon alpha (INF-α)-mediated, constitutive inflammatory response that has a potent effect on neurological development and function.

1.2.3 Temozolomide

Temozolomide is a nonclassic oral alkylating agent, which causes DNA damage by alkylating guanine at position O6. Temozolomide is rapidly and completely absorbed after oral administration and binds minimally to plasma proteins, resulting in limited interactions with concurrently administered drugs[13]. Being a small lipophilic molecule, temozolomide penetrates the blood–brain barrier and is therefore one of the few drugs with central nervous system (CNS) activity. Dose modifications are not needed for liver and renal dysfunction as cytochrome P450 enzymes and kidney are not involved in temozolomide metabolism. Adverse events are predictable and toxicities are usually reversible and not severe. Despite its antitumor activity, favorable pharmacokinetic profile, and tolerability, current use of temozolomide is limited to a subset of CNS cancers [14].

Temozolomide is converted to the active metabolite 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) by nonenzymatic chemical conversion. Among the DNA lesions produced by MTIC, the most common is methylation at the *N*7 position of guanine, followed by methylation at the *N*3 position of adenine and the *O*6 position of guanine. Although the least frequent, methylation of guanine at O6 (O^6-MeG) is critical for temozolomide cytotoxicity (**Figure 4**). In normal cells, direct repair of O^6-MeG by the enzyme O6-methylguanine–DNA methyltransferase (MGMT) effectively removes the methyl adduct, restoring guanine. O^6-MeG that persists in MGMT-deficient cells mispairs with thymine instead of cytosine during DNA replication. This alerts the DNA mismatch repair (MMR) pathway, which exclusively recognizes the mispaired thymine on the daughter strand and excises it, while the O^6-MeG persists in the template strand. The futile cycles of thymine reinsertion and excision result in extensive DNA resection and ultimately apoptosis. MMR-deficient cells do not detect alkylation adducts and hence are resistant to temozolomide even when they lack MGMT[15]. Temozolomide is therefore most cytotoxic in cells with low levels of MGMT and intact MMR.

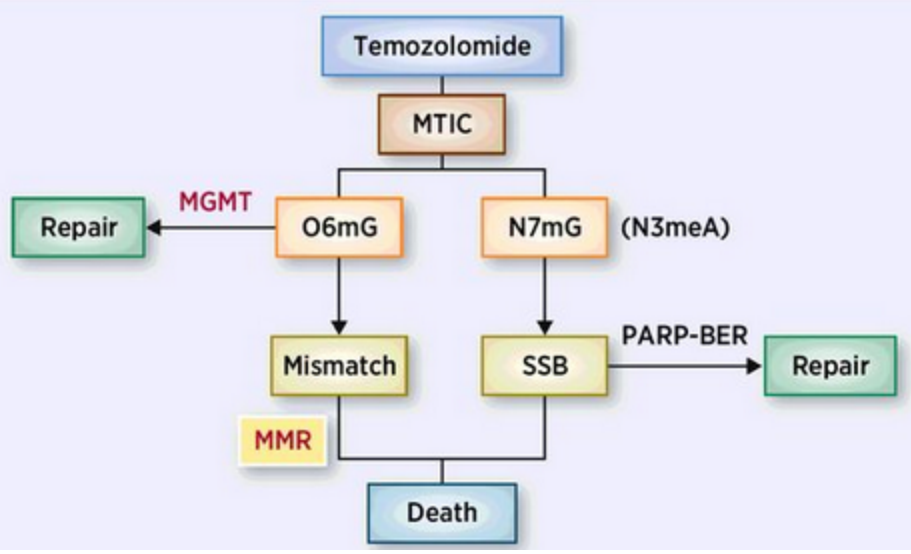

Figure 4. *Temozolomide is most cytotoxic in cells with low levels of MGMT and intact MMR (adapted from: Thomas, Pommier, et al. Cancer Res 2017).*

Temozolomide has single-agent activity for SCLC [16]. In fact the clinical activity of monotherapy with alkylating agents for SCLC has been known since the 1960s [17]. Aberrant methylation of MGMT has been demonstrated in SCLCs, which leads to loss of MGMT activity and improved sensitivity to alkylating agents [18].

Temozolomide was evaluated in a phase II trial in patients with relapsed SCLC [19]. Patients with disease progression after one or two prior chemotherapy regimens received temozolomide at 75 mg/m2/d for 21 days of a 28-day cycle. The primary endpoint was the overall response rate (ORR), which was evaluated separately in platinum sensitive and refractory cohorts. Sixty-four patients were accrued including 48 patients in the sensitive cohort and 16 in the refractory group. One complete response (CR) and 10 partial responses (PRs) were noted in sensitive patients (ORR, 23%), 2 PRs were seen in the refractory cohort (ORR, 13%). As second- and third-line treatment, the ORR was 22% and 19% respectively. Among the entire cohort of 64 patients, there were one CR and 12 PRs for a 20% ORR. The trial however did not meet the prespecified primary end points of 25% and 30% ORRs respectively for refractory and sensitive patients.

In the phase II trial of temozolomide (21-day regimen) had to be discontinued in 7 (11%) patients because of prolonged thrombocytopenia and neutropenia. A follow up study (n=25) assessed the toxicity of a 5-day dosing regimen of temozolomide in sensitive or refractory SCLCs. Patients received temozolomide 200 mg/m2/day orally on days 1–5 of each 28-day cycle. This dose was tolerable and active in patients with relapsed SCLCs (ORR 12%). No treatment-limiting prolonged cytopenias were observed, making this the preferred schedule for further studies[20].

1.2.4 M7824

1.2.4.1 Nonclinical Data

M7824 is a bifunctional fusion protein consisting of an anti-programmed death ligand 1 (PD-L1) antibody and the extracellular domain of transforming growth factor beta (TGF-β) receptor type 2, a TGF-β trap. The in vitro and in vivo pharmacology data clearly demonstrate the biological

activity and therapeutic potential of M7824 for the treatment of cancer. All of the data are consistent with a primary MOA that involves the reversal of T cell suppression via PD-L1 inhibition in the tumor microenvironment combined with the additional benefit of sequestering TGF β , providing enhanced antitumor activity. Importantly, M7824 therapy exhibits hallmarks of a successful immunotherapy: continued tumor regression after treatment discontinuation, long-lasting tumor growth inhibition, and protective immunity against tumor re-challenge in cured mice.

In the pivotal 4- and 13-week repeat-dose primate toxicology studies, heart rate, ECG, arterial blood pressure, respiratory rate, CNS parameters, and body temperature were not affected by the treatment with M7824 at all dose levels tested, with an overall NOAEL at the highest and maximum feasible dose of 140 mg/kg. Aside from moderate effects on red cell parameters which are monitorable, manageable, and demonstrated reversibility in the pivotal 13-week primate toxicology study, the overall nonclinical safety profile established for M7824 iv formulation is favorable. An optimized cytokine release assay demonstrated evidence of cytokine release in PHA prestimulated PBMCs from healthy human volunteers, indicating the potential for immune-mediated infusion reactions. Although pivotal nonclinical safety assessments from primate studies did not suggest infusion-related reactions or hypersensitivity events, such reactions are a risk with any biologic.

Though no effects on the male and female reproductive organs were noted in repeat-dose toxicity studies, strict contraception is mandatory. There is no information on M7824 being excreted in human breast milk, subjects with pregnancy or in lactation period will be prohibited from being enrolled in clinical studies with M7824.

1.2.4.2 Potential Risks

The potential risks of M7824 include infusion-related reactions including hypersensitivity, irAEs/autoimmune disorders, anemia, rash with hyperkeratosis/ keratoacanthomas/ SCC of the skin, embryo-fetal toxicity, and alterations in wound healing or repair of tissue damage. All of these are considered potential risks.

1. Infusion-related reactions including hypersensitivity: A known class effect of monoclonal antibodies and an identified risk for M7824.
2. irAEs/autoimmune disorders: Respective warnings and precautions (e.g., for immune-mediated pneumonitis, immune-mediated colitis, and immune-mediated hepatitis) are included in the prescribing information of Keytruda and Opdivo. These irAEs/autoimmune disorders are known risks for M7824.
3. Anemia: Anemia is a potential risk based on toxicological findings with M7824 in cynomolgus monkey indicating a decrease in Hgb, RBC, and hematocrit which was fully reversible or showed a substantial trend toward recovery.
4. Rash with hyperkeratosis, keratoacanthoma, and squamous cell carcinoma of the skin lesions such as rash with hyperkeratosis, keratoacanthoma, and SCC of the skin (reported once) have been observed in Phase I studies with the anti-TGF β 1, 2, and 3 antibody fresolimumab. Considering that a syndrome known as Ferguson-Smith disease which is caused by mutations in TGF β is associated with similar findings as described for fresolimumab, it is plausible that skin tumors may be related to TGF β inhibition.

5. Alterations in wound healing or repair of tissue damage: Due to the involvement of TGF β in repair of skin and other tissue injuries, alterations in wound healing or repair of tissue damage is considered a potential risk.
6. Embryo-fetal toxicities: Embryo-fetal 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. Embryo-fetal and reproductive toxicities have also been investigated in animal models for a humanized monoclonal antibody targeting TGFβ1. At doses as high as 30 mg/kg, no maternal reproductive toxicity or embryo-fetal lethality were observed. Based on above pharmacological class effects, the clinical study protocol provides respective safety measures which comprise inclusion/exclusion criteria, guidance for prevention, monitoring, and medical management of potential risks as well as guidance on study treatment interruption, modification, or discontinuation of the study drug.

In addition, after discussion among NCI investigators on multiple protocols using M7824, multiple bleeding events ranging from low grade gingival bleeding and epistaxis to more serious hemoptysis, GI bleeding and hematuria have been observed. Some of these events can be attributed to bleeding events related to cancer directly and others bleeding events can be attributed to colitis or cystitis which is a known toxicity of anti-PD-L1 agents including M7824. However, there remains the possibility that M7824 may increase the overall risk of bleeding in ways that may not be directly related to direct tumor bleeding or inflammatory bleeding events described with checkpoint inhibitors like M7824. It is hypothesized that this possible increased bleeding risk may be due to TGF beta inhibition which has an effect on angiogenesis; bleeding has also been observed in patients receiving M7824 and may be drug-related (e.g., gum bleeding, nose bleeds, coughing up blood, blood in their urine, or blood in the stool). Accordingly, patients will be notified of the same possible risk in the informed consent document for this study.

For updated safety information, refer to Investigator Brochure.

1.2.4.3 Clinical data

NCT02517398 (EMR200647-001) is an ongoing phase 1, open label, 3+3 dose-escalation study and this preliminary data was presented at ASCO in June 2017 and final results published in [21]. Eligible patients received M7824 at 0.3, 1, 3, 10, or 20 mg/kg Q2W until confirmed progressive disease, unacceptable toxicity, or trial withdrawal; treatment beyond progression is generally allowable. The primary objective was to determine the safety and maximum tolerated dose of M7824; secondary objectives included pharmacokinetics (PK), immunogenicity, and best overall response per RECIST v1.1. As of Oct 3, 2016, 16 heavily pretreated pts with ECOG performance status 0-1 have received M7824. PK data demonstrated a dose-linear increase in exposure; furthermore, at dose levels of 3mg/kg and higher, M7824 saturates peripheral PD-L1 and sequesters any released plasma TGF-β1, -β2, and -β3 throughout the dosing period. Grade 3 drug-related treatment-emergent adverse events (TEAEs) occurred in 3 patients (skin infection secondary to grade 2 bullous pemphigoid [BP], lipase increased, anemia, and colitis); there were no grade 4-5 drug-related TEAEs (**Table 1**). BP and colitis responded well to steroids. Colitis and its secondary events of anemia and rectal hemorrhage (in a previously radiated area) were considered dose-limiting in 1 patient. (See full **Table 1** of AEs below). There was preliminary evidence of efficacy across all dose levels, including 1 ongoing confirmed complete response (cervical cancer), 1 durable partial response (pancreatic cancer), a 25% reduction in the sum of diameters of target lesions after only 2 doses of M7824 (cervical cancer), and 2 cases of

prolonged stable disease (pancreatic cancer; carcinoid). Preliminary data from this phase 1 dose-escalation study suggest that M7824 has a manageable safety profile in patients with heavily pretreated advanced solid tumors. Early evidence of clinical efficacy warrants further study. The recommended dose for the expansion phase is a flat dose of 1200 mg every 2 weeks (~17 mg/kg for a 70 kg patient). The entire dose escalation study was completed at the NCI. M7824 monotherapy is now in multiple expansion cohorts in 120 centers internationally, given at a flat dose of 1200 mg per infusion once every two weeks.

Table 1. Treatment Related Adverse Events M7824

	n = 16 cohort		**n = 3 backfill data**	
	Any Grade	Grade 3	Any Grade	Grade 3
Patients with any event, n (%)	**7 (43.8)**	**3 (18.8)**	**2 (66.7)**	
Anemia	1 (6.3)	1 (6.3)		
Bullous pemphigoid	1 (6.3)			
Colitis	1 (6.3)	1 (6.3)		
Dermatitis acneiform	1 (6.3)			
Dyspnea exertional	1 (6.3)			
Hyperthyroidism	1 (6.3)		1 (33.3)	
Hypophosphatemia	1 (6.3)			
Hypothyroidism	2 (12.5)		1 (33.3)	
Infusion-related reaction	1 (6.3)			
Keratoacanthoma	1 (6.3)		1 (33.3)	
Lipase increase	1 (6.3)	1 (6.3)		
Nausea	1 (6.3)			
Peripheral motor neuropathy			1 (33.3)	

Pruritus	1 (6.3)			
Rash maculopapular	2 (12.5)		1 (33.3)	
Skin infection	1 (6.3)	1 (6.3)		
Vomiting	1 (6.3)			

For updated information, refer to Investigator Brochure.

1.2.5 Study Rationale

Small cell lung cancer (SCLC) is an aggressive cancer with a poor prognosis. Although highly responsive to chemotherapy initially, SCLC relapses quickly and becomes refractory to treatment within a few months. In patients with disease relapsed after first-line chemotherapy, the median survival ranges from 2 to 6 months. The median survival of newly diagnosed extensive stage SCLC is 8-10 months, two-year survival about 10% and 5-year survival less than 2%. Topotecan is the only FDA-approved treatment for patients with relapsed SCLC and among the agents that are active in relapsed SCLC are temozolomide. Immune checkpoint inhibitors have shown limited activity in SCLC (ORR ~10%), although responses tend to be durable. There is a critical need for effective therapeutic approaches for patients with SCLC.

The dual inhibition mode of PD-L1 and sequestration of TGF-beta through M7824 has the potential to improve efficacy of single PD-1 or PD-L1 inhibition. TGF beta-receptors are expressed on a large proportion of a broad panel of SCLC cell lines which also produce TGF beta mRNAs[8]. In SCLC cell lines, IL-2-dependent T-cell growth was severely suppressed by TGF β1 [10]. A specific anti-TGF beta 1 antibody blocked the immunosuppressive activity induced by TGF β1. The plasma level of TGF-β1 in lung cancer patients is elevated compared with that in normal volunteers, and contributes to the impaired NK function via down-modulation of activating receptors, such as NKG2D[22]. TGF-β1 levels are elevated in bronchoalveolar lavage fluid from patients with lung cancer[23]. In this study, the highest levels of TGF-β1 were seen in SCLC patients relative to other types of lung cancer. High levels of TGF-β are also detected in the serum of patients with lung cancer compared with normal individuals [10].

Given the expanding role of immune checkpoint blockade as a therapeutic strategy, the interaction of tumor DNA damage with the immune system has recently come into focus, and it is now clear that the tumor DNA damage has an important role in driving response to immune checkpoint blockade [24]. Increasing evidence suggests that the effects of chemotherapy are mediated not only though cytotoxic effects, but also through immunological effects, including reducing T-regulatory cell activity and enhancing cross-presentation of tumor antigen[25-28]. Combining immunotherapy, and chemotherapy could thus synergistically improve the anticancer activity of anti-PD-L1 monotherapy. Combination of chemotherapy with immunotherapy improved outcomes in NSCLC and melanoma. The U.S. FDA granted accelerated approval to pembrolizumab in combination with pemetrexed and carboplatin for the treatment of patients with previously untreated metastatic non-squamous non-small cell lung cancer[29]. The trial

demonstrated an improvement in ORR and in PFS for patients randomized to pembrolizumab plus chemotherapy. The ORR was 55% for the pembrolizumab plus chemotherapy arm and 29% for the chemotherapy alone arm.

We hypothesize that increased DNA damage induced by topotecan and temozolomide will complement the anti-tumor activity of M7824, in recurrent SCLC. Results of this pilot trial will inform design of larger more definitive studies of the combinations. A range of PD biomarkers and potential predictors of response will be assessed in tumor and peripheral blood in the context of this study including MMR status, cytokines, STING activation, TOP1 and TOP1 cc antibodies, tumor gene expression and mutation, and peripheral blood immune subsets. The planned correlative studies will inform our understanding of the intersection of DNA damage response and immune response and could provide important insights into design of trials combining immune checkpoint inhibitors and chemotherapy.

Extrapulmonary small cell carcinoma is a distinct clinicopathologic entity that can arise in a wide range of extrapulmonary sites. These tumors have been described most frequently in the urinary bladder, prostate, esophagus, stomach, colon and rectum, gallbladder, larynx, salivary glands, cervix, and skin. They are extremely rare and management of systemic disease with chemotherapy is patterned after the approach used in SCLC [30]. Extrapulmonary small cell cancers of various tissues of origin may arise by different mechanisms. In case of prostate small cell, it arises in the setting of therapeutic resistance to highly potent AR-targeting therapy whereas in EGFR mutated cancers it arises in the setting of potent EGFR-targeting. But in general, extrapulmonary small cell cancers have in common signatures of RB1 loss [31-33] which in turn drives replication stress. A recent paper has shown that AR transcriptional activity was lower in small cell prostate cancers compared to adenocarcinoma [32]. Accordingly, in clinical practice small cell prostate cancer patients are continued on androgen suppression while they are on small cell-directed therapy. In a small retrospective study of 34 extrapulmonary small cell cancers, PD-1 positivity in the tumor, lymphocytes, or macrophages was observed in 35% of cases [34]. Anecdotal reports of the evidence of immune checkpoint blockade has also been reported [35, 36]. Taken together, extrapulmonary small cell cancers are orphan diseases with no standard treatments and it appears that although these cancers can arise by different mechanisms, they have in common high replication stress, that may be susceptible to DNA damage and immune checkpoint blockade.

1.2.5.1 Rationale for M7824 Dose Increase of Arm A and B (Amendment B)

For M7824 monotherapy , 1200 mg q2w was selected as a recommended phase 2 dose. Therefore, for Arms A and B, a dose of M7824 1800 mg q3w dose was initially selected based on the following assumptions: 1) C_{ave} (average concentration throughout dosing interval) observed at 1200 mg q2w is an estimate of C_{eff} (efficacious concentration) that needs to be maintained throughout the dosing interval. 2) Exposures are approximately dose-proportional at the pharmacologically active dose range (supported by preliminary PK analysis of Study 001 and 0008) and 3) Projected C_{max} margin of >1, relative to that observed at 30 mg/kg (the highest dose tested, corresponding to ~2100 mg for a 70 kg subject). However, in combination studies in which concomitant therapies are administered q3w, the same dosing interval for M7824 is preferred for convenience and compliance. The steady-state C_{trough} ($C_{trough,ss}$) at 1200 mg q2w is considered the target efficacious $C_{trough,ss}$ for q3w dosing of M7824 in combination studies with q3w dosing. Based on population PK modeling, median $C_{trough,ss}$ achieved with 2400 mg q3w dosing is similar to that projected with 1200 mg q2w dosing. In addition, for >90% of the

participants to be dosed with 2400 mg q3w, $C_{trough,ss}$ is estimated to be above the lower bound of 95% CI for $C_{trough,ss}$ projected with 1200 mg q2w. Since $C_{trough,ss}$ is 2400 mg q3w is expected to achieve target $C_{trough,ss}$ and full PD-L1 target occupancy and TGFβ trapping in blood in > 90% of the participants. While 1800 mg q3w is projected to maintain similar average steady-state concentration compared to monotherapy RP2D, $C_{trough,ss}$ at 1800 mg q3w is lower compared to that at monotherapy at RP2D. Therefore, as of amendment B, the M7824 q3w dose is 2400 mg q3w. For additional information regarding avelumab (parent antibody for M7824) C_{trough} data, please see data presented at ASCO: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9086.

M7824 1200 mg q2weeks dose will be used for Arm C of the current study (and for patients with progressive disease in arm A).

1.2.6 EMD Serono Investigator Letter Dated 9/23/2021, Discontinuation of 3 Randomized Clinical Trials Using M7824 (REF 564699)

The investigator letter addresses the discontinuation of 3 randomized studies (described below) due to the low likelihood of achieving primary objective and superiority in the efficacy objectives vs standard of care. Additionally, cases of early progression and death (due to progressive disease, signs and symptoms of progressive disease, or known treatment toxicities) were seen more frequently in the M7824 arms than in the standard of care arms.

1.2.6.1 MS200647_0037 study (Bintrafusp alfa versus Pembrolizumab as a 1st line Treatment in Participants with PD-L1 Expressing Advanced Non-Small Cell Lung Cancer [NCT03631706]).

This study randomized patients with metastatic lung cancer who had PDL1 hi disease (≥80% based on Dako 73-10 PD-L1 assay) to pembrolizumab vs. M7824. There were similar response rates seen in both arms however there was a higher discontinuation rate in the M7824 arm in this open label study, and this discontinuation imbalance could not be entirely explained by adverse events. There was a concomitant trend of decreased PFS leading the independent data monitoring committee (IDMC) to recommend discontinuation of the study because it was unlikely to meet its co-primary endpoint of PFS [37].

1.2.6.2 MS200647_0055 study (Gemcitabine Plus Cisplatin with or Without Bintrafusp alfa in Participants with 1st line Biliary Tract Cancer [NCT04066491]).

This was another first line study in patients with biliary tract cancer that randomized patients to receive standard of care chemotherapy with or without M7824. This study showed a statistically better response rate for the combination however the PFS data was similar between the two arms and the IDMC recommended closing the study as it was not likely to meet the endpoint of improvement in OS.

1.2.6.3 MS200647_0005 study (Bintrafusp alfa with concomitant chemoradiation in Unresectable Stage III Non-Small Cell Lung Cancer [NCT03840902]).

This is a study based off the PACIFIC study comparing standard of care (chemoradiation followed by durvalumab) vs. chemoradiation with M7824. This study was very immature with an estimated primary completion date in mid-2024. However, EMD Serono, following IDMC recommendation, decided to discontinue the study due to a low likelihood that the experimental arm would achieve superiority in efficacy vs. standard of care.

1.2.6.4 Additional Data Regarding Deaths and Disease Progression

Deaths within 60 days after start of treatment in M7824 arm vs comparator:

- 16 patients (10.6%) versus 9 patients (5.9%) (p=ns) in MS200647_0037 NSCLC Stage IV 1st line (M7824 versus pembrolizumab)
- 11 patients (7.5%) versus 2 patients (1.3%) (p<0.05) in MS200647_0055 biliary tract cancer (BTC) 1st line (M7824 in combination with chemotherapy versus placebo plus chemotherapy)
- 3 patients (4.1%) versus 2 patients (2.6%) (p=ns) in MS200647_0005 NSCLC Stage III (M7824 plus concurrent chemoradiation followed by M7824 maintenance versus chemoradiation followed by durvalumab)

One explanation for the early PD is due to inferior treatment effect, at least on a subpopulation of patients. It should be noted that in the metastatic lung cancer data and in the BTC cancer data the response rates were either similar or better with M7824 (and the stage III lung cancer is in the adjuvant setting), so if this is the case it would only be a subpopulation that do not fare as well.

Another explanation is that M7824, potentially due to TGF-β sequestration and/or PDL1 inhibition, caused hyperprogression in some patients. Hyperprogression has been well documented in the immunotherapy literature, largely in retrospective studies, and with PD1 inhibition appears to happen in about 15% of patients (range in reported studies of 5-40% in recent Meta-analysis[38]).

1.2.6.5 NIH Data on Early Deaths (Within 60 Days) Due to Toxicity Or PD

In CCR sponsored studies, 320 patients have been treated with M7824 across 18 trials (two additional trials have no accrual yet). There have been 94 patients who have progressed within 60 days (226 not having progressive disease). Of these 94 patients, 72 were alive at 60 days and 22 died (16 from progressive disease and 6 from toxicity). Of those 6 who died from toxicity, 2 were attributable to M7824 (1 bleeding and 1 immune checkpoint inhibitor induced hepatitis). The proportion of deaths within 60 days (6.9%) in these studies is similar to what is seen with other immune checkpoint inhibitors in refractory patient populations. Furthermore, less than 1% grade 5 toxicity were attributable to IND in the first 60 days, similar to other FDA approved agents including immunotherapy.

Correlative data from patients enrolled on CCR/NIH studies points to factors that form a biologically relevant explanation that may help explain early PD. Patients with HPV cancers (n=58, enrolled on 15c1079 and 18c0056) were analyzed for immune parameters and divided by patients who died at <60 days or >60 days from the initiation of treatment with M7824. As seen in **Figure 5**, at baseline there were significantly higher plasma levels of IL-8, TGFβ, IL-6, NOS3, and VEGFA in patients with early death, all of which are associated with immunosuppression and/or more advanced disease. A greater neutrophil to lymphocyte ratio (NLR) and higher absolute monocyte counts (AMC) were also seen at baseline in patients surviving <60 days compared to those with >60 days survival.

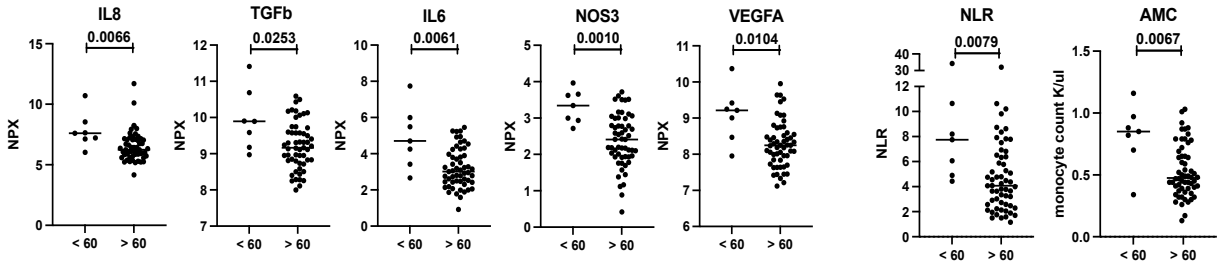

Figure 5. *Baseline plasma levels of IL-8, TGFβ, IL-6, NOS3, and VEGFA in patients with early death.*

1.2.6.6 Clinical activity data in CCR/NIH studies utilizing M7824

There are data from 3 non-randomized phase 2 studies in patients with HPV associated malignances or prostate cancer conducted at the NIH Clinical Center that support the clinical activity of M7824 in monotherapy or combination approaches. In the three studies mentioned below, the level of activity is unprecedented.

1. **18C0056 HPV associated malignancies**
   Preliminary data from this study was published in JITC last year[39]. This showed an ORR by RECIST of 30.5% (n=59) with similar response rates across a wide range of HPV associated malignancies. About 50% of the patients had cervical cancer. In an update presented at ESMO this month with a total of 75 patients, the ORR was holding steady at 28% and if you added in the patients with a delayed response, the total clinical response was 32%[40]. The median duration of response was 17.3 months, and the medial overall survival is 21.3 months. To put this in context, the ORR for PDL1+ patients (n=82) in the cervical cancer study that led to the approval for this indication was 14.6%[41] and in multiple studies of HPV associated malignancies in the second line setting, the median overall survival is ≤12 months.
2. **20C0045 HPV associated malignancies triple therapy**

   In an ongoing trial of M7824, NHS-IL12 (tumor targeted IL12) and an HPV16 targeted vaccine the ORR is 50% (88% in HPV 16+ patients) in patients that are immune checkpoint inhibitor naïve and 30% (38% in HPV 16+ patients) in immune checkpoint inhibitor refractory patients (data updated since oral presentation at ASCO 2021[42]). The expected response rate in immune checkpoint inhibitor refractory patients is <10%. While this data is still early (34 patients total), these response rates observed, especially in immune checkpoint inhibitor refractory, is unprecedented.

3. **18C0078 QuEST (prostate cancer)**
   Subjects in arm 2.2 (M7824, brachyury vaccine and N-803) had a sustained PSA response rate of 46% (6/13 evaluable patients) with 2/3 patients evaluable by RECIST having a PR (data updated since EMSO 2020[43]). The expected response rate in unselected patients with prostate cancer is about 2%[44].

1.2.7 18-C-0110 Trial Summary (as of 10/15/2021)

- Arm A: completed enrollment with 13 patients. Four patients crossed over from Arm A to C at the time of disease progression.

- Arm C: terminated for futility after enrolling 10 patients. Response was not observed in two or more of the first ten patients to allow continued accrual to a total of 22 patients.
- Arm B: enrolled 4 patients.
- Extrapulmonary cohort: enrolled 6 patients

Please refer to **Table 2** for characteristics of the 33 patients enrolled. Patients enrolled so far have several indicators of poor prognosis including extensive stage at diagnosis (76%), platinum resistance (73%), and history of brain metastases (42%).

Table 2. Clinical characteristic of patients enrolled in 18-C-0110

	Arm A (M7824 monotherapy) (n=13) Completed	Arm C SCLC (Temozolomide) (n=10) Terminated	Arm C EP (Temozolomide) (n=6) Recruiting	Arm B (Topotecan) (n=4) Recruiting
Age (years)	64 (48–82)	64 (48–71)	66 (32–74)	64 (57–76)
Sex (M/F)	7/6	7/3	2/4	7/3
VALG Stage at diagnosis (L/E)	3/10	2/8	2/4	1/3
Brain metastasis Hx[1]	5 (38%)	5 (50%)	2 (50%)	2 (50%)
Platinum sensitivity (S/R)[2]	1/12	5/5	2/4	1/3
No. of prior treatment	2 (1–3)	2 (1–8)	2 (1–3)	4 (2–4)
Prior immunotherapy	4 (31%)	7 (70%)	2 (33%)	4 (100%)

Data are n, n (range) or n (percent)
[1]: Patients with asymptomatic brain metastases were allowed to be enrolled
[2]: Platinum resistant: relapsed < 90 days after completion of 1st line platinum chemotherapy

In terms of efficacy, out of 33 evaluable patients, 4 patients have had partial responses, including a patient who is currently in remission 26 months after starting treatment and another patient in ongoing complete metabolic response 10 months after starting treatment.

- Arm A (M7824 only): Of 10 evaluable patients, 1 patient had a partial response before coming off treatment for brain only progressive disease. Patient was alive for 13 months from start of therapy. Of four patients who crossed over two arm C, two patients had partial responses.

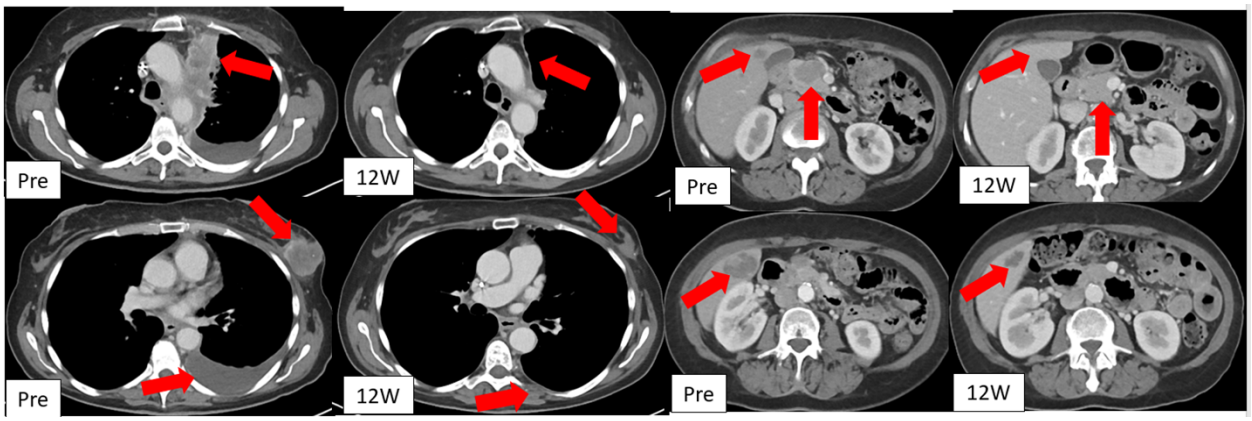

Figure 6. *Partial response in a patient treated with M7824 monotherapy on arm A.*

- Arm C (M7824 + Temozolomide): Of 10 evaluable patients, 1 patient had a PR and was taken off trial after 10 months of treatment for pandemic-related travel restrictions/risks. Patient remains in follow up 26 months after starting treatment with no evidence of recurrent disease.

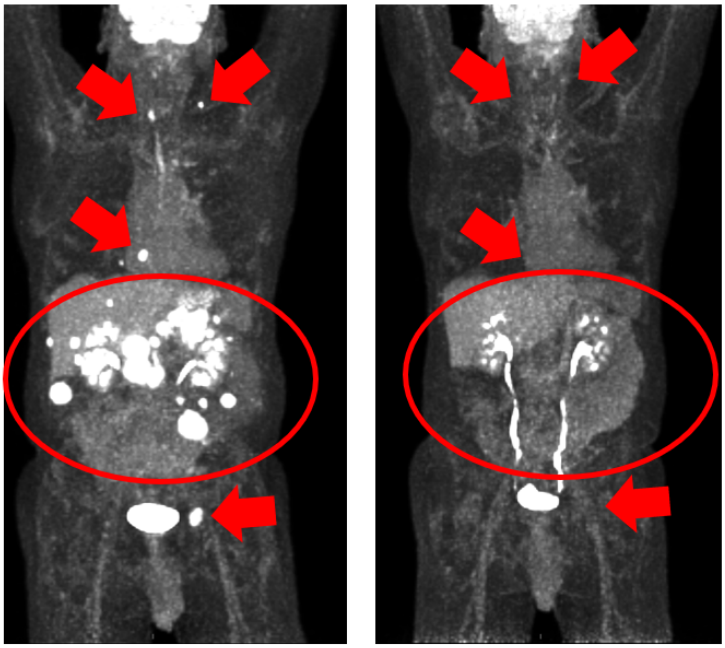

Figure 7. *RECIST partial response (complete metabolic response) in a patient with recurrent SCLC Treated in arm C with a combination of M7824 and temozolomide.*

- Arm B (M7824 + topotecan): Of 4 evaluable patients, all are off treatment for PD.
- Extrapulmonary small cell cancer cohort (M7824 + Temozolomide): Of 3 evaluable patients, two patients had partial responses including a patient with small cell cervix cancer who had PR and remained on treatment for almost 7 months, and a second patient

with small cell cancer of the vocal cord who remains on treatment at 10 months with PR by RECIST and a metabolic complete response.

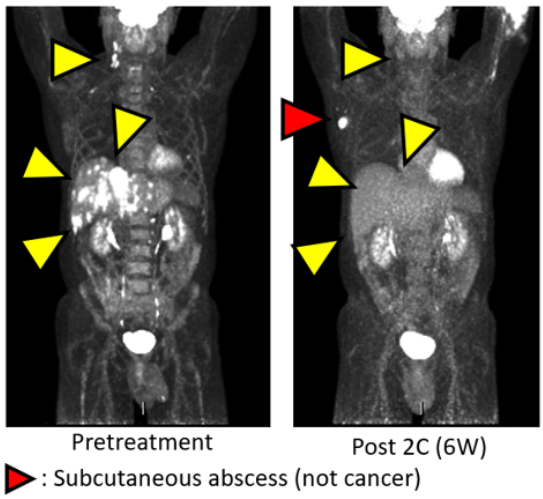

Figure 8. *RECIST partial response (complete metabolic response) in a patient with recurrent Small cell cancer of the vocal cord treated on arm C with a combination of M7824 and temozolomide.*

Toxicities observed on this trial can broadly be classified into three categories, summarized in **Figure 9**:

1. M7824 related immune related AEs: one patient had to be taken off treatment for grade 3 immune related pruritus and rash, one patient reported a flare of grade 1 rheumatoid arthritis, one patient who needed hospitalizations for grade 2 ileus, and one patient developed grade 3 immune related diabetes mellitus, and grade 2 hypophysitis and adrenal insufficiency. Other notable immune AEs were grade 2 adrenal insufficiency and grade 3 pneumonitis.
2. M7824 related bleeding: one patient had grade 1 epistaxis and hemoptysis. 2 patients with gum bleeding, one patient with grade 4 hepatic/intrabdominal hemorrhage, one with grade 3 hematuria and grade 3 anemia.
3. Toxicities related to chemotherapy agents including myelosuppression, nausea, vomiting etc. There was a DLT of one patient treated with topotecan and M7824. Topotecan is known to be associated with high frequency of myelosuppression.

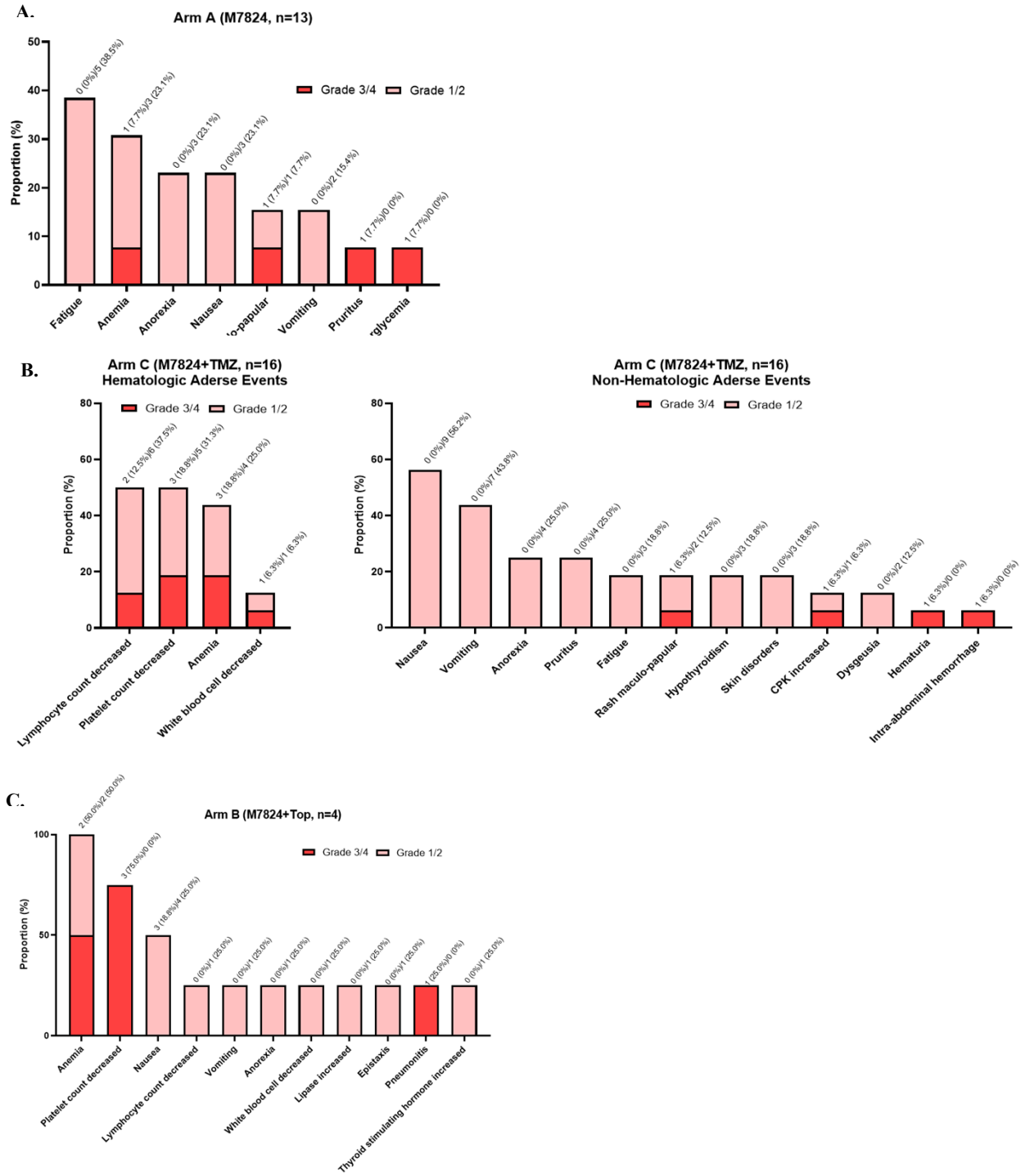

Figure 9. *Toxicities observed in 18-C-0110 arms A-C through 10/15/2021.*

1.2.8 Rationale for Continuing the Trial

Arm B: The study aims to continue the recruitment of participants with SCLC relapse who have progressed on at least one prior chemotherapy and immunotherapy. Standard treatment options for this patient population include topotecan (approved in 1996) [45-49] or lurbinectedin (approved in 2020)[50]. These therapies provide palliation, but yield only short-term responses,

and most patients die within a few months of their relapse (NCCN SCLC guidelines). Response rates are <10% in patients with platinum-refractory or resistant disease (relapse within 3 months of initial therapy) and approximately 25% in patients with platinum-sensitive relapse (relapse after 3 months of initial therapy). Long term responses are exceedingly infrequent to standard therapies. M7824 monotherapy or in combination with chemotherapy (topotecan or temozolomide) produced durable responses in a small but important proportion of SCLC patients, including patients with platinum resistant/refractory relapse. Further studies and understanding the determinants of response could advance SCLC therapeutics.

Assessment of dose limiting toxicity is planned after enrollment of two more patients on Arm B (for a total of 6 patients). One patient in this cohort has had grade 4 thrombocytopenia requiring platelet transfusion. If a total of 2 or more patients within the first 6 patients experience a DLT, then the remaining patients will be treated at dose level -1, with a lower dose of topotecan. If there is adequate safety in these initial patients in Arm B, a total of 10 patients (including the 6 patients evaluated for toxicity and future dose setting) will be enrolled onto the first stage of Arm B. If 0 to 1 of the 10 patients demonstrate a partial response, then no further patients will be accrued onto this arm. If 2 or more of the first 10 patients have a response, then accrual would continue until a total of 22 evaluable patients have been treated in Arm B.

Extrapulmonary small cell cancer cohort: Extrapulmonary small cell cancers are exceedingly rare cancers with small cell morphology arising from non-lung primary sites. They are uniformly fatal and have no standard therapies at relapse following chemotherapy. Given their rarity and heterogeneity, advancing care through clinical trials is challenging. The striking responses in patients who had under-gone extensive previous therapies provide compelling rationale to rigorously investigate the effect of this combination in extrapulmonary small cell cancer patients. Seven additional patients are required to complete enrollment of this cohort.

1.2.9 Arm B Accrual Closure (as of 12/20/2023)

Five patients were enrolled in Arm B as of March 2022. All five patients were evaluable and all had progressive disease as the best response. The toxicities observed include anemia in all patients (2 grade 3, and 3 grade 2) and thrombocytopenia in 4 patients (1 grade 4 requiring a platelet transfusion (DLT), 1 grade 4, 1 grade 3 and 1 grade 1). Four patients experienced the following AESIs: 1 with grade 3 pneumonitis, 1 with grade 2 increased lipase, 1 with grade 2 hypothyroidism and 1 with grade 1 increased thyroid stimulating hormone.

Given the low accrual and competing treatment alternatives, Arm B is being closed.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically or cytologically confirmed SCLC or extrapulmonary small cell cancers.

2.1.1.2 Subjects with relapsed SCLC (diagnosed with limited or extensive stage disease) with tumor progression on or after at least one prior chemotherapy. Patients with SCLC

should in addition have received and have disease progression on or after prior immunotherapy.

2.1.1.3 Male and female subjects ≥ 18 years of age. Because no dosing adverse event data are currently available on the use of topotecan, temozolomide and M7824 in subjects <18 years of age, children are excluded from this study.

2.1.1.4 ECOG performance status ≤2. See **Appendix A**.

2.1.1.5 Subjects must have measurable disease, per RECIST 1.1. See Section **6.3** for the evaluation of measurable disease.

2.1.1.6 Subjects must not have received chemotherapy, or undergone major surgery within 2 weeks and radiotherapy within 24 hours prior to enrollment.

2.1.1.7 Patients must have adequate organ and marrow function as defined below:

a.	hemoglobin	≥ 9.0 g/dL
b.	absolute neutrophil count	≥ $1.5x10^9$/L
c.	platelets	≥$100x10^9$/L
d.	total bilirubin	≤ 2.0 mg/dL
e.	AST(SGOT)/ALT(SGPT)	≤ 2.5 x ULN or if liver metastases were present, ≤ 5 x ULN
f.	creatinine	≤ 1.5 mg/dL OR creatinine clearance ≥ 40 mL/min

2.1.1.8 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.9 The effects of the trial treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly-effective contraception prior to study entry, for the duration of study participation and up to 6 months for women and 3 months for men after the last dose of study drug. Men should not donate sperm during participation in the study and for up to 3 months after the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.2 Exclusion Criteria

2.1.2.1 Subjects with tumor amenable to potentially curative therapy per PI.

2.1.2.2 Subjects who are receiving any other investigational agents. Prior immunotherapy, topotecan and temozolomide are allowed.

2.1.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to (study agent) or other agents used in study.

2.1.2.4 Subjects with symptomatic brain metastases will be excluded from trial secondary to poor prognosis. However, subjects who have asymptomatic brain metastases, and those had treatment for their brain metastasis and whose brain disease is stable without steroid

therapy for 2 weeks may be enrolled (replacement doses ≤ 10 mg of prednisone or equivalent per day are allowed).

2.1.2.5 Subjects with evidence of severe or uncontrolled systemic disease, or any concurrent condition, which could compromise participation in the study, including, but not limited to, active or uncontrolled infection, immune deficiencies (HIV-positive subjects on combination antiretroviral therapy are eligible), Hepatitis B, Hepatitis C, uncontrolled diabetes, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 3 months, uncontrolled cardiac arrhythmia, stroke/cerebrovascular accident within the past 3 months, bleeding diathesis or recent (within 3 months) clinically significant bleeding events or psychiatric illness/social situations which would jeopardize compliance with the protocol.

2.1.2.6 Pregnant women are excluded from this study because topotecan and temozolomide are Class D agents with the potential for teratogenic or abortifacient effects and because the effects of M7824 on the developing human fetus are currently unknown. In addition, because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with topotecan, temozolomide or M7824, breastfeeding should be discontinued if the mother is treated with these agents

2.1.2.7 Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent with the exceptions:

a. diabetes type I, 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 ≤ 10 mg 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.

2.1.2.8 Systemic therapy with immunosuppressive agents within 7 days before enrollment.

2.1.2.9 Administration of live vaccines within 30 days prior to the first administration of study intervention. Seasonal flu vaccines that do not contain a live virus are permitted. Locally approved COVID vaccines are permitted.

2.1.2.10 Subjects unwilling to accept blood products as medically indicated.

2.1.2.11 Known contraindication for topotecan or temozolomide.

2.2 RECRUITMENT STRATEGIES

Trial details will be available on clinicaltrials.gov and personal communications via email will be sent to referring physicians in the area. The study will also be publicized on NIH websites and on NIH social media platforms. Additionally, patients may be recruited from the ResearchMatch online national clinical research registry.

2.3 SCREENING EVALUATION

2.3.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

A waiver of consent for these activities has been requested in section **12.5.1**.

2.3.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the study consent OR the consent for study 01-C-0129 (provided the procedure is permitted on that study) on which screening activities may also be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

Screening must be completed within 2 weeks prior to enrolling subjects onto the protocol unless otherwise indicated.

- History and physical exam (including height, weight, ECOG performance status and vital signs)
- Blood tests (for organ function):
    a. Complete blood count (CBC/Diff)
    b. Acute care panel
    c. Hepatic panel
    d. Mineral panel
    e. Prothrombin time (PT)
    f. Partial thromboplastin time (PTT)
- Viral Markers Protocol Screen (HBsAg, anti-HCV, anti-HIV) (within 3 months of screening)
- Confirmation of pathological or cytological diagnosis (may be done prior to the two-week screening window)
- CT ± PET scan of disease sites. PET scans may be omitted if CT alone can be used to assess disease.
- Electrocardiogram (12 lead)
- Urine or serum HCG for women of child-bearing potential

2.4 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.4.1 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Small cell lung cancer	Subjects with relapsed SCLC
2	Extrapulmonary small cell cancer	Subjects with extrapulmonary small cell cancers

Arms

Letter	Name	Description
A	M7824 monotherapy	M7824 (IV) monotherapy once every 21 days on a 21-day cycle. Patients who progress on monotherapy may be treated with M7824 and temozolomide as per description of treatment in Arm C.
B	M7824 plus topotecan	M7824 (IV) on day 1 plus topotecan (IV) on days 1-5 of a 21-day cycle. At least 6 subjects to receive M7824 plus topotecan to determine safety. 4 more patients enrolled at initial or lower dose for efficacy. If efficacious, an additional 12 subjects enrolled.
C	M7824 plus temozolomide	M7824 (IV) days 1 and 15 plus temozolomide (oral) on days 1-5 of a 28-day cycle. At least 6 subjects with SCLC to receive M7824 plus temozolomide to determine safety. 4 more SCLC patients enrolled at initial or lower dose for efficacy. If efficacious, an additional 12 SCLC subjects enrolled. After the 6 safety SCLC cohort, subjects with extrapulmonary small cell cancers will be enrolled.

Arm Assignment

1. The first 10 evaluable subjects in cohort 1 will be directly assigned to Arm A. After disease progression, these subjects are eligible to receive M7824 plus temozolomide as per description of treatment in Arm C, but will still remain enrolled on Arm A.

2. After arm A is completed, for logistical reasons, the remaining subjects in cohort 1 will be assigned to Arm C. Accrual will be paused after at least 6 subjects are enrolled, then resume at the same or lower doses of the chemotherapy agents depending on the assessment. A second pause will be implemented after 10 patients are enrolled to assess for efficacy. Enrollment will continue after assessment if efficacy thresholds are met.
3. After arm C is completed, subjects will be assigned to arm B. Accrual will be paused after at least 6 subjects are enrolled, then resume at the same or lower doses of the chemotherapy agents depending on the assessment. A second pause will be implemented after 10 patients are enrolled to assess for efficacy. Enrollment will continue after assessment if efficacy thresholds are met.
4. After the enrollment of the 6 SCLC safety subjects in arm C, 10 subjects with extrapulmonary small cell cancer (cohort 2) will be enrolled in arm C.

2.4.2 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and eligibility criteria.

2.5 BASELINE EVALUATION

All studies must be completed within 7 days of first dose of drug. If tests needed at baseline were performed at screening within the 7-day timeframe, they do not need to be repeated.

- History and physical exam (including height, weight, performance status and vital signs)
- Blood tests (for organ function):
    - Complete blood count (CBC/Diff)
    - Acute care panel
    - Hepatic panel
    - Mineral panel
    - Prothrombin time (PT)
    - Partial thromboplastin time (PTT)
    - Thyroid screen: TSH and free T4
    - Pancreatic enzymes: amylase and lipase
    - Creatine kinase, serum aldolase, and anti-acetylcholine receptor antibody titers
    - Serum troponin
- Electrocardiogram (12 lead)
- Complete neurological examination including assessment of cranial nerve function and muscle strength will be performed at screening and subsequent visits on all eligible patients before starting treatment.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a safety run-in and phase II trial of M7824 and topotecan or temozolomide in relapsed small cell lung cancer and extrapulmonary small cell cancer. The primary objective of the trial is to determine the efficacy of M7824 plus topotecan or temozolomide relapsed SCLC.

- Arm A (M7824 monotherapy): 10 patients may be treated with M7824 monotherapy to confirm safety of M7824 in SCLC and to obtain PK data and a preliminary estimate of clinical responses to M7824 in SCLC. Based on the adverse event profile of M7824 available so far (>600 pts treated on this dose of M7824 monotherapy across 13 solid tumor cohorts), as well as the adverse event profiles of PD-1/PD-L1 targeted agents in SCLC, we do not anticipate any unique safety signals in this patient population. Patient with progressive disease on Arm A may receive M7824 and temozolomide as per description of treatment in Arm C, but will remain on Arm A. Their initial response and progression will be part of the primary evaluation for Arm A.
- Following completion of the 10-patient Arm A, for logistical reasons, patients will be assigned to Arm C (M7824 plus temozolomide) then to Arm B (M7824 plus topotecan).
- The trial will be conducted as follows:
    - Arm A:
        - Initially, 10 patients will enroll on Arm A.
    - Arm C:
        - Following completion of the 10-patient Arm A, patients will be assigned to Arm C initially until there are 6 evaluable patients, and then a pause to the accrual of Arm C will take place. These first patients enrolled in C before the pause in accrual will be treated at dose level 1 and evaluated for toxicity. If 0 or 1 of the first 6 patients experiences a dose-limiting toxicity (DLT), then the remainder of the patients in C will be treated at that dose. If 2 or more patients within the first 6 experience a DLT, then the remaining patients will be treated at dose level -1. If 2 or more patients at dose level -1 experience a DLT, then no further accrual will take place in the arm unless a treatment modification is provided via an amendment. The Sponsor's DSMB will review the data. The accrual halt will be lifted if permitted by the DSMB and IRB.
        - If there is adequate safety in these initial patients in Arm C, a total of 10 patients (including the 6 patients evaluated for toxicity and future dose setting) will be enrolled onto the first stage of Arm C. If 0 to 1 of the 10 patients demonstrate a partial response, then no further patients will be accrued. If 2 or more of the first 10 patients have a response, then accrual would continue until a total of 22 evaluable patients have been treated in Arms C.
        - A separate cohort of patients with extrapulmonary small cell cancer (n=10) will be accrued after the enrollment of the first 6 SCLC evaluable patients and will only receive the combination therapy of M7824 and Temozolomide.

- Arm B:
  - After completion of enrollment of SCLC patients in Arm C, patients will be assigned to arm B initially until there are a minimum of 6 evaluable patients in that arm, and then a pause to the accrual of Arm B will take place. These first patients enrolled in Arm B before the pause in accrual will be treated at dose level 1 and evaluated for toxicity. If 0 or 1 of the first 6 patients experiences a dose-limiting toxicity (DLT), then the remainder of the patients in arms B will be treated at that dose. If 2 or more patients within the first 6 experience a DLT, then the remaining patients will be treated at dose level -1. If 2 or more patients at dose level -1 experience a DLT, then no further accrual will take place unless a treatment modification is provided via an amendment. The Sponsor's DSMB will review the data. The accrual halt will be lifted if permitted by the DSMB and IRB.
  - If there is adequate safety in these initial patients in Arm B, a total of 10 patients (including the 6 patients evaluated for toxicity and future dose setting) will be enrolled onto the first stage of Arm B. If 0 to 1 of the 10 patients demonstrate a partial response, then no further patients will be accrued onto this arm. If 2 or more of the first 10 patients have a response, then accrual would continue until a total of 22 evaluable patients have been treated in Arm B.

An interim analysis will be conducted prior to phase 2 expansion as described in section **10.4.6.1.**

It is anticipated that up to 2 patients per month may enroll onto this trial; thus, approximately 2 to 3 years may be required to complete accrual of up to 10+22+22+10=64 evaluable patients. The accrual ceiling will be set at 80 to allow for a small number of inevaluable patients and screen failures.

Optional tumor biopsies will be obtained pre-treatment and C1D15 for arm C; pre-treatment and C2D1 for arms A and B. Attempts will be made to obtain up to five cores if safe and feasible, which will be used for research studies. The use of imaging to facilitate biopsies will be decided upon by members of the interventional radiology team. Biopsy will be obtained percutaneously. Research biopsies will not be obtained bronchoscopically.

Every subject of each arm of the safety run-in will be observed for at least 7 days after first dose of M7824 before the subsequent subject can be treated. Subjects who are not evaluable for DLT will be replaced and not included into evaluation. Patients on Arm A will continue on treatment until criteria in section **3.8.1** are met. Patients on arms B and C will receive M7824 plus chemotherapy until criteria in section **3.8.1** are met. In cases where patients are unable to tolerate the chemotherapy, they will be dose modified and discontinued according to sections **3.1.2** and **3.4**. Patients who discontinue the chemotherapy in Arms B and C for reasons other than progressive disease, may continue on M7824 alone until criteria in section **3.8.1** are met. Patients who discontinue M7824 for reasons other than progressive disease may continue on chemotherapy.

GM-CSF may be administered in Arms B and C as clinically indicated. Although rare, there is a possibility of immune-related progression in some patients. Given this, dosing beyond initial

progression may be considered in selected patients who per PI are clinically stable and are thought to benefit from the treatment.

3.1.1 Dose Limiting Toxicity

Subjects will be monitored for DLTs during the first cycle (Arm B- 3 weeks and Arm C- 4 weeks). DLTs will be defined using the National Cancer Institute (NCI) CTCAE (Version 5).

The occurrence of any of the following toxicities will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug administration:

- Grade 4 non-hematologic toxicity (not laboratory).
- Grade 4 hematologic toxicity lasting ≥7 days.
- Grade 3 non-hematologic toxicity (not laboratory, specifically nausea, vomiting and diarrhea) lasting >5 days despite optimal supportive care.
- Febrile neutropenia Grade 3 or Grade 4:

A. Grade 3 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour

B. Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated.

- Thrombocytopenia <25,000/mm3 if associated with:

C. A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or a life-threatening bleeding event which results in urgent intervention and

D. Admission to an Intensive Care Unit

- Prolonged delay (>3 weeks) in initiating Cycle 2 due to treatment-related toxicity Grade 5 toxicity.

3.1.2 Dose De-Escalation

Dose de-escalation Schedule Arm B		
Dose Level	M7824	Topotecan
Level 1	2400 mg every 3 weeks	1 mg/m2 on days 1-5 every 3 weeks
Level -1	2400 mg every 3 weeks	0.75 mg/m2 on days 1-5 every 3 weeks

Dose de-escalation Schedule Arm C		
Dose Level	M7824	Temozolomide
Level 1	1200 mg every 2 weeks	200 mg/m^2/day on days 1-5 every 4 weeks
Level -1	1200 mg every 2 weeks	150 mg/m^2/day on days 1-5 every 4 weeks

3.2 STUDY ACCRUAL STOPPING RULE

Once the 6th participant had reached the 6 months follow up period (or potentially would have reached the 6 months follow-up if the participant died prior to the 6 months follow-up), the study will be halted for a DSMB review of the available data if more than 5 participants have PD ≤ 6 months following the first dosage.

If two participants experience serious bleeding events within 30 days following the last administration of investigational product, the study will be halted from further enrollment and the data will be presented in an ad-hoc DSMB meeting. Once the study will be put off hold, only bleeding events occurring after the resumption of enrollment will be counted toward the halting rule.

3.3 DRUG ADMINISTRATION

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects. In Arms B and C, M7824 will be administered first followed within 15-30 minutes after the end of infusion by topotecan or temozolomide. The timing of subsequent administrations is then adjusted to maintain cycle length.

For non-medical logistical reasons or for unrelated acute illnesses, dosing can be delayed up to 2 months. Where at all possible, dosing should be restarted to keep in line with the original treatment schedule.

3.3.1 Topotecan Administration

Topotecan is a cytotoxic anticancer drug. Prepare topotecan under a vertical laminar flow hood while wearing gloves and protective clothing. If topotecan solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If topotecan contacts mucous membranes, flush thoroughly with water. Use procedures for proper handling and disposal of anticancer drugs.

Each 4-mg vial of topotecan is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in 50 mL of either 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous Infusion prior to administration. Topotecan will be administered as an intravenous infusion over 30 minutes.

3.3.2 Temozolomide Administration

Temozolomide will be dispensed at the start of each cycle. Patients will be provided with a pill diary (**Appendix B**), instructed in its use, and asked to bring it with them to each appointment. The dose will be determined using the body surface area (BSA) calculated at the beginning of each cycle unless significant (> 3 kg) weight loss or gain is observed. The BSA will be

calculated from the height obtained at the pretreatment visit and from the weight obtained at the visit before each odd cycle. Capsules of temozolomide will be available in 5, 20, and 100 mg for this study. The daily dose will be rounded to the nearest 5 mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules. Temozolomide will be administered and maintained in accordance with SOP #: PM-8 that is available via https://ccrod.cancer.gov/confluence/display/CCRCRO/Documenting+Drug+Accountability+for+Oral+Investigational+Agents. Prior to each treatment cycle with temozolomide a complete blood count (CBC) will be obtained.

3.3.3 M7824 Administration

M7824 will be administered as a 1-hour (-10 minutes / +20 minutes) IV infusion on days 1 and 15 of each cycle in arm C and progressive disease patients in arm A.

For subjects receiving 2400 mg (monotherapy arm A [amendment B onward] and arm B), total infusion time may be up to 120 minutes.

Current experience revealed that infusion related reactions (IRRs) to M7824 seldom occur and are generally mild to moderate in severity. Therefore, administration of a premedication is generally not required.

If an Investigator deems it necessary to administer a premedication to a particular participant, an antihistamine (for example, 25-50 mg diphenhydramine and 500-650 mg acetaminophen intravenously or equivalent oral dose is recommended) approximately 30 to 60 minutes prior to each dose of M7824. If Grade ≥ 2 infusion reactions are seen during the first two infusions, premedication should not be stopped. Steroids as premedication are not permitted.

M7824 should be administered through a peripheral IV or titanium port. A 0.2 micron polyethersulfone (PES) in-line filter is mandatory for [M7824] administration. Please refer to pharmacy manual for details.

Hypersensitivity reactions may require immediate intensive care. 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), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

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.

For prophylaxis of flu like symptoms, a nonsteroidal anti-inflammatory drug (NSAID), e.g., ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each IV infusion.

Vital signs will be measured before, at least one time during the infusion of M7824 and at the end of infusion. Following M7824 infusions, subjects must be observed for a minimum of 1 hour post end of infusion for potential infusion-related reactions with vital signs taken every 30 minutes ±15 minutes. If an allergic reaction occurs, the subject must be treated according to the best available medical practice. Please see the guidelines for handling of infusion-related

reaction in the section on dose modifications. After 3 cycles, if the patient never develops any infusion related reaction, vital signs are only required pre and post infusion.

Investigators should also monitor subjects closely for potential irAEs, 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.

3.4 DOSE MODIFICATIONS

3.4.1 Topotecan Dose Modification

No dose modifications of topotecan may be made during cycle 1.

The dose of topotecan may be reduced other than in Cycle 1 for toxicity using the following guidelines depending on the toxicities (and drug deemed to be responsible for toxicity) observed, see **Table 3**. Topotecan dose reductions will be accomplished by decreasing the dose of topotecan for each of the 5 days.

To initiate subsequent cycles of topotecan the day 1 ANC should be >1500/mm3 and platelets >100,000/mm3. Treatment interruptions may occur for a maximum of 21 days.

Based on the below criteria, a maximum of 2 dose reductions will be permitted.

Table 3. Dose Adjustments

Table 3a. Dose adjustments for renal functions	
Creatinine clearance	Dose adjustment (% decrease in topotecan dose)
>60	no adjustment
40-59	-20%
20-39	-25%
<20	Discontinue

Table 3b. Dose adjustments for non-hematologic toxicities	
Non-hematologic toxicity	Dose adjustment (% decrease in topotecan dose)
Grades 1 and 2	no adjustment
Grades 3 and 4 (except grade 3 nausea)	-20%

Table 3c. Dose adjustments for hematologic toxicities	
Hematologic toxicity	Dose adjustment (topotecan mg/m2)

Grades 1 and 2	no adjustment
Grade 3 neutropenia persisting after day 21	-20%
Grade 4 thrombocytopenia or Grade 4 neutropenia with fever or infection or of duration ≥ 7 days	-20%

In addition, in case of Grade 3 or higher toxicity during any cycle beyond Cycle 1, treatment may be interrupted and may be resumed when all toxicities have returned to Grade 2 or less, at the discretion of the investigator.

Subjects who develop intolerance to topotecan, but who may be benefiting from therapy, may continue on single agent M7824 until disease progression.

3.4.2 Temozolomide Dose Modification

Temozolomide dose is modified only if toxicity is specifically attributed to temozolomide. If during a TMZ dosing period, there is a drop in ANC to < 1000 or platelets < 50 000 a dose reduction should occur in the subsequent cycle. See tables. Sequence cycles of temozolomide will not be started unless ANC is above 1500 and the platelet count exceeds 100,000/μL. A maximum of 2 dose reductions will be permitted.

Dose adjustments for Temozolomide	
Grade	Dose adjustments
Grades 1 and 2	None
Grades 3 and 4	-25%

Subjects who develop intolerance to temozolomide, but who may be benefiting from therapy, may continue on single agent M7824 until disease progression.

3.4.3 Management of M7824 AEs

- M7824 should be withheld for any Grade 2 or 3 adverse drug reactions (ADR) until resolution to Grade ≤ 1 unless the ADR in the opinion of the investigator is not clinically relevant or can be medically managed with minimal risk to the patient.
- Grade 4 isolated laboratory values out of normal range that do not have any clinical correlation may not require treatment discontinuation. Work-up, management, and treatment continuation versus hold versus discontinuation for isolated Grade 4 laboratory abnormalities should be carefully evaluated.
- Should a clinically relevant grade 2 or 3 ADR persist for more than 4 weeks, consideration should be given to discontinuing treatment with M7824 at the discretion of the investigator.
- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.

- Infusion-related reactions and hypersensitivity reactions (Grades 1 to 4) should be handled according to the Guidelines provided below.

3.4.3.1 Infusion-related Reactions

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

Symptoms:

- Fever
- Chills
- Rigors
- Diaphoresis
- Headache

Table 4. Treatment Modification Guidance for Symptoms of Infusion-Related Reactions including Immediate Hypersensitivity

NCI-CTCAE Grade	Infusion of M7824	Treatment	Premedication at subsequent dosing
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	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hold infusion if deemed necessary by the investigator.	None
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. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be pre-medicated	**Monitor symptoms.** Therapy include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically	Subject to be pre-medicated 1.5h (± 30 minutes) prior to infusion of M7824 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1,000 mg PO (or equivalent dose of antipyretic).

NCI-CTCAE Grade	Infusion of M7824	Treatment	Premedication at subsequent dosing
	for the next scheduled dose. If not improving, consider administration of glucocorticoids and stop the infusion for that day. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	stable in the opinion of the investigator.	
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.	Stop the M7824 infusion immediately and disconnect infusion tubing from the subject. If resolved within 6 hours, infusion may be restarted by discretion of PI	Therapy includes but is not limited to: - IV fluids - Antihistamines - NSAIDS - Acetaminophen - Narcotics - Oxygen - Pressors - Corticosteroids - Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Administration of glucocorticoids may be required.	Subject to be pre-medicated 1.5h (± 30 minutes) prior to infusion of M7824 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1,000 mg PO (or equivalent dose of antipyretic).
Grade 4 Life-threatening consequences; urgent intervention indicated.	Subjects have to be withdrawn immediately from M7824 treatment and must not receive any further M7824 treatment		No subsequent dosing.

NCI-CTCAE Grade	Infusion of M7824	Treatment	Premedication at subsequent dosing

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 4** including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion of M7824 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.

3.4.3.2 Severe Hypersensitivity Reactions and Flu-like Symptoms

If a hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice including ACLS guidelines. Hypersensitivity reactions may require immediate intensive care. M7824 should be administered in a setting that allows 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. Potent steroids (e.g. dexamethasone), catecholamines (e.g. epinephrine), allergy medications (IV antihistamines), bronchodilators, or equivalents and oxygen should be available for immediate access.

Subjects should be instructed to report any delayed reactions to the Investigator immediately.

- Symptoms
  - Impaired airway
  - Decreased oxygen saturation (< 92%)
  - Confusion
  - Lethargy
  - Hypotension
  - Pale / clammy skin
  - Cyanosis
- Management
  - Epinephrine injection and IV dexamethasone
  - Patient should be placed on cardiac, blood pressure, heart rate, and oxygen saturation monitor immediately
  - 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. The risk of bleeding will be discussed with participants prescribed/using NSAIDs.

3.4.3.3 Management of Immune-Related Adverse Events

Since inhibition of PD-L1 and TGFβ signaling stimulates the immune system, irAEs may occur. Immune-related AEs are specific to immunotherapies and vary by organ system. The following immune-related AEs are important identified risks for M7824:

- Immune-related pneumonitis
- Immune-related hepatitis
- Immune-related colitis
- Immune-related nephritis and renal dysfunction
- Immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders)
- Immune related rash
- Other immune-related events (myositis, myocarditis, encephalitis)
- The following immune-related AEs are important potential risks for M7824:
- Guillain-Barré syndrome
- Uveitis
- Pancreatitis
- Myasthenia gravis/myasthenic syndrome

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 **Table 5**.

Table 5. Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue M7824 therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens:

		Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL Colitis: abdominal pain; blood in stool	Withhold M7824 therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume M7824 therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL Colitis (Grade 3): severe abdominal pain, , peritoneal signs Grade 4: Life-threatening consequences; urgent intervention indicated	Withhold M7824 for Grade 3. Permanently discontinue M7824 for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume M7824 therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue M7824 therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold M7824 therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume M7824 therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold M7824 for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3.	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume M7824 therapy following steroids taper (for initial Grade 3).

	Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Consider withholding M7824 therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL	Withhold M7824 therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume M7824 therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Permanently discontinue M7824 therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1	Continue M7824 therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.

Grade 1 AST or >ULN – 3.0 x ULN if baseline was normal; 1.5 – 3.0 x baseline if baseline was abnormal and/or Total bilirubin >ULN – 1.5 x ULN if baseline was normal; > 1.0 – 1.5 x baseline if baseline was abnormal		
Grade 2 AST or ALT >3.0 – 5.0 x ULN if baseline was normal; >3.0 – 5.0 x baseline if baseline was abnormal and/or total bilirubin > 1.5 to ≤ 3 x ULN if baseline was normal; >3.0 – 10.0 x baseline if baseline was abnormal	Withhold M7824 therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume M7824 therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: AST or ALT >5.0 – 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal and/or total bilirubin >3.0 – 10.0 x ULN if baseline was normal; >3.0 – 10.0 x baseline if baseline was abnormal Grade 4: AST or ALT >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal and/or total bilirubin >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	Permanently discontinue M7824 therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue M7824 therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold M7824 therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume M7824 therapy following steroids taper. If worsens: Treat as Grade 4.

Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue M7824 therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold M7824 therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult. * Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start M7824 therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue M7824. Guideline based supportive treatment as appropriate as per cardiology consult. * 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).

*Local guidelines, or e.g. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue M7824 therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold M7824 therapy (for type I diabetes until glucose level improves to grade 2 or less per CTCAE version 4) Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume M7824 once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : 1.0 Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women)	Resume M7824 once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume M7824 only once shrinkage of the pituitary gland on MRI/CT scan is documented.

	2.0 Hormone replacement/suppressive therapy as appropriate 3.0 Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue M7824 if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold M7824 if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Continue hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold M7824 therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting M7824 therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold M7824 therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume M7824 therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue M7824 therapy • to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue M7824 therapy (single laboratory values out of normal range that do not have any clinical correlate may not require permanent discontinuation – see section **3.4.3**) • to 2.0 mg/kg/day	If improves to Grade ≤ 1: Taper steroids over at least 1 month

	prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue M7824 therapy Specialty consult	

3.4.3.4 Management of M7824 Mediated Skin Reactions

Monitoring will include skin assessments every cycle with biopsy of suspicious lesions. Dermatological consults should be requested as needed.

TGF-β inhibition mediated skin reactions are considered important identified risk for M7824. Skin assessment must be performed at baseline and at least every 6 weeks during treatment and at the end of treatment or 28 (±5 days) days post-treatment safety follow-up (if not performed in the previous 6 weeks).
• Hyperkeratosis • Keratoacanthoma • Cutaneous squamous cell carcinoma (cSCC) • Basal cell carcinoma • Actinic keratosis
Management

• Baseline skin assessment with detailed medical history
• Discontinuation or termination not required in most cases. Continuation of treatment should be evaluated by the Investigator.
• Emollients may be used
• Develop diagnostic and treatment plan in collaboration with Investigator and dermatologist
• Treatment follow-up will depend on number and localization of lesions.
  o Single lesion: full excision may be recommended
  o Multiple lesion or location not suitable for full excision: Mohrs surgery, cryotherapy or other standard treatment options depending on pathology. Retinoids may be used after discussion with Investigator.
• Close clinical follow-up for re-evaluation, resolution and potential recurrence should be implemented
• In general, treatment of TGF-β mediated skin lesions should be based on local guidelines/standard of care.

Additional consideration: Keratoacanthoma lesions may resolve spontaneously without surgical intervention within weeks after discontinuing M7824. Consult with Medical Monitor as needed for management of TGF-β mediated skin lesions.

3.4.3.5 Management of Impaired Wound Healing

Management should be discussed on a case-by-case basis. Dermatological consults should be requested as needed.

- Impaired wound healing is considered important potential risk for M7824
- Management should be discussed with Medical Monitor for participants requiring surgery on study.
- It is recommended to hold study intervention for approximately 4 weeks post major surgery for observation.
- Post-operative wound healing should be closely monitored

3.4.3.6 Management of Treatment related Anemia

- Anemia is considered an important identified risk for M7824.
- Hematology assessment must be performed at baseline, prior to each M7824 dose, at the end of treatment visit and at 28 (±5 days) days post-treatment safety follow-up.
- Participants must enter the study with Hgb values at least 9g/dl
- All relevant hematological testing for treatment-related anemias should be done prior to a blood transfusion, if clinically feasible

Basic Anemia Evaluation

- CBC with emphasis on red cell indices
- If indicated and at clinical discretion, the following should be considered:
  - Iron studies
  - Serum Folate and Vit B12 values
  - Coagulation factors
  - Fecal occult blood
  - Urinalysis
  - Hormone panel: TSH, Erythropoietin
  - Peripheral blood smear

Further Recommendation Based on Suspected Etiology (in Addition to Basic Anemia Testing)

- Suspected Hemolysis
  - bilirubin, LDH, Coombs test, haptoglobin
- Suspected bleeding:
  - Consider imaging/interventional radiology consultation as indicated
  - Consider imaging and/or endoscopy as clinically indicated
- Suspected aplastic anemia:
  - Hematology consultation
  - Consider bone marrow aspiration/morphologic evaluation

Additional consideration:
In general, blood transfusions and erythroid growth factors are permitted as clinically indicated.

Abbreviation: CBC: complete blood count, TSH: thyroid stimulating hormone, LDH: lactate dehydrogenase

3.4.3.7 Management of Bleeding Adverse Events

Bleeding Adverse Events

- Bleeding adverse events are considered important identified risk for M7824.
- In general, mild and moderate mucosal bleedings resolve without discontinuation of treatment.
- These events may include, but are not limited to the following:
  - Epistaxis
  - Hemoptysis
  - Gingival bleeding
  - Hematuria

Non-tumor Bleeding

Grading	Management

Grade 2	• If resolves to Grade ≤ 1 by the day before the next infusion, study intervention may be continued • If not resolved to Grade ≤ 1 by the day before the next infusion, but is manageable and /or not clinically relevant, consult Medical Monitor to assess if clinically reasonable to administer the following infusion.
Grade 3	• Permanently discontinue treatment unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic events, etc.) • In case of alternative explanations, hold study treatment until the event recovers to Grade ≤ 1
Grade 4	• Treatment must be permanently discontinued if no alternative explanation is identified.
Tumor Bleeding	
Grade ≥ 2	• Study treatment must be held till the event recovers to Grade ≤ 1 • Permanently discontinue treatment if the Investigator considers the participant to be at risk for additional severe bleeding.

3.4.3.8 Dose Interruptions for Adverse Events not Related to Study Drug

In case of Grade 3 and Grade 4 AEs which are not study drug related, the study treatment may be interrupted for up to 2 months based on the Investigator assessment.

3.5 STUDY CALENDARS

Evaluation and drug administration and can be performed +/- 3 days due to holidays, inclement weather, conflicts, or similar reasons. All baseline studies must be completed within 7 days of first dose of drug. If tests needed at baseline were performed at screening within the 7 day timeframe, they do not need to be repeated.

3.5.1 Arm A (M7824 Monotherapy)

Procedure	***Screening*** 2	***Baseline*** 3	***Cycle (3 weeks)***				***End of treatment and follow up visits*** 1
			1		***2***	***3 (forward)***	
			Day 1 3	***Day 2***	***Day 1***	***Day 1***	
History and physical exam	X	X			X	X	X
Vital signs 4	X	X			X	X20	X
ECOG Performance Score	X	X			X	X	X
Labs (CBC+diff, acute care panel, hepatic panel, mineral panel, PT/PTT) 5, 13	X	X	X		X	X	X
TSH, Free T4, Amylase and Lipase 13		X	X		X	X	
*Viral Markers*6	X						
Creatine kinase, serum aldolase, and anti-acetylcholine receptor antibody titers 13		X	X		X	X	
Pregnancy test 7	X		X		X	X	
Complete neurological examination 8, 16		X	X		X	X	X
Optional biopsies 10			X		X		
Confirmation of diagnosis	X						
Blood/Plasma for Correlative Research Studies 11, 14, 17***:***							
Germline exome sequencing			X				
Immune subsets			X		X		
Immune studies			X	X	X	X	X
CtDNA			X	X	X	X	X
Paraneoplastic autoantibodies		X9					
PK 12, 14, 15, 17			X	X	X	X	X
Radiological Assessments 19	X		Every 2 cycles (6 weeks)				
Response Evaluation			Every 2 cycles (6 weeks)				
EKG	X	X					
Blood Troponin 14, 17		X					
Adverse Events and Bleeding Events 18			X	→	→	→	→
Concomitant Medications			X	→	→	→	→
M7824 17, 21			X		X	X	
Hair Follicle Collection (5.1.2)			X	X	X		

1. End of treatment visit will occur approximately 30 days after the last dose of study drug. If the patient cannot return to the Clinical Center for this visit, a request will be made to collect required clinical labs from a local physician or laboratory. If this is not possible, patients may be assessed by telephone for symptoms. Patients will be monitored for survival via phone call every 4 months after the last dose until death.
2. Screening must be completed within 2 weeks prior to enrolling subjects onto the protocol.

3. Baseline studies must be completed within 7 days of first dose of drug. Assessments do not need to be repeated on day 1 if performed within 7 days of drug administration. See footnote 14 below for exceptions.
4. Include height (only required at screening/baseline), weight, heart rate, temperature, blood pressure and respiration rate.
5. **CBC with differential**: Neutrophils, Lymphs, Monos, Eos, Basos, WBC, RBC, Hemoglobin, Hematocrit, RBC Indices, MCV, RDW, Platelet; **Acute Care Panel**: Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, eGFR; **Hepatic Panel**: Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin; **Mineral Panel**: Albumin, Calcium, Magnesium (Mg), Phosphorus.
6. HbsAg, anti-HCV, anti-HIV within 3 months prior to screening.
7. Only for women of child-bearing potential.
8. Assessment of cranial nerve function and muscle strength will be performed at screening and subsequent visits on all eligible patients before starting treatment.
9. One additional red top tube (10 mL) will be collected for future evaluation of paraneoplastic autoantibodies.
10. Please refer to section **5.1**. for details on tumor samples analyses.
11. Collected at pre-treatment. Please refer to section **5.1** for details on blood and plasma correlative samples analyses.
12. 3.5 mL of serum (for M7824) is collected for pharmacokinetics prior to infusion and at the end of infusion (EOI), on day 2 (24 hours after infusion) during dose 1 (C1D1) and prior to infusion and at the end of infusion of dose 3 (C3D1), prior to infusion during doses 2 (C2D1) and 6 (C6D1 – not shown on the calendar) and at the end of treatment (EOT). Please refer to section **5.1** for collection and processing details.
13. Do not need to repeat PT, PTT, TSH, FT4, amylase, lipase, CK, aldolase, or AchRAb on Day 1 of a cycle if they have been done within the last 21 days. These tests are exempt from the 7 day reporting window for baseline/C1D1 labs covered in footnote 4 above.
14. Pre-treatment correlative studies may be drawn any time prior to drug administration.
15. PK sampling: Any change in the actual drawing time will be documented as a deviation and reported per requirements in section **7.2**.
16. A complete neurological exam is to be performed at baseline and at each visit.
17. Patients may be hospitalized for convenience and logistical reasons for drug administration and/or research blood draws.
18. In addition to adverse events, participants will also be asked specific questions relating to bleeding so that participants with hematochezia, hematuria, gum bleeding, hemoptysis or epistaxis can be identified.
19. If a CT scan is not sufficient to assess response, a PET scan may be added.
20. After 3 cycles, if the patient never develops any infusion related reaction, vital signs are only required pre and post infusion. Before cycle 3 and/or if patient develops an infusion related reaction, vital signs will be collected per section **3.3.3**.
21. Patients with progressive disease on Arm A may then receive 1200mg M7824 every 2 weeks plus temozolomide 200 mg/m2/day on days 1-5 every 4 weeks. The study procedures will follow that of arm C but patients will remain in arm A.

3.5.2 Arm B (M7824 Plus Topotecan)

Procedure	***Screening*** 3	***Baseline*** 4	***Cycle (3 weeks)***					***End of treatment and follow up visits***1
			1			***2***	***3 (forward)***	
			Day 1	***Day 2-5***	***Day 7 & weekly***	***Day 1***	***Day 1***	
History and physical exam 2	X	X				X	X	X
Vital signs 5	X	X				X	X23	X
ECOG Performance Score	X	X				X	X	X
Labs (CBC+diff, acute care panel, hepatic panel, mineral panel, PT/PTT) 6,	X	X	X		X7	X	X	X
TSH, Free T4, Amylase and Lipase		X	X			X	X	
Viral Markers 8	X							
Creatine kinase, serum aldolase, and anti-acetylcholine receptor antibody titers		X	X			X	X	
Pregnancy test 9	X		X			X	X	
Complete neurological examination 10		X	X			X	X	X
Optional biopsies 12			X			X		
Confirmation of diagnosis	X							
Blood/Plasma for Correlative Research Studies13, 17, 19***:***								
Germline exome sequencing			X					
Immune subsets 14			X	X		X		
Immune studies 14			X	X		X	X	X
CtDNA 14			X	X		X	X	X
Paraneoplastic autoantibodies		X11						
PK 15, 17, 18, 19			X	X		X	X	X
Radiological Assessments 22	X			Every 2 cycles (6 weeks)				
Response Evaluation				Every 2 cycles (6 weeks)				
EKG	X	X						
Blood Troponin 17, 19		X						
Adverse Events and Bleeding Events 21			X	→	→	→	→	
Concomitant Medications			X	→	→	→	→	
M7824 19			X			X	X	
Topotecan 16			X			X	X	

Procedure	***Screening 3***	***Baseline 4***	***Cycle (3 weeks)***					***End of treatment and follow up visits1***
			1			***2***	***3 (forward)***	
			Day 1	***Day 2-5***	***Day 7 & weekly***	***Day 1***	***Day 1***	
Hair Follicle Collection (5.1.2)			X	X20		X		

1. End of treatment visit will occur approximately 30 days after the last dose of study drug. If the patient cannot return to the Clinical Center for this visit, a request will be made to collect required clinical labs from a local physician or laboratory. If this is not possible, patients may be assessed by telephone for symptoms. Patients will be monitored for survival via phone call every 4 months after the last dose until death. Same procedures will be performed if patients have progressive disease that does not meet criteria in section **6.3.3**.
2. Physical exam will include skin assessment.
3. Screening must be completed within 2 weeks prior to enrolling subjects onto the protocol.
4. Baseline studies must be completed within 7 days of first dose of drug. Assessments do not need to be repeated on day 1 if performed within 7 days of drug administration. PT, PTT, TSH, FT4, amylase, lipase, CK, aldolase, or AchRAb do not need to be repeated at baseline if done within the last 21 days.
5. Include height (only required at screening/baseline), weight, heart rate, temperature, blood pressure and respiration rate.
6. **CBC with differential**: Neutrophils, Lymphs, Monos, Eos, Basos, WBC, RBC, Hemoglobin, Hematocrit, RBC Indices, MCV, RDW, Platelet; **Acute Care Panel**: Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, eGFR; **Hepatic Panel**: Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin; **Mineral Panel**: Albumin, Calcium, Magnesium (Mg), Phosphorus.
7. Patients on this cohort will need weekly CBC diff during cycle 1.
8. HbsAg, anti-HCV, anti-HIV within 3 months of screening.
9. Only for women of child-bearing potential.
10. A complete neurological exam including assessment of cranial nerve function and muscle strength will be performed at baseline and at day 1 of each cycle.
11. One additional red top tube (10 mL) will be collected for future evaluation of paraneoplastic autoantibodies.
12. Please refer to section **5.1** for details on tumor samples analyses.
13. Collected at pre-treatment. Please refer to section **5.1** for details on blood and plasma correlative samples analyses.
14. Collected on days 1-5.
15. 3.5 mL of plasma and 3.5 mL of serum are collected for pharmacokinetics. For M7824, blood collection for serum is to be performed prior to infusion and at the end of infusion (EOI) during doses 1 (C1D1) and 3 (C3D1), prior to infusion during doses 2 (C2D1) and 6 (C6D1 – not shown on the calendar) and at the end of treatment (EOT). For topotecan, blood collection for plasma is to be performed at the following timepoints during C1D1: Pre, EOI, 0.5, 1, 2, 4 (optional), 8 (optional), 24hr (day 2), 48hr (day 3), 96hr (day 5) post EOI of topotecan. Please refer to section **5.1** for collection and processing details.
16. Topotecan is administered on days 1-5 every 3 weeks.
17. Pre-treatment correlative studies may be drawn at any time prior to drug administration.
18. PK sampling: any change in the actual drawing time will be documented a deviation and reported per requirements in section **7.2**.

19. Patients may be hospitalized for convenience and logistical reasons for drug administration and/or research blood draws.
20. Hair follicles are to be collected Day 2 only, not Days 2-5.
21. In addition to adverse events, participants will also be asked specific questions relating to bleeding so that participants with hematochezia, hematuria, gum bleeding, hemoptysis or epistaxis can be identified.
22. Performed after every 2 cycles. If a CT scan is not sufficient to assess response, a PET scan may be added.
23. After 3 cycles, if the patient never develops any infusion related reaction, vital signs are only required pre and post infusion. Before cycle 3 and/or if patient develops an infusion related reaction, vital signs will be collected per section **3.3.3**.

3.5.3 Arm C (M7824 Plus Temozolomide)

Procedure	***Screening 2***	***Baseline 3***	***Cycle (4 weeks)***									***End of treatment and follow up visits 1***
			1					***2***		***3 (forward)***		
			Day 1 3	***Day 2***	***Day 7***	***Day 15***	***Day 21***	***Day 1***	***Day 15***	***Day 1***	***Day 15***	
History and physical exam 4	X	X				X		X	X	X	X	X
Vital signs 5	X	X				X		X	X	X21	X21	X
ECOG Performance Score	X	X				X		X	X	X	X	X
Labs (CBC+diff, acute care panel, hepatic panel, mineral panel, PT/PTT) 6	X	X	X		X15	X22	X15	X	X22	X	X22	X
TSH, Free T4, Amylase and Lipase		X	X					X		X		
Viral Markers 7	X											
Creatine kinase, serum aldolase, and anti-acetylcholine receptor antibody titers		X	X					X		X		
Pregnancy test 8	X		X			X		X	X	X	X	
Complete neurological examination 9		X	X					X		X		X
Optional biopsies 11			X			X						
Confirmation of diagnosis	X											
Blood/Plasma for Correlative Research Studies 12, 16, 18:												
Germline exome sequencing			X									
Immune subsets			X	X		X		X				
Immune studies			X	X		X		X		X		X
CtDNA			X	X		X		X		X		X
Paraneoplastic autoantibodies		X10										

Procedure	***Screening 2***	***Baseline 3***	***Cycle (4 weeks)***									***End of treatment and follow up visits 1***
			1					***2***		***3 (forward)***		
			Day 1 3	***Day 2***	***Day 7***	***Day 15***	***Day 21***	***Day 1***	***Day 15***	***Day 1***	***Day 15***	
PK **13, 16, 17, 18**			X			X		X				X
Radiological Assessments **20**	X		Every 2 cycles (8 weeks)									
Response Evaluation			Every 2 cycles (8 weeks)									
EKG	X	X										
Blood Troponin **16, 18**		X										
Adverse Events and Bleeding Events **19**			X	→	→	→	→	→	→	→	→	
Concomitant Medications			X	→	→	→	→	→	→	→	→	
M7824 **18**			X			X		X	X	X	X	
Temozolomide **14**			X	X				X		X		
*Hair Follicle Collection (**5.1.2**)*			X	X					X			

1. End of treatment visit will occur approximately 30 days after the last dose of study drug. If the patient cannot return to the Clinical Center for this visit, a request will be made to collect required clinical labs from a local physician or laboratory. If this is not possible, patients may be assessed by telephone for symptoms. Patients will be monitored for survival via phone call every 4 months after the last dose until death. Same procedures will be performed if patients have progressive disease that does not meet criteria in section **6.3.3**.
2. Screening must be completed within 2 weeks prior to enrolling subjects onto the protocol.
3. Baseline studies must be completed within 7 days of first dose of drug. Assessments do not need to be repeated on day 1 if performed within 7 days of drug administration. PT, PTT, TSH, FT4, amylase, lipase, CK, aldolase, or AchRAb do not need to be repeated at baseline if done within the last 21 days.
4. Physical exam will include skin assessment.
5. Include height (only required at screening/baseline), weight, heart rate, temperature, blood pressure and respiration rate.
6. **CBC with differential**: Neutrophils, Lymphs, Monos, Eos, Basos, WBC, RBC, Hemoglobin, Hematocrit, RBC Indices, MCV, RDW, Platelet; **Acute Care Panel**: Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, eGFR; **Hepatic Panel**: Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin; **Mineral Panel**: Albumin, Calcium, Magnesium (Mg), Phosphorus.
7. HbsAg, anti-HCV, anti-HIV within 3 months of screening.
8. Only for women of child-bearing potential.
9. A complete neurological exam including assessment of cranial nerve function and muscle strength will be performed at baseline and at day 1 of each cycle.
10. One additional red top tube (10 mL) will be collected for future evaluation of paraneoplastic autoantibodies.
11. Please refer to section **5.1** for details on tumor samples analyses.
12. Collected at pre-treatment. Please refer to section **5.1** for details on blood and plasma correlative samples analyses.

13. 3.5 mL of plasma and 3.5 mL of serum are collected for pharmacokinetics. For M7824, blood collection for serum must be performed prior to infusion of M7824 and at the end of infusion (EOI) during doses 1 (C1D1) and 3 (C2D1), prior to infusion during doses 2 (C1D15) and 6 (C3D15 – not shown on the calendar) and at the end of treatment (EOT). For temezolomide, blood collection for plasma must be performed at the following timepoints during C1D1: pre temozolomide and 1, 2, 4, 8 (optional), 12 (optional), and 24 hours post treatment temozolomide. Please refer to section **5.1** for collection and processing details.
14. Temozolomide is administered on days 1-5 every 4 weeks.
15. Only CBC with differentials is required on C1D7 and C1D21. These may be performed at a local physician and results faxed to research team.
16. Pre-treatment correlative studies may be drawn at any time prior to drug administration.
17. PK sampling: any change in the actual drawing time will be documented as a deviation and reported per requirements in section **7.2**.
18. Patients may be hospitalized for convenience and logistical reasons for drug administration and/or research blood draws.
19. In addition to adverse events, participants will also be asked specific questions relating to bleeding so that participants with hematochezia, hematuria, gum bleeding, hemoptysis or epistaxis can be identified.
20. Performed after every 2 cycles. If a CT scan is not sufficient to assess response, a PET scan may be added.
21. After 3 cycles, if the patient never develops any infusion related reaction, vital signs are only required pre and post infusion. Before cycle 3 and/or if patient develops an infusion related reaction, vital signs will be collected per section **3.3.3**.
22. Do not need to repeat PT/PTT on day 15 of each cycle.

3.7 COST AND COMPENSATION

3.7.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by an insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.7.2 Compensation

Participants will not be compensated on this study.

3.7.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.8.1 Criteria for removal from protocol therapy

- Progressive disease in Arm A after combination therapy of M7824 and Temozolomide
- Progressive disease in Arms A (after combination therapy), B or C which does not meet criteria in **6.3.3**
- Progressive disease in Arm C documented in two consecutive imaging scans
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in section **3.4**
- Investigator discretion
- Positive pregnancy test

3.8.2 Post therapy follow-up period

Patients will be monitored for survival via phone call every 4 months after the last dose until death.

3.8.3 Off-Study Criteria

- Participant requests to be withdrawn from study
- Investigator decision to end the study
- Death
- Permanent loss of capacity to consent
- Screen failure

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 PERMITTED MEDICINES/INTERVENTIONS

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.

4.1.1 Palliative Radiation

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.

4.2 PROHIBITED MEDICINES

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.
- Prophylactic use of corticosteroids for infusion related reactions is prohibited.
- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin).
- Any live vaccine therapies for the prevention of infectious disease. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines).

Subsequent doses of M7824 should be delayed for 14-28 days for patients undergoing major surgeries, and wound healing should be closely evaluated prior to re-dosing with M7824.

4.3 SUPPORTIVE CARE

4.3.1 Pneumocystis Pneumonia Prophylaxis

Prophylaxis may be provided for pneumocystis pneumonia concomitantly with temozolomide administration and may be continued in participants who develop lymphopenia until resolution to grade 1 or less.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

Please note that tubes and media referenced in this protocol maybe be substituted based on availability with the permission of the PI or laboratory investigator.

Test/assay	Volume (approx.)	Type of tube	Collection time-points	Location of specimen storage/ analysis
Exome sequencing RNA sequencing	Tumor sample, up to 5 cores	N/A	<u>All arms (pre-treatment)</u> • C1D1 <u>Arms A/B (pre-treatment)</u> • C1D1 • C2D1 <u>Arm C (pre-treatment)</u> • C1D1 • C1D15	Doug Figg, NCI/NCI COMPASS
Evaluation of paraneoplastic autoantibodies *	1 x 10 mL	Red Top	<u>Baseline</u>	DTB, NCI
Germline exome sequencing	Blood, 1x 5 mL	Purple top EDTA	<u>All arms (pre-treatment)</u> • C1D1	Doug Figg, NCI/NCI COMPASS
Peripheral blood immune subsets	Blood, 2x 8mL	CPT citrate blue/black	<u>Arm A (pre-treatment)</u> • C1D1 • C2D1 <u>Arm B (pre-treatment)</u> • C1D1-5 • C2D1 <u>Arm C (pre-treatment)</u> • C1D1 • C1D2 • C1D15 • C2D1	DTB, NCI
Immune studies (cytokines, TCR sequencing, Antibodies to TOP1 and TOP1cc, STAT1 phosphorylation IFN V score, others)	Blood, 2x 3.5 mL Blood, 1x 8 mL	EDTA (purple top) CPT citrate blue/black	<u>Arm A (pre-treatment)</u> • C1D1 • C1D2 • C2D1 (and D1 of each subsequent cycle) • EOT <u>Arm B (pre-treatment)</u> • C1D1-5 • C2D1 (and D1 of each subsequent cycle) • EOT <u>Arm C (pre-treatment)</u> • C1D1 • C1D2 • C1D15 • C2D1 (and D1 of each subsequent cycle) • EOT	Doug Figg, NCI

Test/assay	Volume (approx.)	Type of tube	Collection time-points	Location of specimen storage/ analysis
M7824 Pharmacokinetics	Serum 1x 3.5 mL	Serum Separator Tubes (SST®) (gold capped) See section **5.1.1** for handling instructions	• Dose 1: Prior to infusion, End of infusion, 24 hr post infusion +/- 1 hr • Dose 2: Prior to infusion – 1 hr • Dose 3: Prior to infusion, End of infusion + 15 min • Dose 6: Prior to infusion • End-of-treatment visit	Serono EMD Processed by Doug Figg, NCI
Temozolomide Pharmacokinetics	Plasma, 1x 3.5 mL	Na Heparin (green top) tube See section **5.1.1** for handling instructions	C1D1: Pre, 1, 2, 4, 8 (optional), 12 (optional), 24hr post treatment +/- 1hr	Doug Figg, NCI
Topotecan Pharmacokinetics	Plasma, 1x 3.5 mL	Na Heparin (green top) tube See section **5.1.1** for handling instructions	C1D1: Pre, EOI, 0.5 hr, 1hr +/- 15 min, 2 hr +/- 15 min, 4 hr (optional) +/- 30 min, 8 hr +/- 30 min (optional), 24 +/- 1hr, 48 +/- 2hrs, 96hr +/- 4hrs post EOI	Doug Figg, NCI
CtDNA	Plasma, 1x 10 mL	EDTA (purple top)	<u>Arm A (pre-treatment)</u> • C1D1 • C1D2 • C2D1 (and D1 of each subsequent cycle) • EOT <u>Arm B (pre-treatment)</u> • C1D1-5 • C2D1 (and D1 of each subsequent cycle) • EOT <u>Arm C (pre-treatment)</u> • C1D1 • C1D2 • C1D15 • C2D1 (and D1 of each subsequent cycle) • EOT	Doug Figg, NCI
Micronuclei, extrachromosomal elements, apoptotic bodies, gamma	Hair:	Microfuge tubes	<u>Arm A</u> • C1D1 before M7824	Mirit Aladjem, NCI

Test/assay	Volume (approx.)	Type of tube	Collection time-points	Location of specimen storage/ analysis
H2AX, phosphoRPA, phosphoIRF3 and or other inflammatory proteins in the CGAS pathway (**5.1.2**)	15-30 hairs containing a full intact follicle and sheath	containing cold PBS and stored on ice	• C1D2 24 ± 1 hours after M7824 • C2D1 before M7824 <u>Arm B</u> • C1D1 before M7824 plus topotecan • C1D2 24 ± 1 hours after M7824 plus topotecan; prior to day 2 topotecan • C2D1 before M7824 plus topotecan <u>Arm C</u> • C1D1 before M7824 plus TMZ • C1D2 24 ± 1 hours after M7824 plus TMZ; prior to day 2 TMZ • C2D15 before M7824	Contact: Christophe Redon, NCI

Additional assays may be performed to address the exploratory objectives of characterizing the immunomodulatory effects of DNA damage-inducing cytotoxic therapy and predictors of response including but not limited to tumor PD-L1 expression and mutational burden.

* One additional red top tube (10 mL) will be collected and frozen at baseline for future evaluation of paraneoplastic autoantibodies. The antibodies of interest include Anti-Hu, Anti-Ri, Anti-amphiphysin, antineuronal antibodies Ma1 and Ma2 and anti-Yo or anti-Purkinje cell antibody. Since these antibodies are not truly paraneoplastic antibodies, as they can also occur in the non-paraneoplastic setting, but their baseline levels will be of use in the work-up of patients who develop paraneoplastic syndromes on the trial.

5.1.1 Pharmacokinetics Samples

5.1.1.1 M7824

Serum M7824 PK measurements will be done at EMD Serono.

M7824 PK blood draws must be kept in fridge or on wet ice immediately, but they must be processed into serum within 1 hour of collection. A non-additive or coagulation discard tube needs to be drawn first. Once the SST blood is drawn, gently invert the tube 5 times to mix the clot activator with blood. Allow blood to clot for 30 minutes at room temperature in a vertical position. After allowing clot to form, centrifuge the tube for 15 minutes at 1100-1300 x g at room temperature (if refrigerated centrifuge is available, set the temperature at 25 degrees Celsius 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). Carefully collect and aliquot the serum equally in 2 separate micronics tubes. Put the tubes immediately in the freezer

in an upright position at -80 degrees Celsius. If not available, store at –20 degrees Celsius (for a maximum of one month). In case of temperature deviations, the affected samples, the length of deviation and maximum temperature reached should be tracked and promptly communicated to the EMD Serono.

Samples will be processed by the Clinical Pharmacology Program per the guidelines in section **5.2.2** and shipped to EMD Serono.

5.1.1.2 Temozolomide

Temozolomide PK measurements will be performed by Clinical Pharmacology Program.

At each sample time point a discard blood volume appropriate for the IV access device must be drawn prior to the sample. Blood (3 mL) will be drawn from a peripheral vein in the patient's arm and collected in green top tubes containing sodium heparin anticoagulant. Promptly mix the plasma collection tube by gently inverting 6-times, then place it on wet ice, until centrifuged at 1,300 x g for 10 min at 4°C. Samples will be centrifuged for harvesting plasma as soon as possible after collection (within 1 hour). Upon centrifugation, the plasma will be separated from the blood cells using a pipette and transferred into an appropriately labeled polypropylene freezer vial. The samples should be processed to plasma within 30 minutes from centrifugation and the pH adjusted to <4 with the use of 8.5% phosphoric acid (15µL of 8.5% phosphoric acid per 0.5mL of plasma). Plasma will then be stored frozen at -70°C until subsequent batch analysis.

5.1.1.3 Topotecan

Topotecan PK measurements will be performed by Clinical Pharmacology Program.

Topotecan PK samples will be processed per section **5.2.2**. Bioanalytical measurements will be conducted on an ultra HPLC-MSMS system using an assay developed and validated by the Clinical Pharmacology Program.

5.1.2 Hair Follicle Studies

The goal of the hair follicle studies is to assess replicative stress (γH2AX, pRPA), evidence of the kind of DNA damage that might trigger an immune response (micronuclei, extrachromosomal elements) and activation of the CGAS pathway (phosphoIRF3) in hair follicles with an immune checkpoint inhibitor alone or with chemotherapy.

Timepoints for hair follicle collection:

Arm A:

- Cycle 1 day 1: before M7824
- Cycle 1 day 2: 24 ± 1 hours after M7824
- Cycle 2 day 1: before M7824

Arm B:

- Cycle 1 day 1: before M7824 plus topotecan
- Cycle 1 day 2: 24 ± 1 hours after M7824 plus topotecan; prior to day 2 topotecan
- Cycle 2 day 1: before M7824 plus topotecan

Arm C:

- Cycle 1 day 1: before M7824 plus TMZ
- Cycle 1 day 2: 24 ± 1 hours after M7824 plus TMZ; prior to day 2 TMZ
- Cycle 2 day 15: before M7824Assays: Micronuclei, extrachromosomal elements, apoptotic bodies, gamma H2AX, phosphoRPA, phosphoIRF3 and or other inflammatory proteins in the CGAS pathway

Hair follicles will be collected at multiple time points as indicated. At least 24 hours prior to the start of the study, the research nurse will contact Dr. Redon in Dr. Aladjem's lab (LMP/CCR/NCI, Bldg 37/ Rm 5056) to inform him when samples will be taken (Tel: 240-760-7338 (L); 301-760-6275 (Cell); redonc@mail.nih.gov). Dr. Redon will provide tubes for collecting the plucked hairs. The tubes contain ice cold PBS labeled with the date/time of sampling, the protocol, and the unique 900 identifier. Dr. Redon will also provide forceps for plucking. Dr. Redon should be notified of when the samples should be picked up.

Single hairs are plucked from the scalp with forceps. Plucked hairs from eyebrows will be collected only if scalp hairs cannot be provided. The aim is to acquire 15-30 hairs that contain a full intact follicle and sheath (**Figure 3**, image in the middle). If it is determined by Dr. Redon that the hairs collected at baseline do not contain a full intact follicle and sheath, hair collection at the next time-point may be omitted. All the hairs from a patient are placed in microfuge tubes containing cold PBS and stored on ice. Upon delivery in Dr. Aladjem's lab, hairs will be fixed with paraformaldehyde and analyzed under a dissection microscope to select those containing a full intact follicle and sheath. Plucked hairs will be fluorescentlystainedforγ-H2AX and images will be recorded by using a confocal microscope.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

All blood samples (except PBMC immune subsets and germline exome sequencing which will go to DTB lab) will initially be sent to the laboratory of Dr. Douglas Figg, where they will be stored until ready for transfer to the recipient labs for the correlative studies. Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred). For sample pickup, page 102-11964. For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

Tumor samples will be sent to and stored in DTB Lab. Tumor biopsy may be obtained by interventional radiology or surgical resection. The site of biopsy will be determined in discussion with interventional radiologist/ surgeon. If it can be safely obtained, 5 cores of tumor tissue will be collected. Two cores will be sent to pathology- one for confirmation of diagnosis and another will be used for making an FFPE block. The other 3 cores will be flash frozen at the time of biopsy. When the patient is scheduled, the DTB lab will be contacted (by email to Sunmin Lee leesun@mail.nih.gov). Interventional Radiology will call the lab at 240-760-6330 when the patient arrives in IR and a lab member will be present at Interventional Radiology for the procedure. The cores will be flash frozen, 2D barcoded, and stored in liquid nitrogen.

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required. Any transfer of materials to other NIH or non-NIH investigators will occur following NIH Intramural Research Program guidelines.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

If the subject withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

5.2.1 Developmental Therapeutics Branch Lab

Samples will be processed immediately by the DTB laboratory. Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality. Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. Specimen labels will indicate: protocol number, order in which the patient enrolled on the trial, type of sample, collection time, and total volume collected, as appropriate. The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

5.2.2 Clinical Pharmacology Program (Figg Lab)

Upon arrival in the Clinical Pharmacology Program, samples will be centrifuged and transferred into cryovials for storage at -80°C until the time of analysis. In addition, samples will be barcoded.

All PK samples will be bar-coded, with data entered and stored in Labmatrix, utilized by the CPP. This is a secure program, with access to PSDM System limited to defined CPP personnel, who are issued individual user accounts. The program creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients with Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer locations. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (e.g. delay in sample processing, storage conditions on the ward, etc.).

Barcoded samples are stored in bar-coded boxes in locked freezers at either -20°C or -80°C according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services in Frederick, MD. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in

Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per IRB approved protocol) and that any unused samples must be returned to the CPP.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested)

Sample bar-codes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of Labmatrix. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.2.3 Laboratory of Pathology NCI COMPASS Program

Participants may undergo genetic analysis through the NCI COMPASS program for tumor-normal exome and transcriptome. For additional information on consenting, ordering and results, refer to CCR SOP ADGC-5, Tumor/Normal Whole Exome Sequencing: Consenting, Ordering, and Obtaining Results found at https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.3.1 Description of the Scope of Genetic/Genomic Analysis

One of the exploratory endpoints of this protocol is to characterize mutations which predict response and changes associated with the development of chemoresistance. To this end, whole and targeted exome sequencing, RNA sequencing and protein analysis will be performed on tumor samples collected pre-treatment and during treatment. Since analysis of germline variants is essential to fully characterize the somatic mutations identified in exome sequencing, these assays will involve both somatic and germline DNA.

5.3.2 Certificate of Confidentiality

Please see section **13.4**.

5.3.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Subjects will be contacted at this time with a request to provide a sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and

counseling to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

For samples undergoing analysis through the NCI COMPASS, results will be reported per CCR SOP ADGC-5, Tumor/Normal Whole Exome Sequencing: Consenting, Ordering, and Obtaining Results found at https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

Document AEs from the first study intervention through 30 days after the subject received the last study treatment administration. Adverse events that are serious need to be recorded through 30 days after the subject received the last treatment administration. Beyond 30 days after the last study intervention, only adverse events which are serious and related to the study intervention need to be recorded.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
- Coded, linked or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through*:*

- An NIH-funded or approved public repository: clinicaltrials.gov; dbGaP.
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 6 weeks (8 weeks for Arm C and patients in arm A that receive treatment with M7824 + temozolomide after progression on M7824 monotherapy). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [51]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

1. By chest x-ray: ≥20 mm;
2. By CT scan:

a. Scan slice thickness 5 mm or under as ≥10 mm with CT scan

b. Scan slice thickness >5 mm: double the slice thickness

3. With calipers on clinical exam: ≥10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [52-54]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [55] .

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
3. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.3.3 Response Criteria

6.3.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Treatment may be continued despite progression in arm C according to RECIST 1.1 at any time if:

- There are no new or concerning symptoms.
- There is no decrease in ECOG PS.
- The Investigator does not consider it necessary to administer a salvage therapy.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.3.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Treatment may be continued despite progression in arm C according to RECIST 1.1 at any time if:

- There are no new or concerning symptoms.
- There is no decrease in ECOG PS.
- The Investigator does not consider it necessary to administer a salvage therapy.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

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

6.3.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.3.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.3.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

6.3.6 Response Review

Tumor measurements will be performed by the Center for Cancer Research Radiology and Imaging Sciences image processing service.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (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 (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- 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.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32).

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESIs) are serious or nonserious AEs that are of clinical interest and should be closely followed.

AESIs include following:

- Infusion-related reactions including immediate hypersensitivity
- Immune-related adverse events
- TGFβ inhibition mediated skin reactions
- Anemia
- Bleeding AEs

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets a protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4**.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at:

https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Waiver of expedited reporting to CCR

As death/hospitalization due to disease progression are part of the study objectives (ORR, PFS, DOR), and captured as an endpoint in this study, they will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

8.5 Safety Reporting Criteria to the Pharmaceutical Collaborators

8.5.1 EMD-Serono

8.5.1.1 The following reportable events must be submitted to EMD Serono by the Sponsor

The following reportable events must be submitted to EMD Serono within 2 business days or 3 calendar days (whichever comes first) using the mandatory MedWatch form 3500a or equivalent. The Sponsor will assume responsibility for submitting the reportable event(s) below to EMD Serono as well as ensuring that any local reporting requirements are completed in parallel.

- Serious Adverse Events (refer to section **8.1.2**):
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)

8.5.1.2 The following reportable events must be submitted to EMD Serono by the PI or designee

- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.
- In addition, all AEs will be collected in tabulated form and reported to EMD Serono as outlined in the Collaborative Agreement.

- Reporting of Overdose of M7824: An overdose is defined as any dose 5% greater than the highest dose included in the clinical trial protocol. Any overdose must be recorded in the trial medication section of the eCRF. For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or non-serious), must be reported. There are no known symptoms of M7824 overdose to date. The Investigator should monitor closely for AEs should an overdose occur and use his or her clinical judgment in providing symptomatic / supportive care as medically indicated. There is no known antidote for M7824.

Contact information for submission of reportable events to EMD Serono:

Fax: +49 6151 72 6914

OR

E-mail: ICSR_CT_GPS@merckgroup.com

Specifying:

PROTOCOL Number and/or Title

EMD Serono assigned Study Number: MS200647-0045

SUBJECT Number

SITE Number/PI Name

SAE/ONSET DATE

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator.

Forms and instructions can be found here:

https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (**8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal Exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months after the last dose of study drug.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies occurring from the date of the first dose until (120 days) after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to

participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 DATA SAFETY MONITORING BOARD (DSMB)

The safety oversight for this protocol will be under the direction of a DSMB composed of individuals with the appropriate expertise, including a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will operate according to the charter which is reviewed and approved as part of the initial DSMB meeting. The charter will define the DSMB reviews for this protocol including the frequency of cumulative data reviews.

Types of DSMB reviews include:

- Initial review for a new protocol:

Review of the Protocol, ICF, presentation from the PI/designee, study-related documents, halting rules, statistical methods, set triggers for data review or analyses, establish guidelines for monitoring, and finalize Report formats.

- Cumulative data review, at least once a year but may be more frequent.
- Ad hoc review as described in the protocol when:
    - Clinical trial halting criteria are met.
    - Occurrence of a specific time point, or event described in the protocol (e.g., interim analysis (see section **10.4.6.1**), dose escalation criteria are not met resulting in a halt in enrollment)
    - At the request of the Sponsor due to a safety concern or clinical trial conduct issue
- Final review meeting at the end of the clinical trial. Additional meetings are not required unless the Sponsor requests consultation by the committee, or a potential safety concern or study-related issue arises.

Following each DSMB review, the DSMB will provide its recommendations to the Sponsor. The recommendations signed by the Committee Chair and the Sponsor determination on the recommendations signed by the OSRO Director, will be distributed to the PI for the protocol under review.

8.9 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING PLAN

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports

will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

Targeting additional immunosuppressive mechanisms beyond PD-1/PD-L1 and amplifying the immune response by causing DNA damage may drive further improve responses to PD-L1 blockade. Increased DNA damage induced by topotecan and temozolomide will complement the anti-tumor activity of M7824, in recurrent SCLC. The primary objective of the trial is to determine an estimate of efficacy of M7824 plus topotecan or temozolomide relapsed SCLC.

10.2 SAMPLE SIZE DETERMINATION

Arm A (M7824 monotherapy): Initially, 10 patients will be treated with M7824 monotherapy to obtain limited safety and PK data on the monotherapy in this population and to obtain a preliminary estimate of clinical responses to M7824 in SCLC. Based on prior publications using other PD-L1 inhibitors, the estimated response rate for M7824 monotherapy may be 10% or slightly higher. In addition to reporting safety data, the responses noted in arm A will be reported along with two-tailed 80% and 95% confidence intervals to aid in interpretation of the findings in the context of the prior data on this treatment.

- Following completion of the 10-patient Arm A, patients will be assigned to Arm C (M7824 plus temozolomide) and then to Arm B. The combination therapy portion of the trial will use a Simon two stage minimax design in each arm to rule out a 15% objective response rate (p0=0.15) and target a modest response rate of 35% (p1=0.35), with alpha =0.10 (10% probability of accepting a poor combination) and beta=0.20 (20% probability of rejecting a good combination).
- The trial will be conducted as follows:
    - Arm A: Initially, 10 patients will enroll on Arm A.
    - Arm C: Following completion of the 10-patient Arm A, then from that point onward, patients will be assigned to C initially until there are a minimum of 6 evaluable in that arm, and then a pause to the accrual of Arm C will take place. These first patients enrolled in Arm C before the pause in accrual will be treated at dose level 1 and evaluated for toxicity. If 0 or 1 of the first 6 patients experiences a dose-limiting toxicity (DLT), then the remainder of the patients in C will be treated at that dose. If 2 or more patients within the first 6 experience a DLT, then the remaining patients will be treated at dose level -1. If 2 or more patients at dose level -1 experience a DLT, then no further accrual will take place unless a treatment modification is provided via an amendment.

      If there is adequate safety in these initial patients in Arm C, a total of 10 patients (including the 6 patients evaluated for toxicity and future dose setting) will be

enrolled onto the first stage of Arm C. If 0 to 1 of the 10 patients demonstrate a partial response then no further patients will be accrued into arm C. If 2 or more of the first 10 patients have a response, then accrual would continue until a total of 22 evaluable patients have been treated in Arm C. If there are 1 to 5 patients with a response in the total of 22 evaluable patients, then this would be an uninterestingly low rate, while if there were 6 or more patients of the 22 who have a response (27.3%), this would be sufficiently interesting to warrant further study of the combination of these agents in later trials. Under the null hypothesis (15% response rate), the probability of early termination in this Arm is 54.4%.

A separate cohort of patients with extrapulmonary small cell cancer (n=10) will be accrued after the enrollment of the first 6 evaluable SCLC Arm C patients and will only receive the combination therapy of M7824 and Temozolomide.

- Arm B: Once enrollment of SCLC patients in arm C is complete, SCLC patients will be assigned to arm B until there are a minimum of 6 evaluable patients in that arm, and then a pause to the accrual of Arm B will take place. These first patients enrolled in Arm B before the pause in accrual will be treated at dose level 1 and evaluated for toxicity. If 0 or 1 of the first 6 patients experiences a dose-limiting toxicity (DLT), then the remainder of the patients in arms B will be treated at that dose. If 2 or more patients within the first 6 experience a DLT, then the remaining patients will be treated at dose level -1. If 2 or more patients at dose level -1 experience a DLT, then no further accrual will take place unless a treatment modification is provided via an amendment.

  If there is adequate safety in these initial patients in Arm B, a total of 10 patients (including the 6 patients evaluated for toxicity and future dose setting) will be enrolled onto the first stage of Arm B. If 0 to 1 of the 10 patients demonstrate a partial response, then no further patients will be accrued onto this arm. If 2 or more of the first 10 patients have a response, then accrual would continue until a total of 22 evaluable patients have been treated in Arm B. If there are 1 to 5 patients with a response in the total of 22 evaluable patients, then this would be an uninterestingly low rate, while if there were 6 or more patients of the 22 who have a response (27.3%), this would be sufficiently interesting to warrant further study of the combination of these agents in later trials. Under the null hypothesis (15% response rate), the probability of early termination in this Arm is 54.4%.

It is anticipated that up to 2 patients per month may enroll onto this trial; thus, approximately 3 to 4 years may be required to complete accrual of up to 10+22+22+10=64 evaluable patients. The accrual ceiling will be set at 80 to allow for a small number of inevaluable patients and screen failures.

10.3 Populations for Analyses

Modified intention to treat: all patients who receive at least one dose of the intended agent(s) will be included in the statistical analyses performed. Subjects with progressive disease on Arm A who are subsequently treated with M7824 and temozolomide will be included in the analysis for both the monotherapy and combination therapy arm per section **10.4.2** and **10.4.9**.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

Separately by arm, the proportion of evaluable patients who experience a PR or CR will be reported along with a confidence interval. Safety will be evaluated by tabulating and describing the toxicities noted in Arm A and any toxicity as well as DLTs in the first 6 patients of the combination therapy arms.

10.4.2 Analysis of the Primary Efficacy Endpoints

In each of the three arms, the fraction of evaluable patients who experience a PR or CR will be determined and this fraction will be reported along with an 80% and 95% confidence interval. The fraction of patients experiencing a DLT will be reported, by arm, along with descriptions of the type and grade of toxicities identified. Patients treated on Arm A who progress and then receive M7824 plus temozolomide will have their initial response to M7824 counted as the response for the Arm A primary evaluation.

10.4.3 Analysis of the Secondary Efficacy Endpoints

Progression-free survival (PFS), duration of response (DOR) and overall survival (OS) of a combination of M7824 plus topotecan or temozolomide in relapsed SCLC will be considered the secondary endpoints. Each of these estimates will be made using the Kaplan-Meier method, and will be reported along with a 95% confidence interval at 6 months. PFS will begin at the on-study date, and will consider progressions as well as death without progression as an event; OS will also begin at the on-study date and will consider any death as an event. DOR will begin at the date that a PR or CR has been identified and will be shown as continuing until the patient is no longer considered to be responding.

10.4.4 Safety Analyses

Safety of the agent will be assessed by determining the grade of adverse events noted in each patient, and reporting the fraction with grade 3 and grade 4 adverse events. The primary safety analyses will be made based on the patients in Arm A as well as first 6 patients enrolled into each of the two combination therapy arms. Safety data will be presented in summaries, overall and by arm. The safety data will consist of the reporting of all adverse events, and may also include reporting vital signs, physical examination data, and laboratory safety data.

10.4.5 Baseline Descriptive Statistics

Limited demographic and clinical characteristics of all patients will be reported.

10.4.6 Planned Interim Analyses

10.4.6.1 Prior to Phase 2 Expansion

Prior to expanding Arm B, if one or fewer of 3 or 6 participants in the safety run in portion of the study experiences a DLT, a report including the supporting safety data and delineation of each criterion met for phase 2 expansion will be provided to the Sponsor by email (OSROSafety@nih.gov). Sponsor approval is required before additional participants will be enrolled onto the study. The Dose Escalation Determination form on the sponsor website: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions may be used for this purpose. This report will also be provided to the DSMB for review.

10.4.6.2 Efficacy Analysis for Simon 2 stage design

As described in section **10.2**, the two-stage Simon minimax design will include interim evaluations of response after 10 evaluable patients have been enrolled in arms B. After the first restaging scan of the last evaluable patient required for the interim analysis, enrollment to the cohort will be halted to allow for an analysis by the study team. An interim analysis report will be created by the study team to document the number of responses in the first stage, and will be reviewed by the PI and study team. The memo will be provided to and approved by the study sponsor prior to continuation of accrual. Alternatively, if the required number of responses is observed before that time, the memo may be generated, reviewed and provided to the study sponsor at that point without a pause in accrual.

For Arm B, an interim evaluation for futility will take place after 6 patients have enrolled on the arm. If any unusual patterns are detected at this time including trends for early and rapid disease progression, this may warrant an early study closure.

The interim analysis report will also be provided to the DSMB.

10.4.7 Sub-Group Analyses

Results will be reported according to the arm in which the patient was treated, but no other subgroup analyses are planned.

10.4.8 Tabulation of Individual Participant Data

No individual participant data is intended to be reported.

10.4.9 Exploratory Analyses

Exploratory analyses may include the following: evaluating the intratumoral immunogenicity of M7824 plus topotecan or temozolomide; evaluating the pharmacokinetic profile of M7824 alone or in combination with topotecan or temozolomide; characterizing the immunomodulatory effects of DNA damage-inducing cytotoxic therapy; and characterizing gene expression and mutations which predict response and changes associated with response and resistance. Each of these analyses will be done with descriptive statistical methods and with exploratory intent. If any statistical tests are performed, such as comparisons of responders vs. non-responders with respect to mutational status using non-parametric tests, they will be presented without any formal adjustment for multiple comparisons but in the context of the number of tests performed.

A small cohort of patients with extrapulmonary small cell cancer patients will be included. Up to 10 patients with extrapulmonary small cell cancer will receive the combination of M7824 and temozolomide. ORR, PFS and OS of patients with extrapulmonary small cell cancer will be evaluated in an exploratory manner. These results will be considered hypothesis generating and an ORR of 30% or greater will be interesting and may lead to consideration of more definitive future trials in this population.

Patients who are enrolled on Arm A and progress, who subsequently receive M7824 plus temozolomide will have their response and PFS based on the combination evaluated separately from the primary results associated with Arm A; response and PFS evaluations based on the data starting with the commencement of the combination therapy will be considered as an exploratory evaluation.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

A CRADA has been executed with EMD Serono for the supply of M7824 (02999).

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

As previously described, the subjects for this study will include all subjects who meet the eligibility criteria outlined in section **2.1**. No gender, racial, or ethnic groups will be excluded from participation in this trial.

Participants who do not accept blood transfusions will be excluded. As there is a risk of severe bleeding with M7824, participants must be willing to receive blood transfusions if medically necessary for their own safety. Participants must be able to receive blood transfusions in order to minimize the risks of receiving M7824. Another reason for this is that including these patients could compromise the scientific validity of the study. For example, death from blood loss could make it difficult to assess other aspects of the investigational immunotherapy's safety—a primary scientific goal in this early-phase immunotherapy trial, which are carried out in small numbers of participants.

12.2 PARTICIPATION OF CHILDREN

Because no dosing adverse event data are currently available on the use of topotecan or temozolomide in combination with M7824 in subjects <18 years of age, children are excluded from this study, but will be eligible for future pediatrics trials.

12.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **12.4.3**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in policy 403 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

12.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

12.4.1 Risks/Benefits Analysis

The **primary objective** of the trial is to determine a preliminary estimate of efficacy of M7824 plus topotecan or temozolomide in relapsed SCLC.

From a **safety** standpoint, overlapping toxicities are not expected with topotecan or temozolomide (largely consisting of myelosuppression) plus M7824 (immune-related adverse events) since the toxicity profile of individual agents are distinct. Safety data from the dose-escalation study of M7824 in solid tumors as well as preliminary data from expansion cohorts demonstrate a similar safety profile to other checkpoint inhibiting compounds. Presumed TGF-β-mediated cutaneous lesions (e.g. keratoacanthomas and cutaneous squamous cell cancers) are unique to this agent compared to other checkpoint inhibitors, but have been reported with prior TGF-β targeting agents[56]. These lesions have so far developed in ~5% of patients on study, are well managed by surgical excision and spontaneously regress following M7824 withdrawal; the lesions themselves are not an indication for discontinuing this agent. The first 10 patients on study will be treated with M7824 monotherapy prior to enrolling patients on combination arms. Chemotherapy will be administered on the same day as M7824 (similar to the FDA approved chemo-immunotherapy combination for NSCLC). Additional safety data were shared in an EMD investigator letter dated 9/23/2021 which include cases of early progression and death (due to progressive disease, signs and symptoms of progressive disease, or known treatment toxicities) seen more frequently in the M7824 arms than in the standard of care arms (refer to section **1.2.6** for more information). Recent evidence suggests that nuclear DNA can be leaked into the cytoplasm upon DNA damage, thereby promoting activation of cGAS-STING signaling[57-60]. Such cytoplasmic DNA leakage can result from the genotoxic agents and can activate an innate immune response. We recently completed a phase I clinical trial of ATR inhibitor M6620 (previously VX-970) combined with **topotecan**. Interestingly, PBMC immune phenotyping data from this study showed evidence of a favorable immunomodulatory effect on the innate immune system. Mutations in certain genes involved in DNA repair have also been associated with syndromes characterized by unchecked inflammatory response in the absence of exogenous stimuli.

A combination of MGMT activity and mismatch repair (MMR) status of the tumor are important parameters that determine sensitivity to **temozolomide**[61]. Temozolomide is most cytotoxic in cells with low levels of MGMT and intact MMR. MMR-deficient cells do not detect alkylation adducts and hence are resistant to temozolomide even when they lack MGMT. Treatment with temozolomide would select for the MMR-deficient cancer cells, which are immune to temozolomide, but hypersensitive to the immune checkpoint inhibitors[62]. A combination of temozolomide and immune checkpoint inhibition could therefore target both mismatch repair proficient and deficient cancer cells. A safe dose of the M7824 plus temozolomide established in this trial and the biomarker results of this trial would inform the design of a planned biomarker trial of the combination in solid tumors.

12.4.2 Risks

12.4.2.1 Study drug risks

The risks associated with the specific study agents are described in Section **14**. Subjects will be adequately monitored for the occurrence of any possible side effects.

12.4.2.2 Biopsy risks

The risks associated with biopsies are pain and bleeding at the biopsy site. In order to minimize pain, local anesthesia will be used. Rarely, there is a risk of infection at the sampling site. CT guidance may be used in obtaining biopsies (see **12.4.2.3** for radiation risk).

There is a possibility that conscious sedation may be used for the procedure. The common side effects of conscious sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These are generally mild and last no more than a few hours.

12.4.2.3 Radiation risks

The risk of radiation exposure is expected from up to 10 CT scans, 10 PET scans and 2 CT guided biopsies. The total estimated effective dose for one year is approximately 21.6 rem. The risk of getting cancer from the radiation exposure in this study is 2.2 out of 100 (2.2%) and of getting a fatal cancer is 1.1 out of 100 (1.1%).

12.4.2.4 CT contrast risks

Itching, hives or headaches are possible risks associated with contrast agents that may be used during CT imaging. Symptoms of a more serious allergic reaction include shortness of breath and swelling of the throat or other parts of the body. Very rarely, the contrast agents used in CT can cause kidney problems for certain patients, such as those with impaired kidney function.

12.4.2.5 Risks related to blood sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

12.4.2.6 Risk related to hair follicle collection

A side effect of hair follicle collection is pain.

12.4.3 Benefits

The benefits include a possible decrease in the size of the tumor and the scientific knowledge that could be acquired through this trial.

12.5 Consent Process and Documentation

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with local policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at:
https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

12.5.1 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in section **2.3.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 Quality Assurance and Quality Control

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 M7824 (IND # 136852)

14.1.1 Source

M7824 will be provided by EMD Serono.

14.1.2 Packaging and Labeling Information

Packaging and labelling 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.

M7824 drug product is supplied by EMD Serono as a sterile liquid formulation. The liquid formulation, compared with the prior freeze-dried formulation, has the same composition in terms of excipients, qualitatively and quantitatively, except for the addition of water. Of note, there is no change to the drug substance process. The Concentrate for Solution for Infusion (liquid formulation) is packaged at a 10mg/mL concentration in USP / Ph Eur type I 50R vials that are filled with drug product solution to allow an extractable volume of 60 mL (600mg/60 mL). The vials are closed with rubber stoppers with the same composition as used for freeze-dried formulation, but in serum format complying with USP and Ph Eur with an aluminium crimp seal closure.

For applications in clinical studies, the liquid formulation is diluted directly with 0.9% NaCl solution. The estimated volumes of delivery are anticipated to be no more than 250 mL, which are clinically acceptable.

14.1.3 Toxicity

Refer to section **1.2** on nonclinical and clinical data that outlines toxicities associated with M7824. Updated clinical data has been presented in **Table 6** and **Table 7**. In addition, at least 2 instances of nodular regenerative hyperplasia have been observed with the use of this agent. Furthermore, a participant on the study experienced enteric dysmotility which may have resulted in anorexia, weight loss and constipation (related to both M7824 and temozolomide).

Table 6. Adverse Drug Reactions by Preferred Term in the Pooled SafetyAnalysis Set

	Pooled Safety Analysis Set (N=765)	
System Organ Class **Preferred Term**	**All Grades** **n (%)**	**Grade ≥ 3** **n (%)**
Blood and lymphatic system disorders		
Anemia	222 (29.0)	132 (17.3)
Blood loss anemia	2 (0.3)	1 (0.1)
Disseminated intravascular coagulation	2 (0.3)	2 (0.3)
Hemolytic anemia	1 (0.1)	1 (0.1)
Increased tendency to bruise	1 (0.1)	0
Microcytic anemia	1 (0.1)	0
Normocytic anemia	1 (0.1)	1 (0.1)
Cardiac disorders		
Myocarditis *	1 (0.1)	1 (0.1)
Ear and labyrinth disorders		
Ear hemorrhage	2 (0.3)	0
Endocrine disorders		
Adrenal insufficiency *	14 (1.8)	6 (0.8)
Autoimmune thyroiditis *	1 (0.1)	0
Basedow's disease *	1 (0.1)	0
Hyperthyroidism *	4 (0.5)	0
Hypophysitis *	3 (0.4)	2 (0.3)
Hypopituitarism *	2 (0.3)	1 (0.1)
Hypothyroidism *	33 (4.3)	2 (0.3)
Lymphocytic hypophysitis *	1 (0.1)	0
Secondary adrenocortical insufficiency *	1 (0.1)	0
Thyroiditis *		
Eye disorders	3 (0.4)	0
Conjunctival hemorrhage	6 (0.8)	0
Retinal hemorrhage	2 (0.3)	0
Vitreous hemorrhage	1 (0.1)	1 (0.1)
Gastrointestinal disorders		
Abdominal pain	111 (14.5)	15 (2.0)

System Organ Class Preferred Term	Pooled Safety Analysis Set (N=765) All Grades n (%)	 Grade ≥ 3 n (%)
Anal hemorrhage	1 (0.1)	0
Autoimmune colitis *	2 (0.3)	2 (0.3)
Colitis *	5 (0.7)	3 (0.4)
Constipation	137 (17.9)	3 (0.4)
Diarrhea	105 (13.7)	5 (0.7)
Diarrhea *	8 (1.0)	5 (0.7)
Diverticulum intestinal hemorrhagic	1 (0.1)	1 (0.1)
Duodenal ulcer hemorrhage	1 (0.1)	1 (0.1)
Enterocolitis *	1 (0.1)	0
Gastric hemorrhage	2 (0.3)	1 (0.1)
Gastritis hemorrhagic	1 (0.1)	1 (0.1)
Gastroduodenal hemorrhage	1 (0.1)	1 (0.1)
Gastrointestinal hemorrhage	14 (1.8)	8 (1.0)
Gastrointestinal vascular malformation hemorrhagic	1 (0.1)	1 (0.1)
Gingival bleeding	38 (5.0)	0
Hematemesis	6 (0.8)	1 (0.1)
Hematochezia	5 (0.7)	0
Hemorrhagic ascites	1 (0.1)	0
Hemorrhoidal hemorrhage	8 (1.0)	2 (0.3)
Intra-abdominal hematoma	1 (0.1)	1 (0.1)
Intra-abdominal hemorrhage	3 (0.4)	3 (0.4)
Lower gastrointestinal hemorrhage	4 (0.5)	1 (0.1)
Melaena	12 (1.6)	2 (0.3)
Mouth hemorrhage	9 (1.2)	0
Nausea	137 (17.9)	12 (1.6)
Esophageal hemorrhage	1 (0.1)	1 (0.1)
Esophageal varices hemorrhage	2 (0.3)	2 (0.3)
Rectal hemorrhage	5 (0.7)	0
Small intestinal hemorrhage	1 (0.1)	0
Upper gastrointestinal hemorrhage	14 (1.8)	8 (1.0)
Vomiting	100 (13.1)	11 (1.4)
General disorders and administration site conditions		
Asthenia	126 (16.5)	15 (2.0)
Chills	3 (0.4)	0
Fatigue	160 (20.9)	24 (3.1)
Mucosal hemorrhage	2 (0.3)	0
Oedema peripheral	79 (10.3)	2 (0.3)
Pyrexia	141 (18.4)	7 (0.9)
Hepatobiliary disorders		
Hepatic function abnormal *	1 (0.1)	1 (0.1)
Hepatic hemorrhage	1 (0.1)	1 (0.1)
Hepatitis *	2 (0.3)	1 (0.1)
Immune system disorders		
Drug hypersensitivity	1 (0.1)	0
Injury, poisoning and procedural complications	1 (0.1)	0
Contusion	9 (1.2)	1 (0.1)
Extradural hematoma	1 (0.1)	1 (0.1)
Infusion related reaction	26 (3.4)	1 (0.1)

System Organ Class Preferred Term	Pooled Safety Analysis Set (N=765) All Grades n (%)	 Grade ≥ 3 n (%)
Subcutaneous hematoma	1 (0.1)	0
Subdural hematoma	1 (0.1)	1 (0.1)
Investigations		
Alanine aminotransferase increased *	6 (0.8)	4 (0.5)
Aspartate aminotransferase increased	87 (11.4)	19 (2.5)
Aspartate aminotransferase increased *	6 (0.8)	5 (0.7)
Blood creatine phosphokinase increased *	2 (0.3)	1 (0.1)
Blood thyroid stimulating hormone increased *	2 (0.3)	0
Hemoglobin decreased	4 (0.5)	3 (0.4)
Transaminases increased *	1 (0.1)	0
Metabolism and nutrition disorders		
Decreased appetite	189 (24.7)	18 (2.4)
Latent autoimmune diabetes in adults *	1 (0.1)	1 (0.1)
Type 1 diabetes mellitus *	1 (0.1)	0
Musculoskeletal and connective tissue disorders		
Back pain	1 (0.1)	0
Myositis *	2 (0.3)	2 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal cell carcinoma	6 (0.8)	1 (0.1)
Bowen's disease	2 (0.3)	2 (0.3)
Intracranial tumor hemorrhage	1 (0.1)	1 (0.1)
Keratoacanthoma	57 (7.5)	5 (0.7)
Lip squamous cell carcinoma	4 (0.5)	2 (0.3)
Skin neoplasm bleeding	1 (0.1)	0
Squamous cell carcinoma of skin	27 (3.5)	11 (1.4)
Tumor hemorrhage	13 (1.7)	10 (1.3)
Nervous system disorders		
Cerebellar hemorrhage	1 (0.1)	1 (0.1)
Cerebral hemorrhage	1 (0.1)	1 (0.1)
Hemorrhage intracranial	3 (0.4)	3 (0.4)
Hemorrhagic transformation stroke	1 (0.1)	0
Headache	86 (11.2)	5 (0.7)
Immune-mediated encephalitis *	1 (0.1)	1 (0.1)
Renal and urinary disorders		
Acute kidney injury *	3 (0.4)	3 (0.4)
Haematuria	22 (2.9)	3 (0.4)
Nephritis *	1 (0.1)	1 (0.1)
Tubulointerstitial nephritis *	1 (0.1)	1 (0.1)
Reproductive system and breast disorders		
Breast hemorrhage	1 (0.1)	0
Vaginal hemorrhage	4 (0.5)	0
Respiratory, thoracic and mediastinal disorders		
Bronchial hemorrhage	1 (0.1)	0
Cough	87 (11.4)	0
Dyspnea	134 (17.5)	31 (4.1)

System Organ Class Preferred Term	Pooled Safety Analysis Set (N=765) All Grades n (%)	 Grade ≥ 3 n (%)
Epistaxis	81 (10.6)	3 (0.4)
Hemoptysis	41 (5.4)	4 (0.5)
Hemothorax	1 (0.1)	1 (0.1)
Interstitial lung disease *	4 (0.5)	2 (0.3)
Laryngeal hemorrhage	1 (0.1)	0
Pharyngeal hemorrhage	1 (0.1)	0
Pneumonitis *	8 (1.0)	3 (0.4)
Pulmonary hemorrhage	4 (0.5)	2 (0.3)
Respiratory tract hemorrhage	1 (0.1)	0
Skin and subcutaneous tissue disorders		
Actinic keratosis	12 (1.6)	0
Blood blister	3 (0.4)	0
Dermatitis acneiform *	14 (1.8)	2 (0.3)
Drug eruption *	1 (0.1)	0
Ecchymosis	1 (0.1)	0
Erythema *	3 (0.4)	0
Hyperkeratosis	12 (1.6)	2 (0.3)
Lichen planus *	1 (0.1)	0
Pemphigoid *	3 (0.4)	3 (0.4)
Petechiae	2 (0.3)	0
Pruritus	143 (18.7)	2 (0.3)
Pruritus *	38 (5.0)	3 (0.4)
Purpura	5 (0.7)	0
Rash *	42 (5.5)	11 (1.4)
Rash erythematous *	4 (0.5)	0
Rash macular *	8 (1.0)	2 (0.3)
Rash maculo-papular *	44 (5.8)	16 (2.1)
Rash papular *	2 (0.3)	1 (0.1)
Rash pruritic *	9 (1.2)	1 (0.1)
Skin hemorrhage	1 (0.1)	0
Toxic skin eruption *	1 (0.1)	1 (0.1)
Vascular disorders		
Flushing	2 (0.3)	0
Hematoma	6 (0.8)	0
Hypotension	5 (0.7)	0
Shock hemorrhagic	1 (0.1)	1 (0.1)

Source: ADSL 23DEC2020 8:38, ADAE 23DEC2020 9:27,OutputID:T-38-aefrq.

* Immune-related adverse reaction as identified via customized MedDRA PT query and assessed based on adetailed medical review using predefined criteria.

Table 7. Serious Adverse Drug Reactions by Preferred Term (reported for ≥ 2 Participants per PT) Considered Expected for the Purpose of SafetyReporting to Regulatory Authorities in the European Union

System Organ Class Preferred Term	Pooled Safety Analysis Set (N=765) Treatment-related SARs n (%)
Blood and lymphatic system disorders	
Anaemia	6 (0.8)
Endocrine disorders	
Adrenal insufficiency	7 (0.9)
Hypophysitis	2 (0.3)
Gastrointestinal disorders	
Colitis	4 (0.5)
Autoimmune colitis	2 (0.3)
Diarrhea	2 (0.3)
Musculoskeletal and connective tissue disorders	
Myositis	2 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Squamous cell carcinoma of skin	19 (2.5)
Keratoacanthoma	10 (1.3)
Lip squamous cell carcinoma	3 (0.4)
Basal cell carcinoma	2 (0.3)
Bowen's disease	2 (0.3)
Renal and urinary disorders	
Acute kidney injury	2 (0.3)
Respiratory, thoracic and mediastinal disorders	
Pneumonitis	5 (0.7)
Interstitial lung disease	4 (0.5)
Skin and subcutaneous tissue disorders	
Rash maculo-papular	3 (0.4)
Rash	2 (0.3)

Source: ADSL 23DEC2020 8:38, ADAE 23DEC2020 9:27,OutputID:T-39-aefrq.

SAR = serious adverse reactions.

14.1.4 Administration procedures

Refer to section **3.3.3** for details on preparation and administration.

14.1.5 Stability, Storage, and Handling of Drug 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, the freeze-dried M7824 drug product must be reconstituted with 4.5 mL of Water for Injection and diluted with 0.9% NaCl solution (sodium chloride injection) while the liquid formulation must be diluted with 0.9% NaCl solution. The chemical and physical in-use stability for the infusion solution of M7824 in 0.9% NaCl 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. Prepared solution for dosing should be kept at room temperature and used immediately after preparation. Prepared solution for dosing is not intended to be stored; however, if dilution has taken place under all of the controlled aseptic conditions in place at the local site, it may be stored for no more than 72 hours after dilution at room temperature, including infusion time. No other drugs should be added to the infusion containers containing M7824. The drug may be administered using a central or peripheral line.

Calculation of Volume of M7824 and Normal Saline Required: based on flat dosing and a total infusion volume of 250 mL.

Dosage: 1200 mg

The volume of M7824 required to prepare the infusion bag is 120 mL (10 mg/mL vial)

The volume of normal saline required to prepare the infusion bag = 250 mL – 120 mL = 130 mL

Dosage: 2400 mg

The volume of M7824 required to prepare the infusion bag is 240 mL (10 mg/mL vial)

The volume of normal saline required to prepare the infusion bag = 250 mL – 240 mL = 10 mL

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.

14.1.6 Clinical Supplies Disclosure

The Investigator is responsible for ensuring drug product accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of M7824, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to EMD Serono. A copy will be archived for the Investigator Site File.
- M7824 dispensing will be recorded on the appropriate drug accountability forms.
- Trial site M7824 accountability records will include the following:

Confirmation of M7824 receipt, in good condition and in the defined temperature range.

The inventory of M7824 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 M7824.

Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for M7824 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 M7824 provided were fully reconciled.

Unused M7824 must not be used for any purpose other than the present trial. No M7824 that is dispensed to a subject may be redispensed to a different subject.

At the conclusion or termination of this trial, trial site personnel 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. 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 that the M7824 is not used

- after the expiry date, and
- after the retest date unless the M7824 is reanalyzed and its retest date extended.

14.2 TOPOTECAN

Refer to the package insert for toxicities, formulation and preparation, stability and storage and incompatibility information.

14.2.1 Source

Topotecan will be purchased from commercial sources by the NIH CC Pharmacy.

14.2.2 Administration Procedures

Please refer to section **3.3.1**.

14.3 TEMOZOLOMIDE

Refer to the package insert for toxicities, formulation and preparation, stability and storage and incompatibility information.

14.3.1 Source

Temozolomide will be purchased from commercial sources by the NIH CC Pharmacy.

14.3.2 Administration Procedures

Refer to section **3.3.2**.

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16 APPENDICES

16.1 APPENDIX A - PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

16.2 APPENDIX B - TEMOZOLOMIDE DRUG ADMINISTRATION DIARY

Today's Date _____ Cycle #_____
Patient Name_____ Patient Study ID _____
(initials acceptable for patient's name)

Please bring your pill bottle and this form to your physician when you go for your next appointment. ***This is required for study compliance.***

1. Complete one form for each cycle (28 days).
2. You will take ___ (number) ____ mg (dosage) capsules(s) once daily.
3. Taking on an empty stomach will minimize nausea.
4. Capsules should not be opened or chewed. They should be swallowed whole with a glass of water.
If capsules are accidentally opened or damaged, precautions should be taken to avoid inhalation or contact with the skin or mucous membranes.
4. Record the date, the number of pills you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column

Date	Day	# pills and when taken:	Comments
	1		
	2		
	3		
	4		
	5		
Patient's signature and date:			

Study Team will complete this section:
1. Date patient started protocol treatment_____
2. Date patient was removed from study _____
3. Patient's planned daily dose_____
4. Total number of pills taken this month _____

Physician/Nurse's Signature _____