MSK PROTOCOL COVER SHEET

A Phase II Study of Oral CHK1 Inhibitor LY2880070 in Combination with Low-Dose Gemcitabine in Patients with Relapsed or Refractory Ewing Sarcoma, Ewing-like Sarcoma, and Desmoplastic Small Round Cell Tumor

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is an investigator initiated, open-label, single institution, Memorial Sloan Kettering Cancer Center (MSK)-sponsored study to determine the best overall response rate according to RECIST 1.1 in patients with relapsed or refractory Ewing,Ewing-like sarcoma, or desmoplastic small round cell tumor treated with the oral CHK1 inhibitor, LY2880070, in combination with gemcitabine. Patients ≥ 48 kg with these histologies will receive LY2880070 orally twice daily and gemcitabine intravenously. Re-staging evaluations and circulating tumor DNA (cfDNA) plasma collection will occur at baseline and following every even numbered cycle (every 6 weeks). Study therapy will continue unless patients have confirmed progression by RECIST 1.1, intercurrent illness that prevents administration, or the study is no longer thought to be in the best interest of the patient. A total of 16 patients with Ewing sarcoma are planned to be enrolled. An additional 8 patients with Ewing-like sarcoma or desmoplastic small round cell tumor may enroll as part of a pilot cohort which will not be formally evaluated for efficacy as long as the study remains open. The anticipated enrollment and completion times are 24 and 30 months respectively.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

PRIMARY OBJECTIVE: Evaluate the efficacy of LY2880070 in combination with gemcitabine as assessed by investigator determined best overall response rate according to RECIST 1.1 in patients with relapsed or refractory EWSR1-rearranged Ewing sarcoma

SECONDARY OBJECTIVES:

1. Estimate the efficacy of LY2880070 in combination with gemcitabine in up to 8 patients with relapsed or refractory Ewing-like sarcoma or desmoplastic small round cell tumor characterized by variant fusions not limited to but including BCOR-CCNB3 and CIC-DUX4
2. Assess the time to progression and overall survival in patients with relapsed or refractory Ewing sarcoma, Ewing-like sarcoma, or desmoplastic small round cell tumor receiving LY2880070 in combination with gemcitabine
3. Describe the toxicities in patients with relapsed or refractory Ewing sarcoma, Ewing-like sarcoma, or desmoplastic small round cell tumor receiving LY2880070 in combination with gemcitabine

CORRELATIVE OBJECTIVES:

1. Explore baseline characteristics and potential effect of LY2880070 and gemcitabine on proposed biomarkers in pre- and post-treatment biopsies in patients with relapsed or refractory Ewing sarcoma, Ewing-like sarcoma, or desmoplastic small round cell tumor receiving LY2880070 in combination with gemcitabine
2. Correlate tumor genomic profiling data with response in patients with relapsed or refractory Ewing sarcoma, Ewing-like sarcoma, or desmoplastic small round cell tumor receiving LY2880070 in combination with gemcitabine
3. Correlate circulating-tumor DNA (cfDNA) analysis of plasma samples with radiographic assessments in patients with relapsed or refractory Ewing sarcoma, Ewing-like sarcoma, or



desmoplastic small round cell tumor receiving LY2880070 in combination with gemcitabine at baseline and throughout protocol therapy

3.0 BACKGROUND AND RATIONALE

Ewing sarcoma: Ewing sarcoma (ES) is a highly malignant small round blue cell tumor of bone or soft tissue characterized by *EWSR1* fusions, the most common of which is *EWSR1-FLI1* (t(11;22)(q24;q12))[1]. With multimodal treatment, the current 5 year overall and event-free survivals for patients with non-metastatic disease at diagnosis are approximately 72% and 69% respectively[2]. However, approximately 25% of new patients have clinically detectable metastatic disease at diagnosis, and outcomes for these patients remain poor with less than 30% survival after standard therapy. Furthermore, approximately 30% of patients with primary localized disease will develop recurrent disease, the majority within 2 years from initial diagnosis. Patients who develop recurrent ES have a less than 20% event-free survival[3-7]. Overall, nearly 40% of patients diagnosed with ES will eventually die from disease, and new therapies are urgently required to improve outcomes.

Desmoplastic small round cell tumor: Desmoplastic small round cell tumor (DSRCT) is a rare and aggressive small round blue cell malignancy which harbors the pathognomonic EWSR1-WT1 t(11;22)(p13:q12) translocation, originally described in the late 1980s and 1990s by William Gerald, Marc Ladanyi, and Juan Rosai[1]. DSRCT occurs predominantly in adolescent and young adult males and is characterized by abdominopelvic sarcomatosis exhibiting multi-lineage cellular nests of epithelial, muscular, mesenchymal, and neural differentiation admixed with desmoplastic stroma. The exact incidence of DSRCT is poorly defined, although since its histopathologic description at least 850 cases have been described in the literature[2]. Overall survival from retrospective series ranges from 11%[3,4] to 28%[5,6]. Several staging systems have been proposed7, with the most recent from our center using imaging characteristics to define intermediate (no liver involvement or ascites), high risk (either liver involvement or ascites), and very high risk disease (both liver involvement and ascites)[6].

Given the rarity of this disease, no randomized trials addressing treatment have been performed, and nearly all available literature describes anecdotal or retrospective experiences. As such, no standard of care therapy has been agreed upon, although treatment almost always includes high-dose alkylator based chemotherapy[8] and an attempt at complete cytoreductive surgery. The inclusion of whole abdomen/pelvis radiation therapy using an intensity modulated approach is advocated for by our center,[3,9,10] but not by others[5]. Additional consolidative local control approaches include investigational treatment with radiolabeled antibody (NCT01099644), as well as hyperthermic intraperitoneal chemotherapy (HIPEC)[11-14]. Recurrence despite high-intensity, multi-modality therapy is common[15-17]. New therapies to improve outcomes for patients with DSRCT are urgently required.

LY2880070 and CHK1 inhibition: LY2880070 is an oral, selective ATP-competitive small molecule inhibitor of checkpoint kinase 1 (CHK1)[8,9]. Inhibitors in this class are thought to block phosphorylation of CHK proteins disrupting DNA replication, inducing DNA damage, and preventing DNA repair, leading eventually to mitotic catastrophe due to the presence of unresolved DNA breaks[10]. Histologic subtypes with high levels of replication stress and/or defects in DNA damage repair pathways, such



as Ewing sarcoma, may therefore be susceptible to CHK1 inhibition[11]. Additionally, inhibition of CHK1 enhances the activity of DNA-damaging cytotoxic chemotherapeutic agents such as gemcitabine by interfering with cell-cycle control and DNA repair[12].

Gemcitabine and Ewing sarcoma: Gemcitabine is a commercially available pyrimidine antimetabolite used in a wide variety of primarily adult-onsent cancers[13]. A wide variety of schedules of administration are utilized, with doses ranging from 800 to more than 2000 mg/m^2 per dose.

Although gemcitabine has been used in combination regimens, most commonly with docetaxel, for salvage therapy in relapsed and refractory Ewing sarcoma for several decades[14], published literature is minimal and largely limited to retrospective descriptions. One prospective trial for the upfront treatment of Ewing sarcoma administered 2 cycles of gemcitabine and docetaxel as a window therapy and reported 7 of 12 and 5 of 12 evaluable patients experiencing partial response and stable disease respectively[15]. A randomized phase 2 study comparing gemcitabine/docetaxel to gemcitabine alone in metastatic soft tissue sarcomas (none of which were Ewing sarcoma) reported objective response rates of 16% and 8% respectively, with increased toxicity noted in the combination arm[16]. Retrospective experiences of gemcitabine and docetaxel in relapsed and refractory Ewing sarcoma report complete response in 3 of 6 patients[17], progressive disease in 2 of 2 patients[18], and stable disease and progressive disease in 1 each of 2 patients respectively[19]. Finally, the largest available study of gemcitabine alone in soft tissue sarcomas (none of which were Ewing sarcoma) reported partial responses in 7 of 39 patients[20].

There is no published data regarding the use of gemcitabine alone in relapsed and refractory Ewing sarcoma. Based on the limited data described above, we hypothesize minimal, if any, activity of gemcitabine as a single agent in the proposed study population, particularly at the low dose (100 mg/m^2) planned.

LY2880070 and Gemcitabine: Pre-clinical[21-23] and clinical studies[24-26] have confirmed the potential of CHK1 inhibitors to augment the efficacy of a variety of DNA-damaging chemotherapeutic agents. Gemcitabine provides exogenous DNA damage by inhibiting ribonucleotide reductase, and via stalling of replication fork progression forces cells to becomes fully dependent upon CHK1 approximately twelve hours following exposure[27]. The use of CHK1 inhibition therefore sensitizes tumor cells to gemcitabine, and is thought to do so by as much as 10-fold[27]. While single-agent activity of CHK1 inhibitors has been reported[28], a combination approach has been chosen for this trial in an effort to maximize potential clinical benefit. The use of a chemotherapeutic backbone rational to relapsed/refractory Ewing sarcoma (gemcitabine), capable of inducing DNA damage, and with an established recommended phase 2 combination dose has been chosen for this trial.

Replication Stress and DNA damage repair inhibition in Ewing sarcoma, Ewing-like sarcoma, and desmoplastic small round cell tumor: There is a wide body of literature which reveals that Ewing sarcoma exhibits replication stress and may therefore be therapeutically vulnerable to the exploitation of a high level of endogenous DNA damage. Nieto-Soler et al. documented higher basal levels of CHK1 and γH2AX expression in Ewing sarcoma cell lines when compared with



rhabdomyosarcoma and osteosarcoma, and thereafter confirmed *in vitro* and *in vivo* sensitivity of Ewing sarcoma cell lines to ataxia telangiectasia and Rad3 related (ATR) inhibition, a closely related kinase just upstream of CHK1[29]. Additionally, David Gordon and colleagues demonstrated Ewing sarcoma's susceptibility to ribonucleotide reductase inhibitors[30], and thereafter described that this susceptibility was mediated through CHK1[31]. This work is particularly relevant to the current proposal as it specifically describes *in vitro* and *in vivo* anti-tumor effect including synergy between gemcitabine and a CHK1 inhibitor in Ewing sarcoma models. Additional mechanistic follow-up work from this group corroborates the potential therapeutic benefit of targeting CHK1 and related pathways in Ewing sarcoma[32]. Subsequently, Ewing sarcoma was also described to have impaired homologous recombination and inappropriate accumulation of R-loops, both higher when compared with the other predominantly pediatric sarcomas of osteosarcoma and rhabdomyosarcoma[33], further solidifying the role of replication stress in Ewing sarcoma.

Ewing-like sarcomas are an emerging subgroup of small round blue cell sarcomas that share various degrees of morphological, immunohistochemical, molecular, and clinical similarity with Ewing sarcoma. Despite these similarities, Ewing-like sarcomas lack the pathognomonic molecular hallmark of Ewing sarcoma, a translocation between a gene of the RNA-binding TET family (*EWSR1* or *FUS*) with a gene of the ETS-transcription family (*FLI1, ERG, ETV1, ETV4*, or *FEV*) and are increasingly considered a group of distinct entities[34-36]. The rarity of these entities, the lack of universal molecular characterization of small round blue cell tumors being treated worldwide, and the relatively limited period that they have been recognized as a potentially distinct group of diseases has resulted in ad hoc treatment in a fashion similar to Ewing sarcoma without significant evidence basis. Thus far there have been no prospective clinical trials specifically dedicated to the study of systemic therapy in this group of diseases.

Although high-dose chemotherapy is frequently employed in the treatment of Ewing-like sarcomas, its benefit in the various molecular subtypes encompassed remains uncertain[37,38]. *CIC-DUX4* rearranged sarcomas are thought be more aggressive and less chemotherapy responsive than those characterized by *BCOR-CCNB3* rearrangements[35,39]. Additionally, the CIC-DUX4 oncoprotein has been shown to drive oncogenesis through transcriptional upregulation of DNA replication genes, specifically resulting in a dependence on the CCNE-CDK2 cell cycle complex[40] and suggesting that inhibition of cell cycle elements as planned in the current protocol are of potential therapeutic benefit. Furthermore, since the time of this initial finding, additional work has confirmed the dependence of CIC-DUX4 sarcomas on the G2/M checkpoint and confirmed the anti-tumor benefit of DNA damage repair inhibitors in *in vitro* and *in vivo* pre-clinical models of CIC-DUX4 sarcomas[41]. These findings corroborate a growing consensus that fusion driven solid tumors occurring in young people tend to be associated with high levels of replication stress and endogenous DNA damage[42], potentially rendering sensitivity to this class of agents as is being tested in this study[29,32,33,43].

A prior investigator-initiated clinical trial (MSK IRB 19-120, NCT NCT04095221) evaluating another CHK1 kinase inhibitor ACR-368 (formerly prexasertib) in combination with irinotecan in relapsed and refractory DSRCT patients achieved a 32% overall response rate[18] but could not be completed due to discontinuation of drug supply. ACR-368 remains unavailable for further study in DSRCT patients and



will therefore be added as an exploratory cohort to this study to continue to acquire data about the use of these agents in DSRCT patients.

Prior clinical experience with LY2880070: A phase 1B study of LY2880070 monotherapy and LY2880070 in combination with gemcitabine is being conducted (ESPS-001; NCT02632448). During the monotherapy phase of the study, 44 patients with advanced or metastatic solid tumors were treated and the RP2D was established at 200 mg orally twice daily. The most common adverse events were nausea, vomiting and fatigue, and 16% of patients were noted to either achieve stable disease or partial response.

In the combination dose escalation portion of the study, 44 patients with advanced solid tumors were enrolled and 25% experienced clinical benefit (partial response + stable disease)[9]. A RP2D of LY2880070 50 mg orally twice daily on days 2-6, 9-13, 16-20 and gemcitabine 100 mg/m^2 on days 1, 8 and optionally on 15 of a 21-day cycle was established. Treatment was generally well tolerated with similar toxicity profile to the monotherapy regimen including common adverse events of nausea, vomiting, and fatigue.

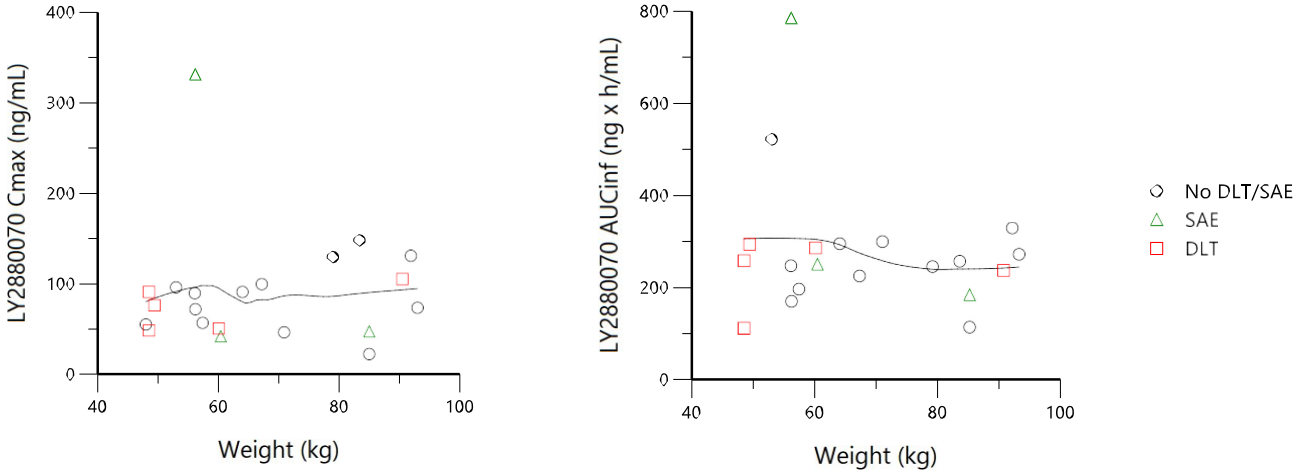
Additional information regarding known toxicities of treatment with LY2880070 are included in section 15.0.

Rationale for dosing strategy: Pharmacokinetic (PK) testing during ESPS-001 revealed that gemcitabine did not have a substantive effect on the PK of LY2880070. Additionally, patients' CYP2D6 metabolizer status did not have a substantive influence on the PK of LY2880070.

Currently, there is no suspension formulation of LY2880070 and drug supply is limited. Given these restrictions but significant enthusiasm for the investigation of DNA damage response inhibition along with an urgent need for new agents in Ewing sarcoma, modified weight-based, instead of age-based, criterion have been developed for this study.

The recommended phase 2 dose (RP2D) as established in the ESPS-001 study is LY2880070 50 mg orally twice daily on days 2-6, 9-13, 16-20 and gemcitabine 100 mg/m^2 on days 1, 8 and optionally on 15, and is therefore considered safe. In general, adolescents who weigh at least 40 kg can receive the same fixed dose as administered to adult patients. Therefore, the lower limit for weight for this study has been set at 40 kg.

Figure 1: LY2880070 exposure versus weight in ESPS-001 patients receiving LY2880070 50 mg and gemcitabine 100 mg/m^2



These data reveal no discernable relationship between weight and exposure in this patient population. However, a high proportion of dose limiting toxicities (3/5) were noted within patients with weight lower than 50 kg. ESPS-001 enrolled patients ranging from 47.9 to 94.3 kg (25th percentile 56.1 kg) and established a recommended phase 2 dose.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is an investigator initiated, open-label, single institution, MSK-sponsored phase II trial to determine the best overall response rate according to RECIST 1.1 in patients with relapsed or refractory Ewing sarcoma, Ewing-like sarcoma, or desmoplastic small round cell tumor treated with the oral CHK1 inhibitor, LY2880070, in combination with gemcitabine.

4.2 Intervention

Patients will receive treatment in 21-day cycles with gemcitabine 100 mg/m^2 intravenously on days 1, 8 and optionally on day 15 (as described in section 10.1) and LY2880070 orally twice daily on days 2-6, 9-13, 16-20 of each 21-day cycle.

Please see section 10.0 for additional details.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

LY2880070: LY2880070 is an investigational agent with Investigational New Drug (IND) number 132,437. MSK is cross-referencing this IND for this protocol.

LY280070 drug substance is a white to pale yellow to beige solid. Capsules for oral administration will be supplied containing 10 or 50 mg LY2880070. The capsules contain only LY2880070 and no other excipients. Each bottle will contain 30 capsules. Gemcitabine will be obtained commercially.

LY2880070 drug product will be supplied by Esperas Pharma, Inc., who is responsible for ensuring that LY2880070 is manufactured according to current Good Manufacturing Practice regulations and requirements.

LY2880070 will be stored at room temperature (15-30˚C).

Handling should be limited to individuals involved in dispensing and administering drug (including the patients for home administration).

Patients will be dispensed LY2880070 capsules at the start of each cycle or weekly if optimal for patient compliance. Patients will be instructed that missed or vomited doses should not be made up.

GEMCITABINE: Gemcitabine will be stored and reconstituted in accordance with the product monograph. Gemcitabine will be administered as per institutional standard. Preparation, dispensing, and storage of study treatments will follow routine pharmacy procedures.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

1. Consent/Assent: all patients and/or their parents or legally authorized representatives must sign written informed consent; assent, when appropriate, will be obtained according to institutional guidelines

2. Weight/Age: patients must be ≥40 kg at the time of study enrollment, but may be of any age

3. Diagnosis: Patients must have histologically documented locally advanced or metastatic disease confirmed at MSK as follows:

    - Main cohort: Ewing sarcoma as molecularly defined by an *EWSR1* fusion with an ETS-transcription factor family member including FLI1, ERG, ETV1, ETV4, and FEV

    - Pilot cohort: Ewing-like sarcomas including CIC-rearranged sarcoma, BCOR-rearranged sarcoma, and sarcomas with a rearrangement between EWSR1 and a non-ETS family gene or desmoplastic small round cell tumor as molecularly defined by an EWSR1-WT1 fusion

      Note: Any patient being enrolled into the pilot cohort that does not have a CIC, BCOR- rearranged sarcoma, or desmoplastic small round cell tumor will be reviewed with study pathologist, Dr. Cristina Antonescu, to ensure the categorization as Ewing-like sarcoma is appropriate.

4. Patients must be able to swallow capsules

5. Therapeutic options: patient's current disease state must be one which has failed standard cytotoxic chemotherapy including cyclophosphamide/doxorubicin/vincristine and ifosfamide/etoposide

6. Disease Status: patients must have measurable disease based on RECIST 1.1

7. Performance level: Karnofsky ≥70% for patients >16 years of age and Lansky ≥70 for patients ≤16 years of age

8. Prior Therapy: patients may have had any number of prior regimens and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment

   Note: Patients who have previously received gemcitabine will be allowed unless they had hypersensitivity or unacceptable toxicity attributed to gemcitabine

   8.1. ≥ 21 days must have elapsed after the last dose of cytotoxic or myelosuppressive chemotherapy and patients must have recovered from the acute toxic effects of these agents (other than alopecia)

   8.2. ≥ 14 days must have elapsed after radiation therapy, and toxicity related to prior radiation therapy must be recovered to grade ≤ 1

   8.3. ≥ 21 days must have elapsed after the last dose of antibody therapy, and toxicity related to prior antibody therapy must be recovered to grade ≤ 1

Organ Function Requirements:

9. Adequate bone marrow function defined as:

   9.1. Absolute neutrophil count (ANC) ≥ 1500/mm^3
   9.2. Platelet count ≥ 100,000/mm^3
   9.3. Hemoglobin ≥ 8 g/dl

10. Adequate renal function defined as estimated glomerular filtration (eGFR) rate ≥ 60 mL/min/1.73m^2:

    10.1. as estimated by CKD-EPI equation for patients ≥ 18 years of age OR

    10.2. As estimated by cystatin C for patients < 18 years of age

11. Adequate liver function defined as:
    11.1. Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal for age
    11.2. AST or ALT ≤ 2.5 x upper limit of normal for patients without liver metastases
    11.3. AST or ALT ≤ 5 x upper limit of normal for patients with liver metastases
    11.4. Serum albumin ≥ 2.5 g/dl

12. Adequate cardiac function defined as:
    12.1. Left ventricular ejection fraction (LVEF) >45% as measured on echocardiogram, cardiac MRI, or MUGA
    12.2. QTc < 470 ms on screening 12 lead electrocardiogram

13. Pregnancy/Contraception
    13.1. Post-menarchal females must have a negative urine or serum pregnancy test at screening and ≤ 24 hours prior to study treatment
    13.2. Males or females of reproductive potential must be willing to use a barrier method of contraception throughout the course of the study and for 6 months after completing study treatment

6.2 Participant Exclusion Criteria

1. Patients for whom the investigator deems that gemcitabine is not appropriate

2. Patients who have an uncontrolled infection

3. Central Nervous System (CNS) Metastases
    3.1. Patients who have symptomatic central nervous system (CNS) metastases.
    Note: patients with treated and asymptomatic CNS metastases are eligible.
    3.2. Patients with CNS metastases requiring corticosteroids for management
    3.3. If the treatment of CNS disease requires anticonvulsants, the dose must have been stable for ≥ 4 weeks.

4. Patients who are pregnant or breast feeding

5. Patients who have a history of Torsades de Pointes, carry a diagnosis of congestive heart failure, or have a family history of prolonged QT syndrome

6. Patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study

7. Patients with known hypersensitivity to gemcitabine

7.0 RECRUITMENT PLAN

The clinical trial will be listed on the clinicaltrials.gov website and will be discussed with relevant patient support groups. Patients will be identified through internal and external referrals to the pediatric and internal medicine sarcoma services.

Potential patients will be approached by investigators with whom they have an existing treatment relationship for discussion regarding screening and enrollment. All participants will be aware that participation is voluntary and that the interventions are investigational. Participants or their legally authorized representatives (LARs) will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration.

Patients will not receive payment for their participation.

Patients are free to withdraw their consent for study participation at any time and will be informed of this right prior to registration.

All eligible patients, regardless of sex, race or otherwise will be approached for participation.

We expect an accrual rate of 10-12 patients per year. The accrual is expected to be completed in 24 months. The total study duration will be approximately 30 months).

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent by following procedures defined in section entitled Informed Consent Procedures. During the registration process, registering individuals will be required to complete a protocol-specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

7.2 Randomization

There is no randomization in this study.

8.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants or their legally authorized representative (LAR) will also be informed that they are free to withdraw from the study at any time. All participants/LAR must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks, and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.0 PRE-TREATMENT/INTERVENTION

The following must be completed within 14 days of starting treatment unless otherwise indicated:

- Signed informed consent and assent, if applicable, within 45 days of starting treatment
- Medical history
- Physical examination
- Vital signs: height, weight, blood pressure, temperature, respiratory rate, oxygen saturation, pulse (HR)
- ECOG or KPS performance status if ≥ 16 years of age or Lansky performance status is < 16 years of age
- Complete blood count with differential
- Comprehensive metabolic panel
- Lactate dehydrogenase
- 2 STRECK tubes for circulating tumor DNA (cfDNA) analyses
- Urine or serum pregnancy test for post-menarchal females of childbearing potential
- 12-lead electrocardiogram
- Echocardiogram, MUGA or cardiac MRI
- Confirmation of RECIST 1.1 measurable disease and tumor assessment via:
    - CT chest/abdomen/pelvis
    - MR of primary site, if applicable
    - PET scan is recommended but not required per protocol
- Collection of archival tissue with minimum of 10 unstained slides if the patient has previously had MSK IMPACT testing, or 25 unstained slides if the patient has not previously had MSK IMPACT testing and has provided consent (lack of availability of archival material will not preclude enrollment)



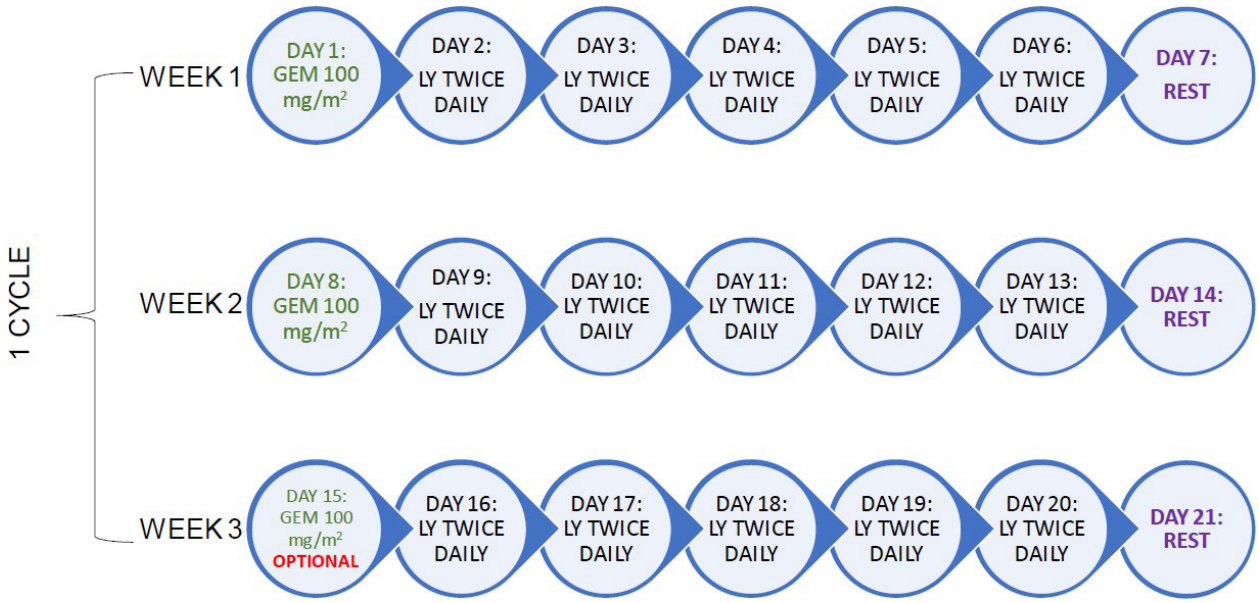
- Biopsy for patients ≥ 18 years of age with safely accessible tumor site for whom archival tissue is unavailable or insufficient

Urine or serum pregnancy test must be repeated within 24 hours prior to the start of treatment.

10.0 TREATMENT/INTERVENTION PLAN

10.1 Administration of Study Drugs

Patients will receive treatment in 21-day cycles with gemcitabine 100 mg/m^2 intravenously on days 1, 8 and optionally on day 15 as described below and LY2880070 orally twice daily on days 2-6, 9-13, and 16-20.



LY2880070 administration:

LY2880070 DOSING	
≥ 40 kg	50 mg orally twice daily

Patients must have platelets ≥100,000 mm^3 to begin cycle 1, and ≥75,000 mm^3 for all subsequent cycles.

Patients will be encouraged to take LY280070 one hour before or two hours after a meal at approximately the same times each day. Administration will be recorded in a medication diary which will be provided to participants by study staff.

Gemcitabine administration: Gemcitabine will be administered as per institutional standard, and should be given 3 times per cycle in the absence of toxicity. Gemcitabine should only be administered on day 15 if participants do not experience hold criteria as detailed in sections 10.4.1, 10.4.2, including:

- ANC <1000/mm^3
- Platelets <75/mm^3
- Grade 3 or higher adverse events *except for*:
    - Grade 3 nausea and vomiting < 3 days duration
    - Grade 3 alkaline phosphatase elevation
    - Grade 3 fever
    - Grade 3 infection
    - Grade 3 electrolyte abnormality if responsive to supplementation
    - ≥ grade 3 electrolyte abnormality that last < 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
    - Grade 3 fatigue < 1 week in duration
    - Alopecia
    - Inadequately treated hypersensitivity reactions
    - Any other grade 3 event lasting < 72 hours which has spontaneously resolved or resolved with appropriate medical intervention without medically significant sequelae that would affect the safe administration of additional protocol directed therapy

Specific questions regarding administration of gemcitabine on day 15 should be directed to the principal investigator.

10.2 Biopsies

When deemed feasible and safe, research biopsies will be performed as detailed in section 11.0 for all patients ≥18 years of age, and will be optional for patients <18 years of age. Biopsies will be performed during screening (only if archival tissue is unavailable or insufficient as described in section 11.0), during week 3 of cycle 1 (on days 15, 16, or 17), and as part of end of treatment evaluations for any patient with confirmed clinical benefit (confirmed stable disease, partial response, or complete response). 4 cores should be collected when clinically feasible (2 cores flash frozen, 2 cores prepared for formalin fixed paraffin-embedded (FFPE). Immunohistochemical (IHC) analyses of CHK1, pCHK1-S345, γH2AX, PDGB5, and cleaved caspase 3/7 will be performed. Frozen tissue will be saved for future whole genome sequencing, RNA-sequencing, and proteomic analyses as indicated by targeted exome and IHC analyses. These samples will be stored for up to 10 years.

Rationale for biopsy collection: Biopsies as planned above have the potential to address critical questions raised by protocol results including:
1) confirmation of inhibition of expected targets

2) mechanisms of response and resistance
3) relationship between molecular profiling and response
4) relationship between protein expression and response

As outlined above, this protocol will generate a rich bank of samples at 3 biologically relevant timepoints (pre-treatment, on treatment, at progression) and will be the only available such resource that we are aware of for adolescent and young adult patients with Ewing sarcoma receiving DNA damage response inhibitors.

In the course of this research it is possible that some patients whose tumors are analyzed through investigational “next-generation” profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding

The following information must be provided to GAP for review:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, saliva)
- Incidental Finding
- Collection Protocol #
- Contact: rtmgapirb@mskcc.org

10.3 Supportive Care Guidelines

Best supportive care and treatment will be given as appropriate per institutional practice and at the investigator’s discretion including antiemetics, antibiotics, packed red blood cell and platelet transfusions, nutritional support, growth factor support etc. Additionally, institutional standards for supportive care for the use of gemcitabine will be followed.

In the event of a suspected infusion-related reaction, institutional guidelines for managing infusion reactions will be followed. For subsequent infusions, premedication with

diphenhydramine hydrochloride and/or other premedication is recommended at the investigator's discretion.

10.4 MODIFICATIONS FOR TOXICITY

General Guidelines for Modifications for Toxicity: If treatment is held for toxicity on day 1 of a cycle, the cycle day number will re-start with day 1 when treatment re-starts. However, once the cycle starts at day 1, it will be continuous regardless of interruptions.

For example:

- if treatment is held on day 1 due to toxicity but then begins 3 days later, the day that the patient restarts therapy will be "day 1" of that particular cycle
- if treatment is held on day 8 due to toxicity each subsequent treatment day until the completion of that cycle will continue in succession despite administration or lack thereof of study therapy

If day 8 or 15 gemcitabine is held for toxicity, it can be given on subsequent days (even if on the same day as LY28800070) if no hold criteria are met.

If a patient requires holding treatment for toxicity for 21 or more days, the patient should only be continued on therapy after discussion with the Principal Investigator, and with a reduction in LY2880070 and gemcitabine as below, even if the first occurrence. In exceptional circumstances, a delay of > 21 days is permitted upon agreement between the treating and principal investigators.

TABLE 1: LY2880070 DOSE REDUCTIONS FOR TOXICITY			
Starting Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
50 mg twice daily	40 mg twice daily	30 mg twice daily	20 mg twice daily

TABLE 2: GEMCITABINE DOSE REDUCTIONS FOR TOXICITY		
Starting Dose	1st Dose Reduction	2nd Dose Reduction
100 mg/m^2	80 mg/m^2	50 mg/m^2

10.4.1 MODIFICATIONS FOR HEMATOLOGIC TOXICITY

HEMATOLOGIC TOXICITY	LY2880070 AND GEMCITABINE DOSE MODIFICATIONS FOR TOXICITY
- Platelets <75/mm^3 on day 1 (other than cycle 1) - Platelets <50/mm^3 on day 8 or 15 - ANC <1000/mm^3 on day 1 (other than cycle 1)	- Check CBC ~every other day at investigator discretion - Hold LY2880070 and gemcitabine until platelets ≥75/mm^3 (Day 1) or <50/mm^3 (day 8 and 15) and ANC ≥1000/mm^3 (Day 1)

	- Consider G-CSF for low ANC using the guidelines below - Consider romiplostim for thrombocytopenia using the guidelines below - Decrease gemcitabine dose level (see Table 2) but maintain LY2880070 if treatment hold is required > 7 days *despite* the addition of growth factor support - Each time an event of similar severity recurs, decrease gemcitabine by one more dose level while maintaining LY2880070 - If a patient reaches 50 mg/m^2 gemcitabine and 10 mg LY2880070 and continues to experience toxicity the patient will be withdrawn from therapy

Guidelines for the Use of Filgrastim: If hold criteria for either gemcitabine or LY2880070 are met as described in the tables above, the use of daily subcutaneous filgrastim is recommended until the patient is able to resume treatment.

Filgrastim will follow institutional guidelines for administration including the following weight-based criteria:

- ≥ 40 to < 60 kg: 300 mcg subcutaneously daily
- > 60 kg: 480 mcg subcutaneously daily

Guidelines for the Use of Romiplostim: If hold criteria for either gemcitabine or LY2880070 are met as described in the tables above, the use of weekly subcutaneous romiplostim as per institutional guidelines is recommended throughout protocol therapy.

10.4.2 MODIFICATIONS FOR NON-HEMATOLOGIC TOXICITY

Grade	Treatment Modification
Grade 1 - 2	- No dose modification required; evaluate causes; provide supportive care - If persistent or recurrent despite maximal supportive measures the patient should continue treatment only if the toxicity does not

	pose a serious health risk or is easily treated at the investigator's discretion
Grade 3 except for: • Grade 3 nausea and vomiting < 3 days duration • Grade 3 alkaline phosphatase elevation • Grade 3 fever • Grade 3 infection • Grade 3 electrolyte abnormality if responsive to supplementation • ≥ grade 3 electrolyte abnormality that last < 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions • Grade 3 fatigue < 1 week in duration • Alopecia • Inadequately treated hypersensitivity reactions • Any other grade 3 event lasting < 72 hours which has spontaneously resolved or resolved with appropriate medical intervention without medically significant sequelae that would affect the safe administration of additional protocol directed therapy	- Hold LY2880070 and gemcitabine until event returns to Grade 1 or baseline - When dosing is resumed, decrease gemcitabine dose by one level (see Table 2) but maintain LY2880070 - Each time an event of similar severity recurs in a subsequent cycle, decrease gemcitabine by one more dose level when dosing is resumed (see Table 2) but maintain LY2880070 - If an event of similar severity recurs at 50 mg/m^2 gemcitabine, decrease LY2880070 by one dose level when dosing is resumed (see Table 1) but maintain gemcitabine - Each time an event of similar severity recurs, decrease LY2880070 by one more dose level while maintaining gemcitabine - If a patient reaches 50 mg/m^2 gemcitabine and 10 mg LY2880070 and continues to experience toxicity the patient will be withdrawn from therapy
Grade 4 except for: • Grade 4 alkaline phosphatase elevation • Grade 4 fever that is appropriately treated and resolves • Grade 4 infection that is appropriately treated and resolves	Permanently discontinue study treatment

11.0 EVALUATION DURING TREATMENT/INTERVENTION

Assessments	Screening	Cycles 1-N						Post-Treatment	
		Day #							
	-14 to 1	1	2 - 6	8 (+1)	9 - 13	15 (+1)	16 - 20	End of Treatment[10]	Follow-up every 3 months
Informed Consent	Within 45 days								
Medical History	X	X							
Physical Exam	X	X		X		X		X	
Vital signs[1]	X	X		X		X		X	
ECOG/KPS	X	X		X		X		X	
Review of Concomitant Medications	X			X		X		X	
Review of Adverse Events	X	X		X		X		X	
Hematology and Chemistry[2]	X	X[2]		X		X		X	
Lactate Dehydrogenase	X	X							
Pregnancy Test	X	X[9]							
ECG	X							X	
Echocardiogram or MUGA or Cardiac MRI	X							X	
cfDNA collection[3]	X				At the same time as the tumor assessment			X	
Tumor Assessment[4]	X				Between days 14-21 of scan cycles as outlined in footnote 4			X	
Collection of Archival Tissue[5]	X								
Research Biopsy[6]	X					Day 15, 16, or 17 of cycle 1		X (if tx stopped due to POD)	
Survival Assessment[7]									X
LY2880070			X		X		X		
Gemcitabine		X		X		X[8]			

1. Vital signs include sitting blood pressure, pulse, oxygen saturation, temperature
2. Hematology includes a CBC and chemistry includes a comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, protein, albumin, bilirubin, AST, ALT, alkaline phosphatase)
    - If hematologic toxicity is experienced CBC should be repeated approximately every other day to determine timing of re-start of medications

- Hematology and Chemistry do not need to be repeated on cycle 1, day 1 if obtained within the preceding 7 days

3. cfDNA collection is 2 STRECK tubes each containing 10 mLs of blood; collection occurs during screening and concurrently with each tumor assessment
4. Tumor assessment should include CT or MR of sites involved with disease; PET scan with each tumor assessment is recommended but not required; tumor assessment occurs during screening, every 6 weeks for 18 weeks, and every 9 weeks thereafter between days 14 and 21 of the cycle (as timed from the start of the current cycle)
5. For patients ≥ 18 years of age:
    - If sufficient archival tissue (10 unstained slides if IMPACT testing already performed and 30 unstained slides if IMPACT testing NOT already performed; separate consent is required for IMPACT testing), then a research biopsy during screening may be omitted
    - If archival tissue is unavailable or insufficient for research purposes, a biopsy will be performed if deemed safe and feasible

    For patients < 18 years of age:
    - If sufficient archival tissue is available (10 unstained slides if IMPACT testing already performed and 25-30 unstained slides if IMPACT testing NOT already performed; separate consent is required for IMPACT testing) analyses will be performed using this tissue
    - Research biopsies will be optional
    - Lack of archival tissue will not preclude enrollment
6. Patients ≥ 18 years of age will undergo biopsies as follows:
    - During screening, only if archival tissue is unavailable as above
    - During week 3 of cycle 1, on days 15, 16, or 17
    - If a patient experiences confirmed clinical benefit (stable disease, partial response, complete response), a biopsy will also be obtained at the time of progression (i.e. as part of end of treatment evaluations)
7. Survival assessment may be done via clinic visit, phone call or medical record review; the intent is to confirm whether the patient is alive and receiving therapy, alive and not receiving therapy, or deceased
8. Gemcitabine administration is optional on day 15 as described in section 10.1
9. Pregnancy test is required on day 1 of each cycle and may be done anytime within 24 hours prior to study treatment.
10. The End of Treatment visit will occur within 4 weeks after the last dose of LY2880070



12.0 CRITERIA FOR REMOVAL FROM STUDY

Treatment may continue until one of the following applies:

- Progression of disease
- Intercurrent illness or other condition precluding further treatment
- Intolerance of study treatment
- Patient withdrawal from treatment
- Inability to comply
- End of study

Patients who discontinue treatment will remain on study for collection of survival data unless they withdraw consent or until the study ends.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

All patients will undergo a baseline staging CT scan of the chest/abdomen/pelvis, PET scan (optional) and MRI of the affected area if deemed necessary by the treating physician. Response evaluations will occur sometime during days 14-21 of each even numbered cycle as described in section 11.0.

Response and progression will be evaluated using the criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1 (Primary response criteria)[44]. 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.

13.2 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 for non-nodal lesions and short axis for nodal lesions) as ≥20mm by chest x-ray, as ≥10mm with CT scan or MRI, or ≥10mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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.

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there is evidence of progression after radiation therapy.

Non-measurable disease – All other lesions (or sites of disease), including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm 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.

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. 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. The baseline sum diameters will be used as a reference to further characterize any objective 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.

13.3 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 not more than 14 days 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 portion of study. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion being followed cannot be imaged but are assessable by clinical exam.

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).

13.3.1 Primary Response Criteria (RECIST 1.1)

13.3.1.1 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 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).

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

13.3.1.2 Evaluation of Non-Target Lesions

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

Non-CR/Non-PD: Persistence of one or more non-target lesion.

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.

13.3.1.3 Evaluation of Best Response

The best response is defined as the best response recorded during the 6 months following the start of the treatment. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Best Response	Best Response for This Category also Requires:
CR	CR	No	CR	≥ 4 wks. Confirmation
CR	Non-CR/ Non-PD	No	PR	≥ 4 wks. Confirmation
PR	Non-CR/ Non-PD	No	PR	
SD	Non-CR/ Non-PD	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	

* 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.

13.4 Confirmation of response

Complete or partial response will only be claimed if the criteria for each are met at a subsequent time point (≥4 weeks later). No confirmation of progressive disease will be required.

13.4.1 Special note on target lesions that become "too small to measure"

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes, lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

13.5 Not evaluable (NE)

When no imaging/measurement is done at all at a particular time point, the patient is considered not evaluable (NE) at that time point.

13.6 Early death

If the patient has no repeat tumor assessments following initiation of study therapy resulting from the death of the patient due to disease or treatment, it is considered early death.

13.7 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time be recorded as “symptomatic deterioration”. Every effort should be made to document objective progression even after discontinuation of treatment.

13.8 Time-to-progression (TTP) and Overall Survival (OS)

TTP is defined as the period from the start of study treatment until recurrent or progression of disease (POD) is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study). Patients alive without documented recurrence or progression will be censored at their date of last contact. Death from causes other than disease progression before evidence of disease progression will be considered as a competing event.

OS is defined as the observed length of life from start of study treatment to death. Patients alive will be censored at their date of last contact.

13.9 Criteria for Study Endpoint Evaluability

Evaluable for toxicity – All patients will be evaluable for toxicity from the time of their first dose with LY2880070.

Evaluable for efficacy – Patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable and determined to be non-responders. Patients who are not evaluable for response will be replaced.

14.0 BIOSTATISTICS

Populations for analysis

The Safety set will include all patients evaluable for safety (as defined in section 13.9). The Efficacy set for the main cohort will include all patients with EWSR1-rearranged Ewing sarcoma (not Ewing-like sarcoma) evaluable for efficacy (as defined in section 13.9). The Efficacy set for the pilot cohort will include patients accrued in the pilot cohort who are evaluable for efficacy (as defined in section 13.9).

Rationale for primary endpoint

A systemic review of phase I/II clinical trials either specific for or containing a specific relapsed/refractory Ewing sarcoma stratum conducted between 2005 and 2018 revealed overall poor response rates across more than 750 patients evaluable for response[45]. The largest randomized experience with chemotherapy in relapsed/refractory Ewing sarcoma (primarily first relapse) is being evaluated in the ongoing rEECur study on which patients receive cyclophosphamide/topotecan, irinotecan/temozolomide, gemcitabine/docetaxel, or high-dose ifosfamide. Interim results shared in 2020 revealed a lack of efficacy in the gemcitabine/docetaxel arm and a lower than expected response rate of 20% in the irinotecan/temozolomide arm[46]. Additional studies evaluating the insulin-like growth factor 1 receptor (IGF1R) inhibitors ganitumab, robatumumab, and R1507 demonstrated response rates of 6%[47], 7%[48], and 10%[49] respectively. A more recent phase 2 trial evaluating the use of multi-kinase inhibitor cabozantinib revealed 26% of 39 patients achieved partial responses[50], although another phase 2 study conducted by the Children's Oncology Group (ADVL1622) including 13 Ewing sarcoma patients reported no responders, and only 2 of 13 patients with stable disease[51]. These data in combination with the size of the cohort based on the rarity of the disease and scarcity of resources, support a null response rate of 5% and a 25% response rate as positive and worthy of further investigation.

There is no accepted standard of care specifically for patients with relapsed/refractory Ewing-like sarcoma, and these patients are often treated analogously to those with Ewing sarcoma.

Primary Objective

The primary objective is to evaluate the efficacy of LY2880070 in combination with gemcitabine in patients with Ewing sarcoma. The endpoint is the best overall response rate during the first 6 months of treatment according to RECIST 1.1.

The study will include 16 patients. The ORR will include complete response and partial response (CR+PR) as defined using RECIST 1.1 criteria. ORR along with exact 95% confidence interval will be given.

Following an exact, single-stage, phase II design, 16 patients will distinguish between an unpromising ORR of 5% and a promising ORR of 25%, with a type-I error of 5% and a power of 80%. If 3 or more responses are observed, the combination of LY2880070 with gemcitabine in patients with Ewing sarcoma will be considered promising. These 16 patients will comprise the "efficacy set" for the main cohort.

Secondary objectives

Time-to-progression and overall survival are defined in section 13.8. Time-to-progression will be estimated using a cumulative incidence curve with death from other causes as a competing risk, using the Aalen–Johansen estimator. Overall survival will be estimated using Kaplan-Meier curves. This will be estimated on both the safety and efficacy sets separately.

Up to 8 patients with Ewing-like sarcoma can be included as part of a pilot cohort. The pilot cohort will open at the same time as the main cohort, and remain open as long as the main cohort is accruing. Patients with Ewing-like sarcoma with measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will still be assessed for estimated response rate. ORR along with exact 90% confidence interval will be determined. This analysis may be used to make hypotheses about the efficacy of LY2880070 and gemcitabine in patients with Ewing-



like sarcoma for further studies, and will be based on the patients from the efficacy set for the pilot cohort.

Adverse event graded using CTCAE v5.0 (as described in section 15) will be tabulated for all types and grades. This analysis will be done for all patients treated on the study, separately for the main and the pilot cohort.

Correlative objectives

IHC analysis will be performed on pre- and post-treatment biopsy samples, and any change will be described. Pre- and post-treatment levels of expression of measured proteins, and their changes if any, will be described with respect to baseline characteristics in patients and their tumors. Results from these analyses will be primarily descriptive and explorative, and no statistical tests will be performed.

Tumor genomic profiling will be described for responders versus non-responders. Frequency of gene mutations will be compared between responders and non-responders using Fisher exact tests. Benjamini-Hochberg procedure will be used to control for the false discovery rate.

The distribution of cfDNA (measured continuously) according to radiographic findings (responders versus non-responders) will be described graphically and compared using a Mann-Whitney-Wilcoxon test at baseline, and will be described in subsequent timepoints.

Correlative studies will be done on all patients treated on the study, separately for the main and the pilot cohort.

Stopping Rule for Toxicity

The number of patients who require reductions of LY2880070 or gemcitabine, and/or must stop investigational therapy due to grade 4 toxicity will be monitored. If 10% of patients require reductions in LY2880070 or gemcitabine or discontinuation due to a grade 4 event, this toxic event is acceptable, while if 30% of patients require reductions/discontinuation, this event is not acceptable. The number of dose reductions/discontinuations for patients ≥48 to <56 kg and ≥56 kg will be noted throughout the study. If the number of patients with these events reaches the numbers below, then the accrual will be suspended, and the end of the trial for excessive toxicity will be discussed.

Number of failures needed to stop the study	Failure rate in the population	Probability to stop for toxicity
2 within the first 4 patients 3 within the first 9 patients 4 within the first 15 patients 5 within the first 16 patients	0.10	0.11
	0.30	0.75

15.0 TOXICITIES/RISKS/SIDE EFFECTS

Table 3 summarizes serious adverse events (SAEs) reported during the ongoing study ESPS-001 as March 2, 2020.

Table 3 Serious Adverse Events (Study ESPS-001)

	LY monotherapy N=39 n (%) | n*	LY + GEM N=44 n (%) | n*	LY monotherapy Poor metabolizer N=5 n (%) | n*
Number of patients with at least one SAE	12 (30.8) | 19	13 (29.5) | 25	1 (20.0) | 1
Abdominal pain	0	3 (6.8) | 3	0
Dyspnea	1 (2.6) | 1	2 (4.5) | 2	0
Pyrexia	1 (2.6) | 1	2 (4.5) | 2	0
Pulmonary embolism	2 (5.1) | 2	0	0
Sepsis	2 (5.1) | 2	0	0
Vomiting	1 (2.6) | 1	0	1 (20.0) |1
Abscess	1 (2.6) | 1	0	0
Alanine aminotransferase increased	0	1 (2.3) | 1	0
Aspartate aminotransferase increased	0	1 (2.3) | 1	0
Back pain	0	1 (2.3) | 1	0
Cardiac failure	1 (2.6) | 1	0	0
Central nervous system hemorrhage	0	1 (2.3) | 1	0
Cerebrovascular accident	0	1 (2.3) | 1	0
Chills	0	1 (2.3) | 1	0
Constipation	0	1 (2.3) | 1	0
Duodenal obstruction	0	1 (2.3) | 1	0
Embolism	0	1 (2.3) | 1	0
Gastrointestinal hemorrhage	1 (2.6) | 1	0	0
Hypotension	0	1 (2.3) | 1	0
Intestinal obstruction	0	1 (2.3) | 1	0
Large intestine perforation	1 (2.6) | 1	0	0
Localized infection	1 (2.6) | 1	0	0
Liver abscess	1 (2.6) | 1	0	0
Metastases to bone	1 (2.6) | 2	0	0
Nausea	1 (2.6) | 1	0	0
Pain	0	1 (2.3) | 1	0
Pelvic pain	0	1 (2.3) | 1	0
Pneumonia	0	1 (2.3) | 1	0
Pleural effusion	0	1 (2.3) | 1	0
Pubis fracture	1 (2.6) | 1	0	0
Pulmonary hemorrhage	1 (2.6) | 1	0	0
Respiratory disorder	0	1 (2.3) | 1	0
Small intestine obstruction	1 (2.6) | 1	0	0
Syncope	0	1 (2.3) | 1	0

	LY monotherapy N=39 n (%) | n*	LY + GEM N=44 n (%) | n*	LY monotherapy Poor metabolizer N=5 n (%) | n*
Wound infection	0	1 (2.3) | 1	0

Abbreviations: LY = LY2880070; N = number of patients in a treatment arm; n = number of patients with an event; n* = number of events; GEM = gemcitabine

Table 4 summarizes treatment-emergent adverse events (TEAEs) reported in ≥10% patients receiving LY2880070 monotherapy and combination therapy. The most commonly reported TEAEs were vomiting, nausea, fatigue, decreased appetite, and anemia. The majority of the reported TEAEs were either from system organ class gastrointestinal disorders or blood and lymphatic system disorders.

Table 4 Treatment-emergent Adverse Events (Study ESPS-001)

Preferred Term	Reported in ≥10% patients receiving LY2880070 monotherapy N=44 n (%)	Reported in ≥10% patients receiving LY2880070 combination therapy N=44 n (%)
Number of patients with at least one TEAE	44 (100)	43 (97.7)
Vomiting	29 (65.9)	26 (59.1)
Nausea	27 (61.4)	28 (63.6)
Fatigue	19 (43.2)	27 (61.4)
Decreased appetite	17 (38.6)	15 (34.1)
Constipation	16 (36.4)	14 (31.8)
Diarrhea	13 (29.5)	10 (22.7)
Abdominal pain	10 (22.7)	9 (20.5)
Back pain	9 (20.5)	10 (22.7)
Dizziness	8 (18.2)	5 (11.4)
Headache	8 (18.2)	9 (20.5)
Anemia	8 (18.2)	15 (34.1)
Oedema peripheral	6 (13.6)	9 (20.5)
Arthralgia	5 (11.4)	0
Dysgeusia	5 (11.4)	0
Dyspnea	5 (11.4)	12 (27.3)
Myalgia	5 (11.4)	0
Pyrexia	0	14 (31.8)
Aspartate aminotransferase increased	0	10 (22.7)
Alanine aminotransferase increased	0	10 (22.7)
Cough	0	8 (18.2)
Pain in extremity	0	7 (15.9)
White cell blood count decreased	0	8 (18.2)
Chills	0	7 (15.9)
Hypomagnesaemia	0	5 (11.4)
Neutropenia	0	7 (15.9)

Abbreviations: n = number of patients at each level of summarization; TEAE = treatment-emergent adverse event

Note: The TEAEs are listed in decreasing order of events reported in LY2880070 monotherapy arm

All adverse events (AEs), either reported by the patient or observed by the study staff, will be recorded for up to 30 days after the end of study treatment. AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

An AE is any untoward medical occurrence temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.



Events that do NOT meet the definition of an AE include:

- Medical or surgical procedure; the condition that leads to the procedure is the AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease or condition present or detected at the start of the study that do not worsen
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the patient's condition

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (for example, a screening biopsy) must be reported. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- date the adverse event occurred

- adverse event
- grade of the event
- relationship of the adverse event to the treatment(s)
- if the AE was expected
- detailed text that includes the following:
    - explanation of how the AE was handled
    - description of the participant's condition
    - indication if the participant remains on the study
- if an amendment will need to be made to the protocol and/or consent form
- if the SAE is an Unanticipated Problem

15.2. SAE Reporting to Esperas, Inc.

Esperas, Inc. will be notified of any serious adverse event within 24 hours of study staff notification for any event occurring on a business day, and on the next business day for any event occurring on a weekend or holiday. Redacted SAE reports will be emailed to Caroline Fortier (caroline.fortier@esperasinc.com) with a cc to Virginia Wood (wood_virginia@lilly.com) and Patricia Smith (smith_patricia_s@lilly.com).

16.0 PROTECTION OF HUMAN PARTICIPANTS

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

A clinical research coordinator (CRC) will be assigned to the study. The CRC will ensure compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into a secure internet-based system, Medidata Rave. Source documentation will be available to support the electronic record. MSK will be the

data coordinating center for this single institution protocol. The principal investigator will maintain ultimate responsibility for the clinical trial.

16.3 Quality Assurance

Regular registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, as an ongoing review process.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety, and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.



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18.0 APPENDICES

Appendix 1: Pill Diary

Appendix 2: Investigational Scan Considerations

Patients on study may have investigational CT guided biopsies performed as follows:

- During screening, only if archival tissue is unavailable
- During week 3 of cycle 1, on days 15, 16, or 17
- If a patient experiences confirmed clinical benefit (stable disease, partial response, complete response), a biopsy will also be obtained at the time of progression

Patients undergoing investigational CT guided biopsies are exposed to an additional 0.626 Gy (+/- 0.132) dermatologically, an additional 29.9 mSv in for scan done in helical mode and an additional 18.9 mSv for scans done in axial mode.

It is estimated that each patient will have up to 3 additional scans for CT-guided biopsies.

The informed consent will include the necessary risk language on contrast use and low-level radiation.