Abbreviated Title: SG in gynecologic cancers
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Title: Phase II Pilot Study of Sacituzumab Govitecan for Relapsed Ovarian, Endometrial, and Cervical Carcinomas

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Drug Name:	Sacituzumab govitecan (IMMU-132; Trodelvy)
IND Number:	166593
Sponsor:	NCI Center for Cancer Research
Manufacturer:	Gilead Life Sciences, LLC
Supplier	Gilead Life Sciences, LLC

PRÉCIS

Background:

- Human trophoblast cell-surface marker (TROP2) is a surface glycoprotein originally identified in human placental tissue and highly expressed in gynecologic malignancies. TROP2 overexpression in ovarian, endometrial, and cervical cancers is linked to tumorigenicity and poor overall survival.
- Sacituzumab govitecan (SG) is an antibody-drug conjugate (ADC) of an IgGκ1 monoclonal antibody targeting TROP2 with a chemotherapeutic payload of SN-38. SN-38 is an active metabolite of irinotecan and acts as a topoisomerase I inhibitor.
- Preclinical data suggest that SG induces DNA damage, replication stress, and tumor shrinkage in drug-resistant ovarian, endometrial, and cervical cancer *in vitro* and *in vivo* preclinical models.
- Further clinical and translational studies are needed to better understand SG's clinical activity and biology in relapsed gynecologic cancer patients.

Objective:

- To determine the objective response rate (ORR) of sacituzumab govitecan (SG) in participants with recurrent gynecological malignancies, calculated for each individual tumor histology by RECIST v1.1.

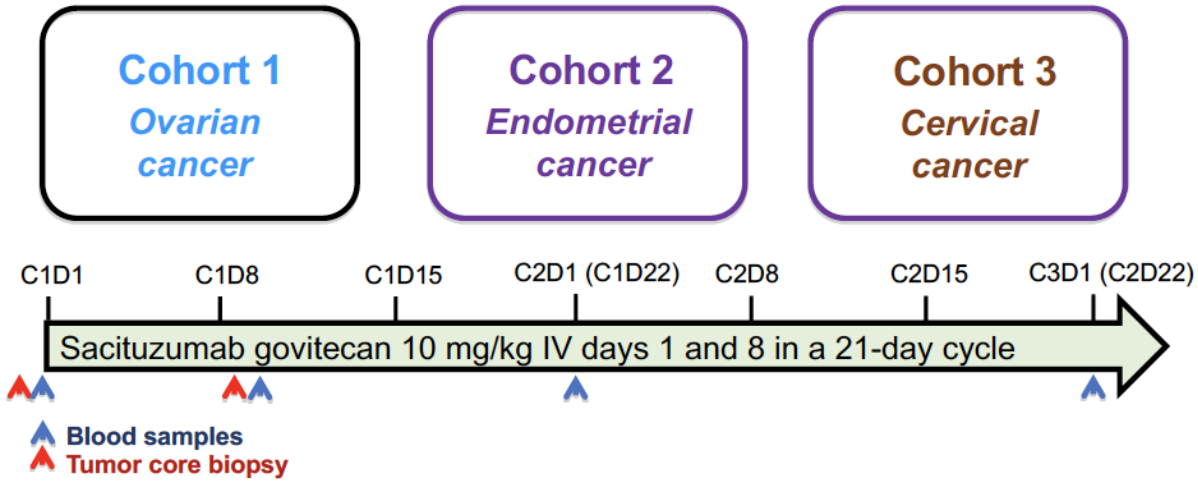
Eligibility:

- Age ≥ 18 years
- ECOG performance status ≤ 1
- Histologically documented, recurrent platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer (referred to as ovarian cancer); recurrent endometrioid or serous endometrial cancer; or recurrent epithelial cervical cancer
- At least two prior systemic therapeutic regimens
- Measurable disease by RECIST v1.1 criteria with lesions that can be safely biopsied
- No prior TROP2-targeting ADC

Design:

- This is an open label, non-randomized Phase II pilot study with one Arm.
- SG will be administered intravenously (IV) at 10 mg/kg on Days 1 and 8 each 21-day cycle.
- Tumor assessments will be time-based: every 9 weeks (± 1 week) for the first year and every 12 weeks (± 1 week) thereafter until disease progression. Pre-treatment biopsies and serial blood samples will be collected for the correlative studies.
- Treatment will be given for a maximum of 5 years or until disease progression or unacceptable toxicities.
- Up to 66 evaluable participants will be enrolled.

Schema


Cohort 1
Ovarian cancer
Cohort 2
Endometrial cancer
Cohort 3
Cervical cancer
C1D1
C1D8
C1D15
C2D1 (C1D22)
C2D8
C2D15
C3D1 (C2D22)
Sacituzumab govitecan 10 mg/kg IV days 1 and 8 in a 21-day cycle
Blood samples
Tumor core biopsy

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for 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 objective response rate (ORR) of sacituzumab govitecan (SG), in participants with recurrent gynecological malignancies, calculated for each individual tumor histology by RECIST v1.1

1.1.2 Secondary Objectives

- To determine the safety of SG
- To determine the progression-free survival (PFS) of participants receiving SG
- To determine the overall survival (OS) of participants receiving SG
- To determine the duration of response (DOR) of SG

1.1.3 Exploratory Objectives

- To evaluate the concordance (or discordance) of TROP2 expression between archival tissues and pretreatment fresh biopsies
- To identify baseline characteristics of gene expressions of DNA repair pathways in participants with or without clinical response
- To identify mutations of TROP2 gene (*TACSTD2*) in tumors with resistance against SG
- To investigate systemic pharmacodynamic biomarkers before and after SG treatment (i.e., circulating tumor DNA [ctDNA], circulating tumor cells [CTC], and γH2AX expression)
- To evaluate *UGT1A1**28 allele as a predictive marker for gastrointestinal and hematologic toxicities

1.2 BACKGROUND AND RATIONALE

1.2.1 Ovarian Carcinoma

There are several different types of epithelial ovarian carcinoma including high grade serous (70%), endometrioid (high and low grade, 20%), clear cell (5%), low grade serous (3%) and other rare subtypes (<2%). High grade serous ovarian cancer (HGSOC) is the most common subtype of ovarian cancer and the most lethal gynecologic malignancy in developed countries, with 5-year survival rate <40% [1]. This unfavorable prognosis is closely related to presentation of the disease at late stages, a high (>80%) relapse rate, and intrinsic or acquired resistance to conventional chemotherapy. The standard of care treatment includes optimal debulking surgery [2, 3] followed by platinum-based chemotherapy. The most commonly used taxane/platinum based chemotherapeutic regimen [4, 5] has been well established for some time. These regimens produced response rate (RR) in the 60 to 80% rage, with median progression free survival (PFS) of about 15 to 20 months and median overall survival (OS) of 30 to 45 months [6, 7] but at least 75% of these patients will relapse [8]. Attempts to identify alternative regimens with more activity have not been successful [9]. Alternatively, patients who are not considered appropriate for successful upfront debulking surgery are treated with neoadjuvant combination chemotherapy that improves the odds for optimal debulking surgery outcomes and additional adjuvant chemotherapy but these patients also relapse at similar rates [10, 11].

While the standard adjuvant treatment regimens demonstrated benefit for many patients, durable complete responses were uncommon and the search for additional effective agents continued. There have been a number of large randomized controlled trials (GOG218, ICON7, OTILLA, JGOG3022, ROBOT, ROSiA) assessing the addition of the anti-angiogenic agent bevacizumab to the chemotherapeutic regimen in the first line treatment [12-19]. While benefit in terms of improvement in PFS, OS, and RR were documented in some of these trials, there was not consistent evidence of substantial improvement in these important clinical endpoints. Two clinical studies (NCT01847677 and NCT01739218) examining the impact of bevacizumab to standard neo-adjuvant chemotherapy showed no improvement in resectability at surgery or other clinical endpoints [20, 21]. Three large, randomized trials (NCT00434642, NCT00976911, and NCT00565851) assessing the addition of bevacizumab to standard chemotherapeutic regimens not all platinum based in the second line [22-24] demonstrated more consistent improvement in the clinical endpoint of PFS or OS and sometimes in RR that supports the addition of bevacizumab to the standard chemotherapeutic regimens. In addition to being administered as part of adjuvant combination chemotherapy regimens, bevacizumab has also been shown to be effective as maintenance therapy and as monotherapy in relapsed patients (RR ≈ 15 to 20%) [25, 26].

As the core chemotherapeutic regimens are nearly all platinum-based, platinum sensitivity is generally the most important element in choosing a treatment regimen. Patients who progress during their initial treatment are platinum refractory and are not offered other platinum containing regimens. Patients who relapse within 6 months of completing their initial or subsequent platinum-based regimen are considered platinum resistant and generally are offered a non-platinum regimen. Intrinsic or acquired resistance to platinum drugs is the norm for advanced metastatic ovarian cancer patients even with the addition of other classes of cytotoxic drugs or anti-vascular endothelial growth factor (VEGF) agents [27, 28]. Compared to the other histologic types of ovarian cancer, HGSOC initially are very sensitive to platinum containing regimens because of underlying homologous repair deficiencies (HRD) present in about 50% of these cancers, alterations in p53, and up to 25% of HGSOC have mutations in BReast CAncer gene (BRCA)1

and 2 that are mostly germline [29-32]. Because of the high incidence of HRD, HGSOC are also very sensitive to poly(ADP-ribose) polymerase inhibitors (PARPi) which are given to platinum refractory and resistant patients including as maintenance therapy for patients who achieve remissions to their initial or later treatment regimens.

PARPi have been proven to be an important addition in the treatment of ovarian cancers especially HGSOC for the reasons mentioned above. In addition to their role in combination with the standard cytotoxic regimens, they have an important role in maintenance therapy for patients with HRD or BRCA mutations. But the development of resistance has tempered some of the enthusiasm for these agents [33-36]. There are four standard chemotherapeutic drugs (liposomal doxorubicin [Doxil®], gemcitabine, paclitaxel, and topotecan) that are commonly given to relapsed or refractory ovarian carcinoma sometimes as part of a combination with bevacizumab or as single agents. Even in patients with more indolent progressive disease, RR (10 to 15%), PFS (3 to 4 months), and OS (≈ 12 months) are underwhelming [36, 37], highlighting the unmet medical need of novel treatments.

ADCs are novel therapeutic agents designed to target antigens specific to tumor cells with direct delivery of cytotoxic agents while limiting systemic toxicity. The first ADC, mirvetuximab soravtansine, was approved for platinum resistant ovarian cancer patients with high folate receptor-alpha (FRα)-expressing platinum resistant ovarian cancer. Mirvetuximab demonstrated a RR of 32.4%, including five complete responses (CR), and median duration of response of 5.9 months (NCT04296890) [38]. In the confirmatory trial (NCT04209855), the anti-tumor activity of mirvetuximab was verified and improved PFS and OS, compared to standard-of-care chemotherapy, was reported [39]. Despite these major advances, alternative therapies and novel combinations are still needed for patients not eligible to mirvetuximab and those who progress after this therapy.

1.2.2 Endometrial Carcinoma

Endometrial cancer is the most prevalent gynecologic cancer in the U.S. and usually is low grade histology and early stage limited disease at presentation, resulting in a better chance of survival [40]. The majority of endometrial cancer is the type I endometrioid endometrial cancer driven by obesity and hormonal imbalance and associated with endometriosis [41, 42]. Conversely, serous endometrial cancer (SEC; type II endometrial cancer), which comprises ~15% of endometrial cancer, exhibits more aggressive phenotypes with a high recurrence rate [43, 44]. High grade endometrial carcinoma has been grouped into four molecular subtypes; polymerase ε ultramutated (POLEmut), mismatch repair (MMR) deficient, p53 mutant (p53abn) and the 4th group without these particular defects referred to as non-specific molecular profile (NSMP) [45, 46]. Like HGSOC which is characterized by universal TP53 mutation and DNA repair defects, SEC exhibits similar genomic characteristics such as TP53 mutation [47]. Surgical resection is generally the standard first therapeutic intervention [48, 49]. Brachytherapy rather than external beam radiation with adjuvant or neoadjuvant chemotherapy has been a standard component for the treatment of early-stage high risk patients including stage I disease invading more than 50% of the myometrium, grade 1 or 2 tumors with lymphovascular space invasion (LVSI) or any lymphatic involvement and locally advanced stage III endometrial carcinoma [50, 51].

There is evidence that the addition of external beam or brachytherapy to chemotherapy with standard platinum/taxane doublets for stage III disease leads to improvements in survival [52, 53]. However the recently reported 10-year follow-up for GOG258 (NCT00942357) showed no

difference in survival when radiation was added to chemotherapy indicating that the impact on OS is still not entirely clear [54] but is appropriate only for a limited number of patients [53]. Even with the small percentage of patients initially diagnosed with stage III or IV disease, about 20-25% of endometrial cancer patients eventually develop recurrent or metastatic disease [55-57]. Patients with locally recurrent disease are treated with surgery, surgery plus radiation therapy, or combined modality chemoradiation ± surgery [58, 59]. The initial systemic chemotherapy for metastatic disease is most often the standard platinum/taxane doublets sometimes given with a third agent (i.e., doxorubicin or bevacizumab for patients with good performance status who are still platinum sensitive). Treatment choices beyond these regimens are very similar to the algorithm for HGSOC: single agent platinum, taxanes, doxorubicin, liposomal doxorubicin, topotecan or bevacizumab. Hormonal therapy with tamoxifen, aromatase inhibitors (AIs), or fulvestrant can have benefit for less vigorous patients with more indolent disease [60, 61].

Because of the high frequency of PTEN loss, *PIK3CA* mutation and MMR deficient tumors, molecular therapies are given as part of investigational trials with occasional successes. Endometrial carcinomas have high level of programmed death-ligand 1 (PD-L1) expression and led to testing combinations of immune checkpoint inhibitors (ICI) with other drugs that have activity against endometrial carcinoma [62-65] and the combination of lenvatinib (a multi-kinase inhibitor including VEGFRs) with pembrolizumab was approved by the Food and Drug Administration (FDA) for the treatment of advanced non-microsatellite instability (MSI) high, non-MMR deficient endometrial cancer patient who have progressive disease after at least one systemic therapy and are not radiation therapy candidates based on the data in KEYNOTE-775 (NCT03517449) [66]. More recently, anti-programmed cell death protein 1 (PD-1) dostarlimab given with carboplatin and paclitaxel was approved for the treatment of endometrial carcinoma in patients who are MMR deficient based on the results from the RUBY trial (NCT03981796) [67]. Similarly, GY018 trial (NCT03914612) also confirmed the benefit of adding anti-PD-1 pembrolizumab to carboplatin/paclitaxel in advanced or recurrent endometrial cancer in both deficient MMR and proficient MMR cohorts in the randomized phase III registration trial [68].

ADCs are now actively investigated as one of the emerging therapeutic options in advanced/metastatic endometrial cancer [69]. TROPiCS-03, a Phase II multi-center basket study of SG in advanced solid tumors (NCT03964727) [70] reported preliminary clinical data of 20 patients with endometrial cancer who had prior platinum-based and anti-PD-L1 therapies at the 2023 ASCO meeting. In 20 patients with ≥13 weeks of follow-up as of 10/11/2022, ORR was 25% (95% CI, 8.7-49.1). Clinical benefit rate (CBR; confirmed complete response + partial response [PR] + stable disease [SD] ≥ 6 months) was 35% (95% CI, 15.4-59.2). Median PFS was 5.6 months (95% CI, 2.3 months-not reached [NR]). Grade ≥3 treatment-related adverse events (TRAEs) occurred in 64% of patients; most common grade ≥3 TRAEs were neutropenia (25%), febrile neutropenia (14%), and diarrhea (14%). Discontinuation rate due to TRAEs was 7%. Of note, no ovarian or cervical cancer patients were included in TROPiCS-03 study and the study is ongoing. Despite the recent advances in the standard of care therapy and emerging results from novel therapeutics such as ADCs in endometrial cancer, there are still limited understanding of ADC's mechanisms of actions (or resistance) and its impacts on DNA damage response pathways in patients.

1.2.3 Cervical Carcinoma

Cervical cancer is the fourth most frequent cancer in women across the world after breast, colorectal, and lung with an estimated 604,127 new cases and 341,831 deaths in 2020 [71]. In

2024, it is estimated that there will be 13,820 new cases in the U.S. and an estimated 4,360 people will die of this disease [72]. The frontline therapy after initial diagnosis is either surgery or a combination of chemotherapy and radiation depending on the stage and the patient factors. Although most patients present with early-stage disease, distant metastases or multiple recurrence sites develop in 15 to 61% of cases, usually within the first two years after completion of primary treatment, and prognosis for recurrent/metastatic cervical cancer still remains poor [73].

For women with recurrent/metastatic cervical cancer, the first-line treatment includes platinum-based chemotherapy and bevacizumab. The addition of bevacizumab to platinum-based doublet regimen has shown a survival benefit, leading to the current first-line standard of care based on the findings from GOG240 Phase 3 trial. More recently, two Phase 3 studies demonstrated adding anti-PD-L1 (GOG3030; atezolizumab [74] [irrespective of PD-L1 status] or KEYNOTE-826; pembrolizumab [75] PD-L1 positive disease only] to a standard bevacizumab plus platinum regimen significantly improved PFS and OS in metastatic or recurrent cervical cancer and became a new first-line therapy. However, despite these advances with combination therapies in cervical cancer treatment, there is still compelling need for newer biologic agents due to significant side effects and narrow therapeutic window of these drugs.

Single-agent therapy is generally indicated in the second line setting for patients who progress following first-line chemotherapy and those who are not candidates for combination therapy. Tisotumab vedotin-tftv is a tissue factor-specific ADC with a microtubule inhibitor approved by the US FDA for recurrent or metastatic cervical cancer that has progressed on chemotherapy. In a single-arm multi-center Phase II trial (innovaTV204/GOG-3023/ENGOT-cx7; NCT03438396), 101 patients with recurrent or metastatic cervical cancer who had received no more than two prior systemic regimens in the recurrent or metastatic setting were treated with tisotumab. The ORR was 24% (17% PR and 7% CR) [76].

Other ADCs are also actively investigated in advanced/metastatic cervical cancer. Recently, the interim analysis from the Chinese multi-center, single-arm phase 2 basket study of SG (EVER-132-003, NCT05119907) was reported at the 2024 Society of Gynecologic Oncology (SGO) meeting. 18 Chinese patients with recurrent/metastatic cervical cancer were enrolled. Approximately 80% had prior immunotherapy and two thirds (66%) had at least two prior regimens in the recurrent or metastatic setting. ORR was 50% (95% CI, 26%-74%) with a median duration of response of 9.2 months (95% CI, 2.9 months-not estimable). Median PFS was 8.1 months (95% CI, 4.1-10.6 months) in this heavily pretreated population. No new safety signals were reported. The accrual for EVER-132-003 study is now ongoing and the verification of data is needed.

1.2.4 Sacituzumab govitecan (SG)

TROP2 is a 36 kDa transmembrane glycoprotein encoded by the *TACSTD2* gene that is involved in intracellular calcium signaling in many cells. In many cancers including ovarian or endometrial carcinomas [77-80], TROP2 overexpression is linked with tumorigenicity and poor OS. TROP2 is a trophoblast cell-surface antigen which is overexpressed on many other epithelial tumors [81, 82]. TROP2 expression is relatively common in gynecologic malignancies. In a comprehensive tissue microarray study with 18,563 tumor samples including HGSOC (n = 344) and endometroid endometrial cancers (n = 160), approximately 80-90% of HGSOC and endometrial cancer were TROP2 positive [83]. Also, Santin's group evaluated the primary surgical samples from 147 cervical cancer patients. Of 147, 113 were squamous cell carcinomas (SCCs), and 34 were

adenocarcinoma/adenosquamous carcinomas. Moderate to strong diffuse TROP2 staining was seen in 95% (108/113) of SCCs, and 81% (29/34) of adenocarcinoma/adenosquamous cancers on immunohistochemistry (IHC) [84].

SG is a novel ADC, comprising a topoisomerase 1 (TOP1)–inhibiting camptothecin, SN-38 (7-ethyl-10-hydroxycamptothecin, the active metabolite of irinotecan, a TOP1 inhibitor), linked to a humanized antibody targeting TROP2. SG has a high drug-to-antibody ratio with 7.6 molecules of moderately toxic SN-38 conjugated to each antibody via the unique hydrolyzable and proprietary linker, CL2A [85]. The linker allows for intratumoral release of therapeutic concentrations of SN-38, as well as release extracellularly within the surrounding tumor microenvironment, providing a bystander effect [85].

The TOP1 inhibitors (TOP1is), irinotecan and topotecan are widely used against a broad spectrum of malignancies including colon, ovarian, pancreatic, and small cell lung cancers [86]. In gynecologic cancers, topotecan is an FDA-approved regimen for women with recurrent ovarian and cervical cancers [87] and is one of the recommended drugs for relapsed endometrial cancer [88] per National Comprehensive Cancer Network (NCCN) guidelines and showed ~15-20% of ORR across the diseases. There are currently 10 ADCs approved by the FDA, and of the three approved in the past 3 years, two are ADC-TOP1i including SG and trastuzumab deruxtecan [89].

SG's benefit has been seen in breast cancer and urothelial carcinoma independent of TROP2 expression, thus no need for a companion diagnostic test for TROP2 expression [90-92]. It is noteworthy that most post-hoc TROP2-specific biomarker studies used the archival tissue samples and investigated TROP2 expression as prognostic or predictive biomarkers. For instance, an exploratory post-hoc subgroup analysis from TROPiCS-02 study revealed SG improved PFS and OS across both TROP2 IHC H-score groups (<100 or ≥100) and SG benefit was also seen in ORR, CBR, and DOR compared with chemotherapy regardless of *TACSTD2* mRNA expression [93]. However, it is unclear whether SG can modulate TROP2 expression in patients after treatment.

1.2.4.1 Preclinical Studies

First, Dr. Jung-Min Lee's lab (Women's Malignancy Branch, CCR, NCI) performed flow cytometric analysis to determine TROP2 expression in various drug-sensitive and drug-resistant ovarian cancer cell lines (**Figure 1**A, unpublished data). TROP2 was highly expressed in most HGSOC cell lines independent of their BRCA mutation or PARPi or platinum resistance status. TROP2 expression also was evaluated on RNAseq data from fresh biopsy samples of recurrent HGSOC patients who were enrolled in the NCI Phase 2 trial of cell cycle checkpoint inhibitor prexasertib (NCT02203513) (**Figure 1**B, unpublished data). TROP2 was highly expressed in HGSOC compared to normal ovary tissues and was not associated with clinical benefit by prexasertib, in both BRCA mutant (BRCAmut) and BRCA wild-type (BRCAwt) patients.

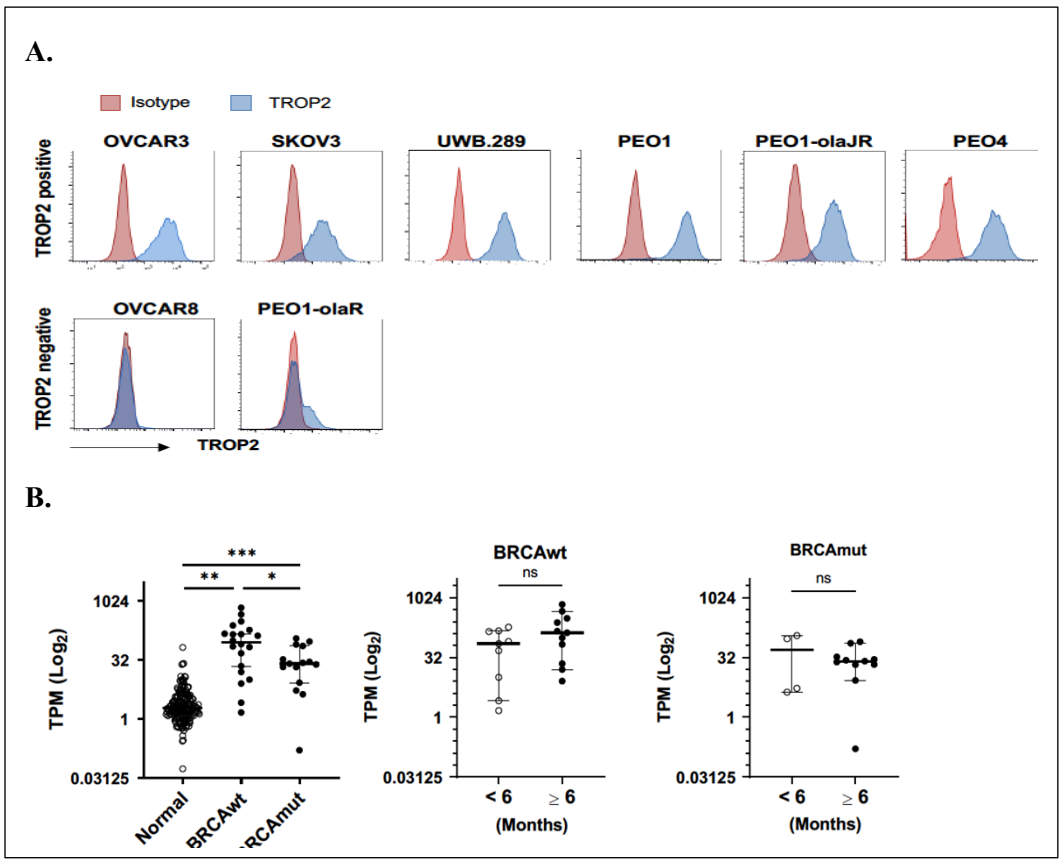

Figure 1, *TROP2 expression.* *Screening ovarian cancer cell lines for TROP2 expression (A) and RNAseq analysis of HGSOC tumors for TROP2 expression (B). Expression values (TPM, Transcripts per million) (Log2) for TROP2 (TACSTD2) from both BRCAmut (n = 15) and BRCAwt patients (n = 20) were compared against TPM values of TROP2 from normal ovarian tissues (normal) gleaned from the GTEx database (n = 180). TROP2 values were not associated with clinical benefit (defined by ≥ 6 months PFS) by prexasertib therapy. * P < 0.05, ** P < 0.01, and *** P < 0.001; ns, not significant.*

Also, Dr. Lee's lab found that SG monotherapy induces DNA damage and replication stress in HGSOC cell lines (**Figure 2**, unpublished data). Increased percentage of cells with pan-nuclear γH2AX and γH2AX foci by IF and elevated levels of γH2AX by immunoblotting were seen upon SG treatment in both PARPi-sensitive and PARPi-resistant HGSOC cell lines (**Figure 2** A and B). Surprisingly this DNA damage was not further enhanced by the addition of an ataxia telangiectasia and RAD3-Related (ATR) inhibitor (ATRi) berzosertib. Similarly, increased replication stress measured by a DNA fiber assay was observed by SG alone but not augmented by the addition of berzosertib to SG in PARPi-resistant HGSOC (**Figure 2**C).

In ovarian cancer cell lines, preliminary immunoblotting data showed no significant changes of TROP2 levels by SG and/or ATRi treatment, although this requires further validation (data not shown). In breast cancer preclinical models, Zhu et al. reported that inhibitors of AKT, RSK, and p38 MAPK suppressed the TROP2 expression while tamoxifen treatment significantly increased TROP2 expression in luminal breast cancer cell lines [94]. Further studies are needed to better understand SG's impact on target proteins such as TROP2 in patients for the future pharmacodynamic studies and combination trials.

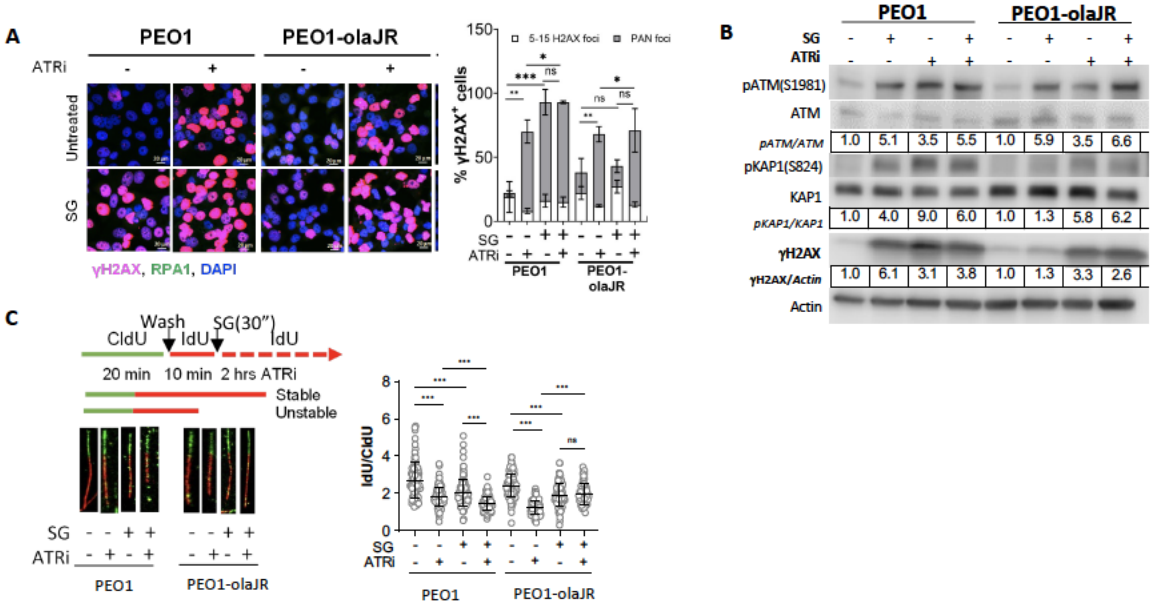

Figure 2, ***Effect of SG and berzosertib on DNA damage (A, B) and replication fork (RF) stability (C).*** *A. Representative images of TROP2 positive PEO1 (PARPi-sensitive) and OlaJR (PARPi-resistant) HGSOC cells that were pretreated with SG and then exposed to berzosertib (ATRi) (1 μM) overnight. Slides were then probed for γH2AX-S139 (pink) and RPA1 (green dots). Approximately 100–200 cells were analyzed for γH2AX foci and counted as pan nuclear (> 15 foci/nucleus) or below (5–15 foci/nucleus) and plotted as bar charts. B. Cells were pretreated (30 minutes at 37℃) with SG and then exposed to berzosertib (ATRi) overnight at the given concentrations. Western blot analysis of downstream proteins of ATR/ATM pathways and DNA double strand break marker pH2AX-S139 (γH2AX) is shown. Effect of berzosertib (ATRi), SG or a combination of both on γH2AX levels and corresponding effect on ATM activity as measured by activated ATM (pATMS1981) or its specific phosphorylated substrate KAP1 are shown. All experiments were performed at least three times with similar outcomes. C. DNA fiber assays for studying DNA RF stability was performed as detailed previously. About 200 DNA fibers were selected and the length of both red (IdU) and green (CldU) strands were measured using Fiji™ software and the ratio of IdU/CldU were plotted as column charts using GraphPad prism®. Basically, the lower ratio of IdU/CldU compared to the control indicates a deficit in replication fork protection or blocked fork progression. Representative strands are shown below the corresponding columns. P values for all figures are marked as asterisks. * P < 0.05, ** P < 0.01, and *** PP < 0.001; ns, not significant.*

In xenograft studies, SG alone induced tumor shrinkage in both PARPi-sensitive (PEO1-Luc, TROP2 positive) and PARPi-resistant (PEO1-olaR-Luc, TROP2 negative) HGSOC mouse models, again ATRi berzosertib did not further induce tumor shrinkage (**Figure 3**, unpublished data). As a result of these preclinical findings, Dr. Lee's group decided to identify the better drug candidate for the future combination trials with SG for gynecologic cancer patients and are now conducting mechanistic studies with SG in gynecological cancer preclinical models.

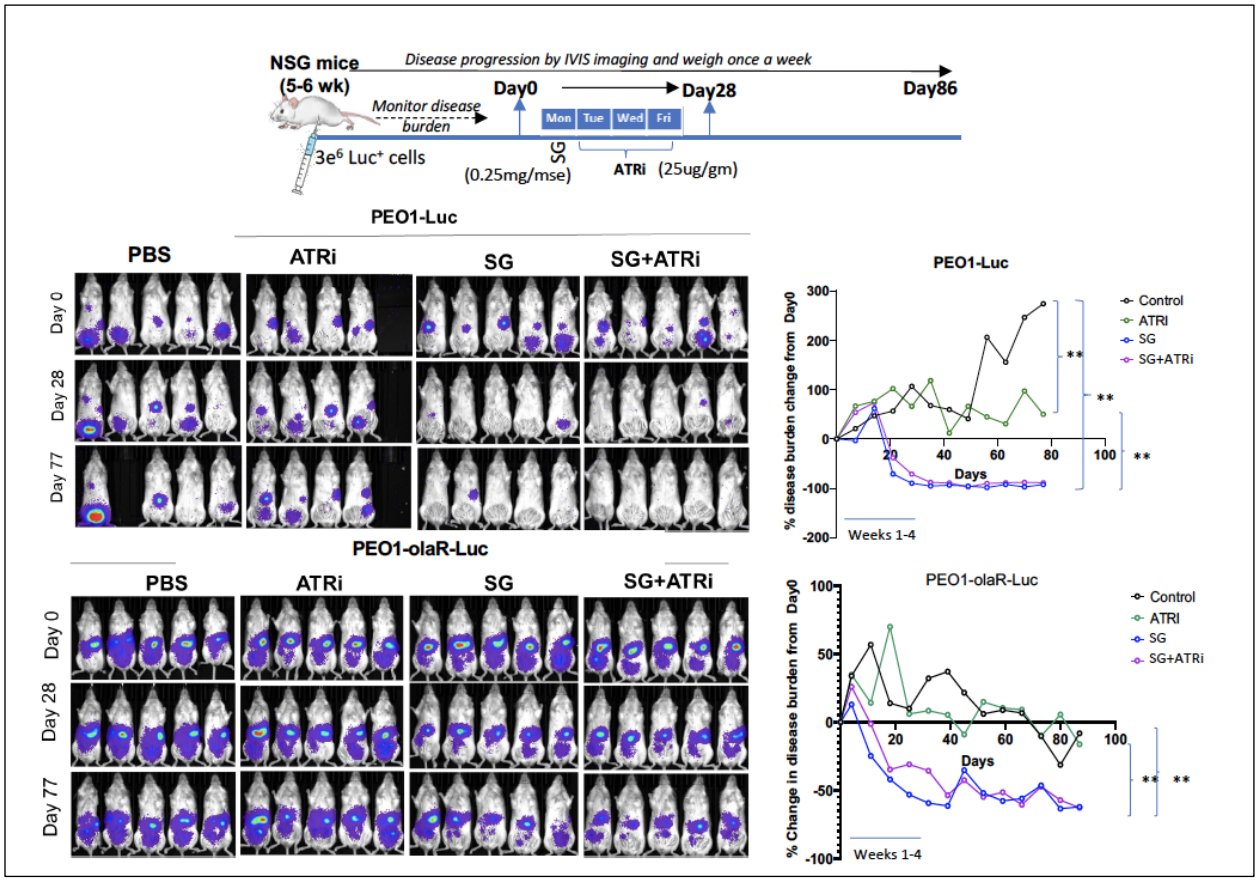

Figure 3, *Mouse studies.* *Top: Schematic of treatment strategy for mice treated with single treatments of SG or berzosertib (ATRi) or a combination of both. Disease bearing mice (10 per group) were treated with sterile saline/PBS, or with SG alone (IP) or with berzosertib (25 µg/gm) (oral gavage) three times a week or a combination of both over 4 weeks, with first dose given 24 hours after SG treatment. Mice were imaged on Fridays of every week for the duration of the experiment. Representative images of luciferase imaging of TROP2 positive PARPi-sensitive PEO1 (Middle) and TROP2 negative PARPi-resistant PEO1 OlaR (Bottom) HGSOC xenograft models that show change in disease burden from Day 0 to Day 77, and a line plot of the same data from 8-10 mice plotted on the right. P values are shown to the right of vertical parenthesis encompassing relevant groups being compared. P values, * $P < 0.05$ and ** $P < 0.01$.*

Santin's lab also tested SG in other gynecologic cancer preclinical models including uterine carcinosarcoma (**Figure 4**) and cervical cancer (**Figure 5**). TROP2 positive uterine carcinosarcoma cell lines (SARARK4, SARARK9) showed higher sensitivity to SG *in vitro* when compared to TROP2 low/negative (SARARK14) cell lines [95]. In xenografts, SG alone induced a significant tumor growth inhibition when compared to control, to ADC control and to the naked Antibody (AB) (p=0.004, p=0.007 and p=0.0007, respectively). SG significantly improved OS at 90 days when compared to control groups (p<0.0001) (**Figure 4**) [95]. In cervical cancer, SG also induced a difference in tumor growth inhibition beginning on day 18 ($p < 0.001$) in SG-treated group and improved OS at 90 days ($p = 0.014$) when compared to the other control groups in TROP2 positive cervical cancer xenografts (CVX8) (**Figure 5**). Animals tolerated SG treatment well with no significant toxicity [95]. It is also noteworthy that SG demonstrated a significant bystander killing effect, which could aid in treating tumors with heterogeneous antigen expression.

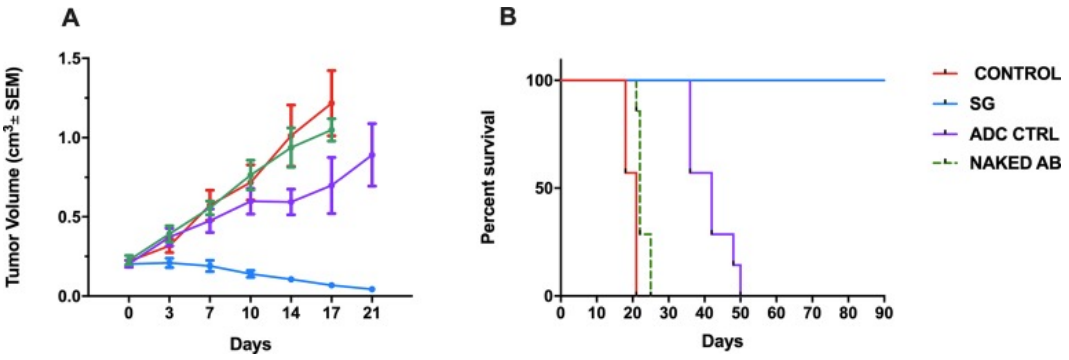

Figure 4, *SG monotherapy in endometrial carcinosarcoma xenografts.* *Antitumor activity (A) and Survival (B) of the SG versus controls in TROP2 positive uterine carcinosarcoma (SARARK9) xenografts. Mice were treated twice per week for three weeks by IV injection of saline, SG, ADC control, and naked AB (A) SG significantly inhibited tumor growth when compared to saline, ADC control, and naked AB beginning at day 7 of the treatment (p=0.004, p=0.007 and p=0.0007 respectively). (B) Overall survival at 90 days was significantly improved in the SG group (p<0.0001).*

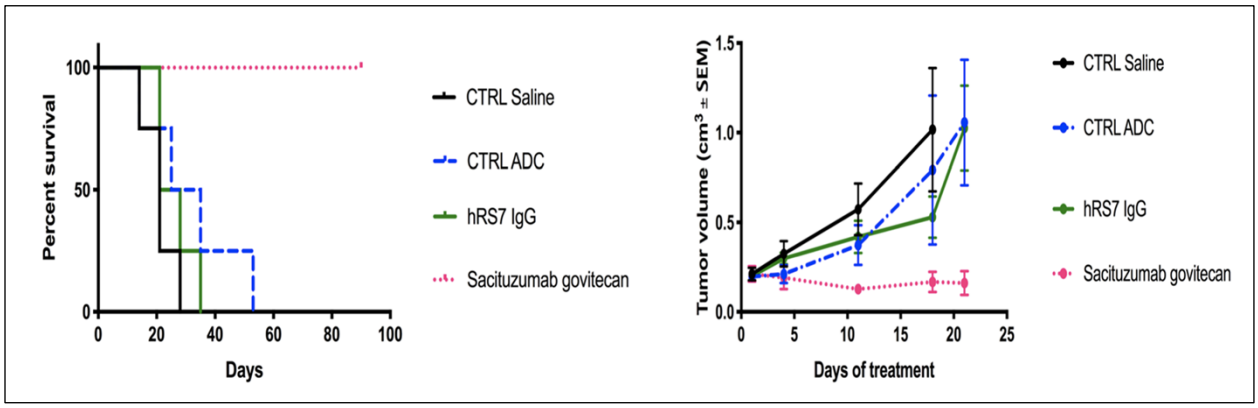

Figure 5, *SG monotherapy in cervical cancer xenografts.* *Antitumor activity of SG was compared to controls including, CTRL ADC isotype, hRS7 IgG and CTRL saline, in cervical cancer xenograft models (ie, CVX8, 2 + TROP2 positive) (4 mice per group) All treatments were given twice per week for 3 weeks by intravenous injection of 500 µg of SG, control ADC, saline and hRS7 IgG. (A) Overall survival. (B) Tumor growth inhibition.*

These preclinical results combined with the recent Phase II clinical trial data demonstrating promising clinical responses in multiple solid tumors that are resistant to chemotherapy, strongly support the design of SG clinical trials in recurrent or advanced gynecologic cancer patients.

1.2.4.2 Clinical Studies

As of April 2024, there are two completed studies of SG for solid tumors and 23 ongoing studies of SG with at least one participant enrolled. The final safety and efficacy report of the phase I/II basket study (NCT01631552) (n=495) [85] included 18 patients with recurrent/refractory endometrial cancer who had relapsed after or were refractory to ≥1 prior standard therapeutic regimen. 4 of 19 endometrial cancer patients achieved PRs yielding 22.2% of ORR. Also, the interim data from the ongoing TROPiCS-03 phase 2 basket study (NCT03964727) showed 25% ORR in endometrial cancer patients. With respect to cervical cancer, the recent interim analysis from Chinese's multicenter phase 2 basket study of SG (EVER-132-003, NCT05119907) showed 50% ORR (9/18) in recurrent cervical cancer patients. Also, Santin's group recently (4Q 2023) opened the pilot single arm Phase II trials of SG monotherapy in recurrent/metastatic ovarian (NCT06028932), endometrial (NCT04251416) and cervical cancers (NCT05838521); 20 patients

per each cohort. The data from these small pilot studies will require confirmation for further development of SG.

Table 1 shows common adverse events (AE)s of SG monotherapy reported in advanced/metastatic triple negative breast cancer (TNBC) patients. The most frequent AEs (all grades) included gastrointestinal toxicity (diarrhea, nausea/vomiting, abdominal pain, anorexia, constipation), fatigue, neutropenia, anemia, and alopecia. Although grade ≥ 3 neutropenia was relatively common (34.5%), it was rare to have febrile neutropenia. Other grade 3 or 4 AEs were limited to fatigue, diarrhea, anemia, or neutropenia.

Table 1, Adverse events with SG

	SG (N = 258)			TPC (N = 224)		
Preferred Term	**All n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Diarrhea	168 (65.1)	29 (11.2)	0	38 (17.0)	2 (0.9)	0
Nausea	161 (62.4)	7 (2.7)	1 (0.4)	68 (30.4)	1 (0.4)	0
Fatigue	133 (51.6)	11 (4.3)	0	89 (39.7)	19 (8.5)	0
Alopecia	121 (46.9)	0	0	36 (16.1)	0	0
Neutropenia	110 (42.6)	65 (25.2)	24 (9.3)	57 (25.4)	25 (11.2)	20 (8.9)
Anemia	101 (39.1)	24 (9.3)	0	61 (27.2)	13 (5.8)	0
Constipation	96 (37.2)	1 (0.4)	0	52 (23.2)	0	0
Vomiting	86 (33.3)	3 (1.2)	1 (0.4)	36 (16.1)	3 (1.3)	0
Decreased appetite	71 (27.5)	4 (1.6)	0	46 (20.5)	2 (0.9)	0
Neutrophil count decreased	71 (27.5)	32 (12.4)	22 (8.5)	46 (20.5)	24 (10.7)	10 (4.5)

MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SG = sacituzumab govitecan; TPC = treatment of physician's choice
Data Cutoff Date: 11 March 2020
The denominator for percentages is the number of patients in the Safety Population for each treatment group.
Treatment-emergent adverse event is defined as an adverse event with start date on or after the date of first dose of study treatment and up to 30 days after date of last dose of study treatment.
Patients may report more than 1 event per preferred term and are counted once for the preferred term. Table is sorted by descending frequency of preferred term in SG group.
MedDRA Version 22.1 was used for coding.

1.2.5 UGT1A1 and Mutation for SN-38 Metabolism

SN-38 (the active metabolite of irinotecan) is metabolized by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1). Irinotecan-treated subjects who are homozygous for the *UGT1A1**28 allele are at increased risk for neutropenia and diarrhea (Camptosar Prescribing Information, 2018). Preliminary results from study IMMU-132-01 (NCT01631552) suggest that the frequency of some exposure-related AEs (i.e., neutropenia and febrile neutropenia) may be higher in subjects homozygous for the *28 allele as well; however, the frequencies of neutrophil count decreased and other treatment-related adverse events, notably diarrhea, did not differ among the subgroups. Concomitant administration of strong inhibitors or inducers of UGT1A1 with SG should be avoided due to the potential to either increase (inhibitors) or decrease (inducers) the exposure to SN-38. In the phase I/II basket study (NCT01631552), the influence of *UGT1A1* genotype status on the incidence of AEs was analyzed in 403 (81.4%) patients for whom *UGT1A1* genotypes were available [85]. Most patients were either wild type for the *UGT1A1* allele (∗1/∗1) or heterozygous for the ∗28 allele (∗1/∗28). Only 9.3% (n = 46) were homozygous for the ∗28 allele (∗28/∗28). The pattern and incidence of AEs were broadly similar in heterozygous and wild-type patients. Neutropenia was numerically more frequent in homozygous patients (28/46; 60.9%) compared

with heterozygous (69/180; 38.3%) and wild-type patients (59/177; 33.3%). The frequency of diarrhea was generally similar between heterozygous and wild-type patients, although slightly higher in homozygous patients (60.9%, 51.7%, and 54.8%, for homozygous, heterozygous, and wild-type patients, respectively). Anemia occurred in 50.0%, 31.7%, and 37.3% in homozygous, heterozygous, and wild-type patients, respectively. The percentage of patients who permanently discontinued treatment for any reason was similar among patients who were either wild type, heterozygous, or homozygous, with rates of 98.3%, 96.7%, and 97.8%, respectively. Of note, the FDA-approved drug label for Trodelvy (SG) indicates that screening for UGTIA1 testing is not required for SG treatment and the dose should be adjusted on the basis of individual patient tolerance because the appropriate dose for these patients is unknown [96].

1.2.6 Rationale

There is an urgent need for the novel therapeutic agents for relapsed gynecologic cancer patients because single agent chemotherapy generally yields low ORRs (10-15%) with median PFS of 3-4 months [25, 26].

ADCs are currently FDA approved in ovarian (FR alpha-specific ADC) and cervical (TF-specific ADC) cancers and are a rapidly emerging class of therapeutic agents, with ongoing research to improve outcomes in the various settings of gynecologic cancer. Yet, there is insufficient information on the TROP2-sepcific ADC, specifically, SG's clinical activity and biology in heavily pretreated (three or more previous systemic therapies) gynecologic cancer patients, underscoring the importance of further clinical and mechanistic translational studies.

We and others have demonstrated the monotherapy activity of SG in gynecologic cancer preclinical models and found that SG alone can induce DNA damage, replication stress, and tumor shrinkage in drug-resistant HGSOC preclinical models. While small basket clinical trials are currently testing SG in gynecologic malignancies, there is still a need to confirm the clinical activity in heavily pretreated gynecologic cancer patients, also to do correlative studies prior to moving forward with large randomized clinical trials. Hence, our proof-of-concept Phase II pilot study will provide important insights of SG's activity and biology in patients by studying fresh biopsies and serial blood samples.

In summary, recurrent/metastatic gynecologic cancers are incurable, highlighting the urgent need for new therapeutic options. We aim to investigate the clinical activity of SG in heavily pretreated patients and to better understand the biology of SG in gynecologic cancer patients, particularly, concerning DNA damage repair pathways and TROP2 expression. As several ADCs show promise in subsets of gynecologic cancers, continued translational/correlative studies are necessary to determine the best therapeutic approaches for SG and to identify the targets for the future combination trials.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Cohort 1 (Ovarian Cancer)

2.1.1.1.1 Participants must have histologically or cytologically confirmed recurrent platinum-resistant (defined as less than six months of platinum-free interval) epithelial (i.e., high

grade serous, endometrioid, low grade serous, or clear cell) ovarian carcinoma that is refractory to standard treatment.

2.1.1.1.2 Participants with known BRCA mutated tumors should have received a PARP inhibitor maintenance or treatment.

2.1.1.1.3 Participants without known BRCA mutation and platinum-resistant tumors must have had prior bevacizumab or not eligible for bevacizumab-based therapy (i.e., history of proteinuria).

2.1.1.2 Cohort 2 (Endometrial Cancer)

2.1.1.2.1 Participants must have histologically or cytologically confirmed recurrent epithelial (i.e., endometrioid or serous) endometrial carcinoma that is refractory to standard treatment.

2.1.1.2.2 Participants must have received prior anti-PD-1/PD-L1-based therapy or not eligible for anti-PD-1/PD-L1-based therapy.

2.1.1.3 Cohort 3 (Cervical Cancer)

2.1.1.3.1 Participants must have histologically or cytologically confirmed recurrent epithelial cervical (i.e. squamous or adeno) carcinoma that is refractory to standard treatment. Note: Participants with a history of human papilloma virus infection (i.e., positive HPV DNA testing) are eligible.

2.1.1.3.2 Participants must have received prior bevacizumab-based therapy or not eligible for bevacizumab-based therapy (i.e., history of proteinuria).

Note: Platinum chemotherapy administered concurrent with primary radiation (i.e., weekly cisplatin) is not counted as a systemic chemotherapeutic regimen for management of persistent or recurrent carcinoma of the cervix.

2.1.1.4 All Cohorts

2.1.1.4.1 Participants must have received at least two systemic therapies including at least one platinum-based therapy regimen.

2.1.1.4.2 Participants must have radiographically measurable disease, per RECIST 1.1, and safely biopsiable lesion.

2.1.1.4.3 Age ≥ 18 years

2.1.1.4.4 ECOG performance status ≤ 1 (see **Appendix A: Performance Status Criteria**)

2.1.1.4.5 Adequate organ and marrow function as defined below:

- Hemoglobin (Hgb) ≥ 9.0 g/dL
- Absolute neutrophil count (ANC) ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- White Blood Cell count (WBC) ≥ 3,000/mcL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (≤ 3 x ULN in participants with known/suspected Gilbert's disease)

- Aspartate aminotransferase (AST) / Alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Serum creatinine ≤ 1.5 x ULN or estimated GFR ≥ 30 ml/min/1.73 m^2

2.1.1.4.6 Participants with suspicion or prior history of treated central nervous system (CNS) metastases with no evidence of active disease (assessed by MRI or contrast CT scan of the brain and spinal column) are eligible if pretreatment brain MRI demonstrate no evidence of disease in the past 4 weeks prior to entry.

2.1.1.4.7 Major surgical procedure, other than for diagnosis, must not occur within 4 weeks prior to the first dose of study treatment. Participants must have recovered adequately from the toxicity and/or complications from the intervention prior to starting the study drug.

2.1.1.4.8 Participants with prior cancer-directed therapy must have a washout period of 3 weeks prior to the first dose of study treatment.

2.1.1.4.9 Participants with prior cancer-directed immunotherapy-based therapy must have a washout period of 4 weeks prior to the first dose of study treatment.

2.1.1.4.10 Human immunodeficiency virus (HIV)-infected participants are eligible if on stable dose of highly active antiretroviral therapy (HAART), a CD4 count ≥ 200 cells/mcL, and an undetectable viral load (VL).

2.1.1.4.11 Hepatitis B virus (HBV) positive participants are eligible if they have been treated or are on an appropriate course of antivirals at study entry.

2.1.1.4.12 Participants with a history of hepatitis C virus (HCV) infection (i.e., positive HCV antibody test) must have been treated and cured (undetectable HCV VL at screening). Participants with HCV infection who are currently on treatment are eligible if they have an undetectable HCV VL.

2.1.1.4.13 Individuals of child-bearing potential (IOCBP) must agree to use an effective method of contraception (barrier, surgical sterilization, abstinence) prior to study entry, for the duration of study participation, and for at least 6 months after the last dose of study drug.

2.1.1.4.14 IOCBP must undergo pregnancy testing at screening and must not be pregnant in order to take part. Note: In these cases, a negative β-human chorionic gonadotropin (β-hCG) (urine or blood) is required.

2.1.1.4.15 Nursing participants must discontinue nursing and/or not begin nursing until 1 month after the last dose of study drug.

2.1.1.4.16 Ability of participants to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Participants who are receiving any other investigational agents

2.1.2.2 Primary platinum-refractory ovarian cancer (defined as progression while on the upfront platinum-based therapy)

2.1.2.3 Participants with any other concomitant invasive malignancies

2.1.2.4 History of severe hypersensitivity or allergic reactions attributed to compounds of similar chemical or biologic composition to SG, SN-38, or irinotecan.

2.1.2.5 Prior treatment with TROP2-targeting ADC. Participants with prior use of other ADCs are eligible.

2.1.2.6 Prior treatment with topoisomerase 1 inhibitors i.e., topotecan

2.1.2.7 Symptomatic or untreated brain/CNS metastases

2.1.2.8 Participants who require treatment with UGT1A1 inhibitors (see Section **4.1**).

2.1.2.9 Participants with known homozygous *UGT1A1**28 allele if tested during the previous treatment.

2.1.2.10 Participants with active infection requiring antibiotics.

2.1.2.11 Participants who have not recovered from toxicities or AEs related to prior therapy to Grade ≤ 1 with the following exceptions.

- Participants with platinum related hypomagnesemia (on replacement) are eligible.
- Participants with auto-immune thyroid dysfunction on stable replacement therapy are eligible.
- Participants with any grade alopecia or grade 1 or 2 neuropathy are eligible.

2.1.2.12 Participants with a history of gastrointestinal (GI) perforation or hemorrhage (> 30mL bleeding/episode) fistula or hemoptysis within 3 months prior to initiation of study therapy, intra-abdominal abscess in the 6 months prior to entry, history of ascites or pleural effusion requiring paracentesis or thoracentesis in the 4 weeks prior to initiation of study therapy or history of bowel obstruction within 3 months prior to initiation of study therapy.

2.1.2.13 Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during SG treatment or within 5 months after the final dose of SG. Note: Seasonal flu vaccines that do not contain a live virus and locally authorized/approved COVID-19 vaccines are permitted (see also Section **4.1**)

2.1.2.14 Participants with severe uncontrolled intercurrent illness that would limit compliance with study requirements, evaluated by history, physical exam, and chemistry panel.

2.2 RECRUITMENT STRATEGIES

All participants will be enrolled and generally expected to be recruited from, but not limited to, the United States.

The protocol may be abstracted into a plain language announcement-information to be abstracted includes-study title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information) and posted/distributed on the below media without IRB approval. Should we add additional descriptive information about the study to these announcements, we will seek IRB approval.

Recruitment strategies *may* include:

1. The study may be publicized on
    a. NIH official websites; (e.g., www.clinicaltrials.gov., NCI cancer clinical trial listing [PDQ], CCR)
    b. NIH moderated social medical platforms (e.*g.,* Facebook, X, Instagram. These sites comply with government terms of service per the NIH Social Media Guidelines)
    c. Research Match (https://www.researchmatch.org/about/)
2. Newsletters (if intent is to recruit)
3. Television advertisements/radio advertisements
    a. Clinical Center TV (CCTV) – Clinical Center Television - CCTV | NIH Clinical Center - America's Research Hospital TVs placed all around the NIH Clinical Center will rotate through various messages including one for this study.
4. Newspaper advertisements
5. Videos
6. Publicly posted recruitment flyers and posters
7. Brochures
8. Clinical Center Office of Patient Recruitment Services (OPR) including OPR Listservs (Email list of those interested in receiving study recruitment updates). Includes the OPR Protocols and OPR Healthy Volunteers listservs and 3 NIH listservs (NIH Post bac, NIH Clinical Fellows & NIH Study Volunteers)
9. Recruitment Letters
    a. Doctor to patient informational letter: distribution of letters to private health care physicians/providers- these professionals will share study information with potential participants. This information will be made available in electronic and/or a hard copy as needed. (Note: if material is not to be shared with participants, these are not submitted to the IRB)
    b. Investigator to potential participant letters

Prior to distribution of any individual recruitment materials not excepted in item #1, such materials will be submitted for IRB review, as appropriate.

2.3 SCREENING EVALUATION

2.3.1 Screening activities performed prior to obtaining informed consent.

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

- Email, written, in person or telephone communications with prospective participants
- 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

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

The following activities will be performed only after the participant has signed the consent for this study. Assessments performed at outside facilities or on other NIH protocols within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

The following screening evaluations must be completed:

2.3.2.1 Performed within 10 years prior to treatment initiation

- Confirmation of diagnosis: Obtain archival tumor specimen (one block of tissue or 20 paraffin-embedded unstained slides) for all participants for confirmation of histology by the NCI Laboratory of Pathology (LP) or by an outside pathologist. Results from any US or Canadian certified labs may be acceptable for eligibility and treatment initiation. If archival tumor specimen is unavailable for confirmation of diagnosis, then samples from the fresh tumor biopsy will be used for confirmation of diagnosis by NCI LP.
- Documentation of BRCA mutation (Cohort 1 only) by any US or Canadian certified lab

2.3.2.2 Performed within 4 weeks prior to treatment initiation

2.3.2.2.1 Radiographic studies

- CT scan of chest, abdomen, and pelvis (CAP) with contrast. MRI abdomen/pelvis with gadolinium may be performed in participants unable to tolerate contrast for CT.
- Brain MRI in participants with suspicion or prior history of treated CNS metastases

2.3.2.3 Performed within 3 weeks prior to treatment initiation

2.3.2.3.1 Clinical examination

- Complete medical history and physical examination (including height, weight, vital signs)
- ECOG performance status evaluation (see **Appendix A: Performance Status Criteria**)
- Review of concomitant medications
- Review of contraception

2.3.2.3.2 Clinical laboratory data

- Complete blood count (CBC) with differential: includes Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, WBC, RBC, Hemoglobin, Hematocrit, MCV, RDW, Platelet
- Serum Chemistries:
    - Acute care panel (sodium, potassium, chloride, total CO2, creatinine, glucose, urea nitrogen)
    - Mineral panel (albumin, calcium total, magnesium total, phosphorus)

- Hepatic panel (alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin)

- PT/INR and aPTT (required for pretreatment biopsy)
- HIV screening antibody, CD4 count and VL if positive
- Hepatitis B surface antigen
- Hepatitis C antibody panel with reflex VL
- Pregnancy test (serum or urine β-hCG) in IOCBP*

*IOCBP: Any person who is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries, fallopian tubes and/or uterus) or another cause as determined by the treating investigator (e.g., Müllerian agenesis). Per this definition, a person with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

2.3.2.3.3 Other evaluations

- 12-lead electrocardiogram (EKG) to rule out cardiotoxicity from previous therapy

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://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

2.4.1 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. 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.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a transient underlying condition not related to the condition under study may be rescreened once after the underlying condition has resolved.

2.4.2 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Cohort 1	Participants with recurrent/metastatic ovarian carcinoma
2	Cohort 2	Participants with recurrent/metastatic endometrial carcinoma
3	Cohort 3	Participants with recurrent/metastatic cervical carcinoma

Arms

Number	Name	Description
1	Arm 1	Treatment with SG

Arm Assignment

Participants in Cohorts 1, 2, and 3 will be assigned to Arm 1.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is an open-label Phase II, single arm, pilot study to investigate the anti-tumor activity of SG in recurrent gynecologic cancers.

Participants will receive SG at 10mg/kg by intravenous (IV) infusion on Days 1 and 8 of every 21-day cycle in the outpatient setting. The standard dose adjustment algorithm defined in the SG package insert will be used to make decisions on dose reductions, interruptions or discontinuation of SG treatment based on adverse events that may occur during participants' treatments.

Restaging will be time-based and performed every 9 weeks (± 1 week, approximately every 3 cycles) for the first year, and every 12 weeks (± 1 week, approximately every 4 cycles) thereafter until disease progression or up to 5 years.

SG will be administered for a maximum of 5 years, or until participants experience adverse events requiring treatment discontinuation (see Section **3.2.1**), trial withdrawal, progression, or as determined by the Principal Investigator (PI) after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). All study participants will be followed-up for 10 years after completion of therapy (see Section **3.3.1**).

3.2 DRUG ADMINISTRATION

SG may be dispensed only under the supervision of the PI or an authorized designee and only for administration to the study participants. The FDA-approved product labeling for SG includes a boxed warning for neutropenia and withhold if ANC < 1500 on D1 or < 1000 on D8) on the day of scheduled treatment.

SG is administered as an IV infusion on days 1 and 8 of a 21-day cycle. Dosing is based on the participant's body weight on day 1 and day 8 of each cycle. If the participant's body weight is within 10% of the previous cycle, the same dose may be carried forward based on local site procedures.

Do not administer as an IV push or bolus. Do not administer other drugs concurrently with SG through the same intravenous line.

SG has a known risk of infusion-related reactions. Therefore, for each participant, the first infusion will be run over 3 hours. If well-tolerated, subsequent infusions may be given over 1-2 hours. Participants will be monitored, including vital signs during each hour of the infusion and for at least 30 minutes following the completion of the infusion.

SG should be administered in a setting that allows for immediate access to an intensive care unit and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), intramuscular epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

To prevent or reduce the severity of infusion-related reactions, premedication with an antipyretic, an H1 and H2 blocker approximately 30 to 60 minutes prior to each dose of SG is mandatory for the first 2 infusions and is optional and at the discretion of the treating investigator after the second infusion.

If an allergic reaction occurs, the subject must be treated according to the best available medical practice. Please see the guidelines for anaphylaxis management in **Appendix B: Anaphylaxis Precautions**.

See Section **13.1.3** for drug preparation information.

3.2.1 Dose Modifications

Dose modification is allowed for infusion-related reactions. In these cases, SG infusion will be slowed or interrupted. For life-threatening infusion-related reactions, SG will be permanently discontinued. Other adverse events attributable to SG will be managed as per **Table 2**.

Table 2 reflects additional appropriate dose reduction and/or medical management [97].

Table 2: Recommended Dose Modification Schedule for SG

Adverse Reaction	Occurrence	Dose Modification or Action
Severe neutropenia		
Grade 4 neutropenia ≥ 7 days or less if clinically indicated, OR Grade 3 or Grade 4 febrile neutropenia, OR At time of scheduled treatment, Grade 3 or Grade 4 neutropenia that delays dosing by up to 3 weeks for recovery to ≤ Grade 1	First	Reduce dose to 7.5 mg/kg and administer granulocyte – colony stimulating factor (G-CSF) as soon as clinically indicated
	Second	Reduce dose to 5 mg/kg and administer G-CSF as soon as clinically indicated
	Third	Discontinue treatment and administer G-CSF as soon as clinically indicated
At time of scheduled treatment, Grade 3 or Grade 4 neutropenia that delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment and administer G-CSF as soon as clinically indicated
Severe nonneutropenic toxicity		
Grade 4 nonhematologic toxicity of any duration, OR	First	Reduce dose to 7.5 mg/kg

Adverse Reaction	Occurrence	Dose Modification or Action
Any Grade 3 or Grade 4 nausea, vomiting, or diarrhea due to treatment that is not controlled with antiemetics and antidiarrheal agents OR At time of scheduled treatment, Grade 3 or Grade 4 nonneutropenic hematologic or nonhematologic toxicity that delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	Second	Reduce dose to 5 mg/kg
	Third	Discontinue treatment
In the event of Grade 3 or Grade 4 nonneutropenic hematologic or nonhematologic toxicity, Grade 3 nausea, or Grade 3-4 vomiting that does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment
Infusion-related toxicities		
Grade 2 or Grade 3 infusion-related reaction despite optimal management	Recurrent	Discontinue treatment
Grade 4 infusion-related reaction	First	Discontinue treatment

3.2.1.1 Adverse Event Management

3.2.1.1.1 Gastrointestinal toxicities

Nausea, vomiting, and diarrhea are frequent toxicities associated with SG. Appropriate monitoring and treatment, including fluid and electrolyte replacement as clinically indicated, is required to minimize the risk of serious consequences such as dehydration. Instructions for SG dose modification for treatment-related toxicities are provided in **Table 2**.

3.2.1.1.1.1 Nausea and Vomiting

For prevention of chemotherapy-induced nausea and vomiting, a 2- or 3-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or a neurokinin 1 (NK1) receptor antagonist, as well as other drugs, as indicated) should be used as premedication.

Additional antiemetics and other supportive measures may also be employed as clinically indicated. All participants should be provided with a prescription with clear instructions for antiemetics to take at home for prevention and treatment of nausea and vomiting.

3.2.1.1.1.2 Diarrhea

At the onset of diarrhea, an evaluation for infectious causes should be performed and, if negative, loperamide should be promptly initiated at 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Loperamide should be discontinued 12 hours after the diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated.

Participants who exhibit an excessive cholinergic response to treatment with SG (e.g., abdominal cramping, diarrhea, salivation) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

If a participants develop diarrhea, anti-diarrheal agents and hydration will be initiated.

- The recommended treatment includes loperamide (Imodium) and 20 mg of diphenoxylate/atropine (Lomotil) administered according to package insert guidelines. If grade 2 diarrhea is seen in 2 subjects early in the trial, prophylactic antidiarrheals will be administered for all subsequent doses and cohorts.
- In case of diarrhea while on prophylactic loperamide, continue loperamide and start immediately two Lomotil tablets four times daily or 10 ml (two regular teaspoonfuls) of Lomotil liquid four times daily (20 mg per day). Most participants will require this dosage until initial control has been achieved, after which the dosage may be reduced to meet individual requirements.
- If no improvement in 48 hours after starting Lomotil, add Tincture (50 mg/5 mL) 6 mg (0.6 mL) by mouth (PO) every 6hr; not to exceed 6 mL/day. Prophylactic or therapeutic treatment with atropine in participants experiencing early onset diarrhea with cholinergic symptoms (0.25 mg to 1 mg, administered intravenously or subcutaneously), should be considered unless contraindicated.

3.2.1.1.2 Anemia

Anemia is a known adverse effect attributed to SG.

For anemia events assessed as treatment-related, items queried may include, but are not limited to, detailed relevant past medical and treatment history, bruising tendency, history of blood transfusions and/or dependency, and a request for an updated electronic Case Report Form (eCRF) including details such as concomitant medications, all laboratory data, updated dosing information and recent tumor evaluation scans.

A thorough investigation of new anemia cases of unspecified etiology is requested. Safety laboratory testing of relevant blood parameters is conducted per schedule of assessment.

General Guidance for anemia management and evaluation:

- Participants must enter the study with Hgb values at least 9 g/dL
- All relevant hematologic testing for treatment related anemias should be done prior to blood transfusion, if clinically feasible.
- Transfusion should be performed at the discretion of the treating investigator, based on clinical assessment and considered when participant experiences significant anemia.

Guidance for evaluation of suspected treatment-related anemias is provided in **Table 3**.

Table 3: Diagnostic workup for anemia

Baseline anemia evaluation (prior to transfusion, if feasible)	
CBC with differential (i.e., hemoglobin, hematocrit, MCV, RDW, WBC/ANC) and reticulocyte count Evaluation of CBC post-transfusion for adequacy of increase in hemoglobin/hematocrit Evaluation of CBC post iron repletion (PO or IV) for increase in hemoglobin/hematocrit, reticulocyte count, and RDW Complete metabolic panel, including liver function panel (AST/ALT, bilirubin), LDH, renal function, and serum folate/B12 Coagulation indices (PT, PTT, INR) Urinalysis and urine culture Iron panel (iron, TIBC, ferritin, transferrin saturation) TSH Fecal-occult blood testing Haptoglobin	
Further recommendation based on suspected etiology (in addition to baseline anemia testing)	
Unknown etiology, suspect hemolysis	Coombs test, fibrinogen, d-dimer, LDH Peripheral blood smear for cell morphological assessment Consider hematology consultation
Unknown etiology, suspect possible bleeding	Consider blood transfusion at clinical discretion. Consider gastroenterology consultation/ endoscopy (upper/lower) Consider surgical/interventional radiology (IR) consultation. Consider advanced imaging, as clinically indicated (e.g., FAST scan, CT scan, MRI, angiography).
Unknown etiology despite above work-up (including suspected aplastic anemia	Hematology consultation Consider bone marrow aspiration/morphologic evaluation
Management Options	
Packed red blood cell (PRBC) transfusion Iron repletion (in case of iron deficiency, as revealed above) – PO or IV iron repletion Erythroid growth factor support (i.e., erythropoietin) Addressing source of blood loss (endoscopy, vessel embolization by Interventional radiology (IR) Consideration for discontinuation of study medication	

3.2.1.1.3 Participants with reduced UGT1A1 activity

Participants homozygous for the *UGT1A1**28 allele are potentially at increased risk for adverse reactions, including neutropenia, febrile neutropenia, and anemia and are excluded from entry into this trial, but participants heterozygous *UGT1A1**28 allele are still at higher risk for grade 3 to 4 neutropenia, grade 3 to 4 febrile neutropenia and grade 3 to 4 anemia compared to patients homozygous for wild type allele as shown below in **Table 4**. These AEs will be managed as per **Table 2**.

Table 4: Incidence of Adverse Reactions in Patients with Reduced UGT1A1 Activity

Adverse event	Homozygous for *UGT1A1**28 Allele (N = 112) N (%)	Heterozygous for *UGT1A1**28 Allele (N = 420) N (%)	Homozygous for Wild-type Allele (N = 416) N (%)
Grade 3 to 4 neutropenia	65 (58%)	204 (49%)	180 (43%)
Grade 3 to 4 febrile neutropenia	16 (14%)	22 (5%)	23 (6%)
Grade 3 to 4 anemia	24 (21%)	41 (10%)	39 (9%)

3.3 On Study Assessments/Evaluations

3.3.1 Timing of Procedures

The following describes all tests and procedures to be conducted during treatment.

Refer to Study Calendar (Section **3.4**) for timing and applicable windows.

For each time period, consider the following order of assessments:

- **Screening**: Refer to Section **2.3**.
- **Baseline/Cycle 1 Day 1**: The results of all assessments must be available and reviewed prior to initiation of the study drug administration to ensure results still meet standards defined in eligibility criteria. All subjects are required to complete baseline evaluations per the Study Calendar (Section **3.4**) within 10 days prior to the first planned dosing of the study drugs, except for imaging tests that are required to be done within 14 (+3) days prior to treatment initiation. Any screening tests performed within the specified time frame for baseline do not need to be repeated.
- **Subsequent Cycles**:
    - Each cycle is 21 days. Beginning with Cycle 2, a permitted range of ±7 days due to scheduling or logistical reasons is permitted; however, day 1 of SG in a new cycle may be dosed no less than 14 days from the previous dose of SG (Day 8; [i.e., the Day 8 infusion will be counted as the first day of that 14-day period]). The Day 8 dose of SG may be given no earlier than 6 days from the Day 1 dose (-1/+2 days). The scheduled Day 1 and Day 8 infusions may be delayed for up to 3 weeks for treatment-related toxicities.
    - Pre-Day 1 of each cycle assessment may be done up to 4 days (-4) prior to the start of the cycle.
    - The results of all assessments must be available and reviewed prior to initiation of study drug administration in a new cycle to confirm safety and eligibility for ongoing treatment administration. Components of these panels that are specifically relevant to monitoring the effects of the study drug are specified in "Laboratory Assessment" later in this section. The remaining laboratory values collected on these panels are part of standard of care assessments and unrelated to research. The cycle should be delayed if these criteria are not met (refer to Dose Modifications, Section **3.2.1**).

- **Study Drug Administration:**
    - SG will be administered IV on D1 and D8 of 21-day cycles.
    - Treatment will be outpatient and will be given until unacceptable toxicity, trial withdrawal, progression/loss of clinical benefit as determined by the treating investigator (refer to Section **3.6.1**), or up to a maximum of 5 years.
- **Unscheduled Visits:** In the event of an unscheduled/unplanned visit (e.g., additional clinical assessment(s) due to toxicity), the treating investigator should use best clinical judgement as to the necessary assessments. In the event that the decision is made to continue treatment, all tests/assessments as required by the next visit on the Study Calendar (Section **3.4**) should still be conducted (or repeated) within the applicable windows. If a decision is made to discontinue treatment, the participant should move to the End of Treatment (EoT) visit, with tests/assessments completed (or repeated) within the applicable windows.
- **End of Treatment Assessments:** The EoT visit will be performed up to 14 days after the participant comes off treatment (see Section **3.6.1**) or before the initiation of a new anti-cancer treatment, whichever comes first.
- **30-day Safety Visit**: The mandatory Safety Follow-up (FU) visit should be conducted approximately 30 (+ 14) days after the last dose of study drug or before initiation of a new anti-cancer treatment, whichever comes first (see assessments, Section **3.4**). In addition, the study team will confirm contact information for participant and a designated family member and remind participant of follow-up contact that will be conducted for survival status. If the participant cannot return to the study center for this visit, the participant may complete assessments locally, including seeing a local physician for a physical exam and local clinical laboratories, and the study team will follow-up with the participant remotely.
- **Long-term Follow-up**: Overall survival will be collected for 10 years for all study participants. Participants will be contacted remotely (e.g., phone or email) approximately every 6 months (± 30 days) after the safety visit.
- **Additional Information:** If a physical exam and vital signs are required by the study calendar for participants on study therapy, then an in-person clinic visit is required. However, if participants are unable to travel to the study site for assessment during the specified window due to extenuating circumstances such as illness, travel restrictions, inclement weather, etc., every effort should be made for the participant to complete the required evaluation with their local medical provider. For safety visit, a telehealth visit may be conducted so that participants need not travel to the study site for evaluation unless preferred by the participant or felt to be clinically indicated by the provider. In these instances, participants will be contacted by phone, email or other institutional approved remote platform used in compliance with local policy (e.g., including HRPP Policy 303 for NIH participants).

3.3.2 Description of Procedures

The following is a description of all procedures:

- Symptom assessment: verbal review of participant's current symptoms to establish a baseline.
- Physical exam, including height, and weight: review of organ systems, weight (kg), height (at screening only)to determine eligibility and establish a baseline.
- Vital signs (i.e., temperature, blood pressure, heart rate and respiratory rate) performed at screening to determine eligibility and establish a baseline, and before, during and after each SG administration to monitor safety.
- Documentation of BRCA mutation (Cohort 1 only) from any certified lab to assess eligibility
- Documentation of and MMR status (Cohort 2 only) and HPV infection status (Cohort 3 only) from any certified lab to establish a baseline.
- Performance status (ECOG): an assessment of activities of daily living; see **Appendix A: Performance Status Criteria** to assess eligibility, and to assess response to therapy at subsequent timepoints.
- Laboratory assessments: the following comprises the required tests/analytes to assess eligibility at the time of screening, determination of baseline and treatment continuation per Section **3.2.1**, and/or the safety of the study drug at subsequent timepoints unless otherwise noted. Additional laboratories may be ordered as part of panels (e.g., acute care panel, comprehensive chemistry, etc.). Given that the methodologies utilized are similar across all laboratories, no significant variability is expected and there is no anticipation that study data will be affected.
    - CBC with differential
    - Serum Chemistries:
        - Acute care panel includes Sodium (Na), Potassium (K), Chloride (Cl) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen
        - Hepatic panel includes alkaline phosphatase (AP), ALT, AST, Total Bilirubin, Direct Bilirubin
        - Mineral panel includes Albumin, Calcium, Magnesium, Phosphorus
    - PT/INR and aPTT
    - CA125 (Cohorts 1 and 2 only)
    - Ionized calcium, amylase, lipase
    - Lactate dehydrogenase (LDH)
    - Viral screen: HBsAg, HIV and HCV antibody,
    - CD4 count and HIV VL if HIV positive; HCV viral load if HCV antibody positive
    - HPV DNA testing (Cohort 3 cervical cancer patients only)

  - Urinalysis
  - Pregnancy test (serum or urine β-hCG) in IOCBP
- Other evaluations:
  - Electrocardiogram (EKG) to determine eligibility
- Imaging scans:
  - Brain MRI – performed to assess eligibility
  - CT CAP scans with intravenous contrast. If a CT scan with intravenous contrast is contraindicated (e.g., in participants with impaired renal clearance), a non-contrast CT scan of the chest and MRI scans of the abdomen and pelvis should be performed.

    Imaging will be performed every 9 weeks (3 cycles) ± 7 days for the first year and every 12 weeks (4 cycles) ± 7 days thereafter until disease progression.
- Review of concomitant medications: Concomitant medications will be collected throughout the study until 30 days after the last dose of the study drug or start of new anticancer treatment, whichever comes first (also see Section **6.1**).
- Contraception review: Review of contraception use for IOCBP to assess eligibility and to determine continuation of treatment per Sections **2.1.1.4.13**.
- Correlative research samples: Refer to Section **5**.

3.4 STUDY CALENDAR

Procedure	**Screening**	**Cycle = 21 days**				**End of Treatment Assessments**	**30-day Safety Visit**	**Long-term Follow-up**
		Baseline/ C1D1	**C1D8**	**Subsequent Cycles D1**	**Subsequent Cycles D8**			
Window(s):	*≤3 weeks*	*≤10 days*	*-1/ +2 days*	*-4 days*		*+14 days*	*+14 days*	*every 6 months ±30 days for 10 years*
	Section 2.3.2	*Section 3.3.1*						
Confirmation of pathology/biopsy	X[1]							
Medical history	X							
Symptom assessment/Adverse events		X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X	
Vital Signs	X	X[5]	X[5]	X[5]	X[5]	X		
Weight	X	X	X	X		X		
Height	X							
Performance status (ECOG)	X	X	X	X	X	X	X	
Documentation of BRCA mutation (Cohort 1 only)	X[1]							
Documentation of MMR status (Cohort 2 only) and HPV infection status (Cohort 3 only)		X[1]						
Concomitant medications	X	X	X	X	X	X	X	
Review contraception	X						X	
Permitted as remote visits							X	
Ongoing survival assessment by phone, email, or other remote platform								X
Clinical Laboratories								
CBC with differential	X	X	X	X	X	X		
Acute care, mineral, and hepatic panels	X	X	X	X		X		
PT/INR and aPTT	X							

Procedure	Screening	Cycle = 21 days				End of Treatment Assessments	30-day Safety Visit	Long-term Follow-up
		Baseline/ C1D1	C1D8	Subsequent Cycles D1	Subsequent Cycles D8			
Window(s):	*≤3 weeks*	*≤10 days*	*-1/ +2 days*	*-4 days*		*+14 days*	*+14 days*	*every 6 months ±30 days for 10 years*
	Section 2.3.2	*Section 3.3.1*						
CA125		X[6]						
Ionized calcium, amylase, lipase		X						
LDH		X						
HIV, CD4 count, and reflex VL	X							
HBV	X							
HCV with reflex VL	X							
HPV DNA (Cohort 3 only)		X						
Urinalysis		X						
Pregnancy Test (serum or urine β-hCG)	X	X		X				
Radiology/ Other Assessments								
EKG	X							
CT scans	X[2]	X *within 14 (+3) days*		X *from C3 every 3 cycles ±7 days for the first year and then every 4 cycles ±7 days until PD or up to 5 years*		X		
Brain MRI [3]	X[2]	X *within 14 (+3) days*						
Study Drugs								
SG		X	X	X	X			
Correlative Studies								
Blood (5.1.2)		X	X[4]	X (*C3 only*)		X		

Procedure	Screening	Cycle = 21 days				End of Treatment Assessments	30-day Safety Visit	Long-term Follow-up
		Baseline/ C1D1	C1D8	Subsequent Cycles D1	Subsequent Cycles D8			
Window(s):	*≤3 weeks*	*≤10 days*	*-1/ +2 days*	*-4 days*		*+14 days*	*+14 days*	*every 6 months ±30 days for 10 years*
	Section 2.3.2	*Section 3.3.1*						
Tumor biopsy (5.1.3)		X				X (*optional*)		

1. *Performed within 10 years prior to treatment initiation*
2. *Performed within 4 weeks prior to treatment initiation*
3. *In participants with suspicion or prior history of treated CNS metastases only*
4. *Approximately 24-48 hours after the second dose of treatment*
5. *SG administration vital signs will include temperature, blood pressure, heart rate, and respiratory rate within 30 minutes prior to infusion, every 60 minutes during the infusion (±10 minutes), at end of infusion (±10 minutes), and 30 minutes post-infusion (±10 minutes)*
6. *For Cohorts 1 and 2 only.*

3.5 COST AND COMPENSATION

3.5.1 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.

3.5.2 Compensation

Participants will not be compensated on this study.

3.5.3 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.

3.6 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 after the last dose of study medication.

3.6.1 Criteria for removal from protocol therapy

- Completion of study therapy
- Progressive disease (see Section 6.3)
- Participant request/voluntary withdrawal from the study therapy
- Adverse events that require treatment discontinuation as explained in Section **3.2.1**
- Intercurrent illness that prevents further administration of treatment
- The treating investigator determines further treatment on this study is not in participant's best interest
- Pregnancy
- Requirement for use of prohibited therapies as listed in Section **4.1**

3.6.2 Off-Study Criteria

- Screen failure or failure to maintain eligibility prior to initiation of treatment
- Completion of 10-year follow-up period
- Study is stopped for any reason
- Participant request to be withdrawn from study
- Non-compliance with study treatment and/or testing
- Lost to follow-up.
- Death

3.6.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled clinic visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit for 2 months and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB-approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

Concomitant therapy consists of any medication (e.g., prescription drugs, over the counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the treating investigator and recorded in the participant's medical records.

4.1 PROHIBITED MEDICATION

- Drugs that inhibit UGT1A1 should not be administered while on study treatment. UGT1A1 inhibitors include indinavir, atazanavir, nilotinib, and sorafenib (as well as certain herbal extracts). UGT1A1 inducers should also be avoided. Additional guidance can be found in the following link: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority−approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section **2.1.1**), and during study treatment, until disease progression is documented and the participant has discontinued study treatment with the exception of palliative radiotherapy and local therapy.
- Any live attenuated vaccine therapies (e.g., FluMist®) for the prevention of infectious disease in the 4 weeks prior to initiation of study treatment, during and for 5 months following study treatment. Administration of inactivated vaccines (e.g., inactivated influenza vaccines), mRNA-based vaccines (e.g., Pfizer/BioNTech or Moderna vaccines against SARS-CoV-2) and monoclonal antibody treatment for acute treatment of SARS-CoV-2 is allowed per local regulatory guidelines.

- If the administration of a non-permitted concomitant drug becomes necessary during the trial, the subject will be withdrawn from trial treatment.

4.2 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 trial medication may be given at the treating investigator/designee's discretion.

In case of surgery, SG should be interrupted for one week prior to surgery, if possible, and 2 weeks after the surgical procedure; restarting may be delayed for 4 weeks for major surgery (e.g., abdominal surgery, cranial surgery). Participants should be clinically stable prior to restarting treatment.

Participants are permitted to use the following therapies during the study:

- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as. influenza, SARS-CoV-2)
    - Live, attenuated vaccines are not permitted (see Section **4.2**).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

4.2.1 Prevention of Infusion-Related Reactions

- Corticosteroids are permitted prior to the administration of SG for the prevention of infusion-related reactions or as part of an antiemetic regimen.
- Premedication with antipyretics and H1 and H2 blockers prior to the start of the SG infusion.

In general, the treating investigator should manage a participant's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Section **4.2**) as clinically indicated, per local standard practice. Participants who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2–receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated.

4.2.2 Growth Factor Support

Febrile neutropenia may occur with SG. Growth factors (i.e., G-CSF) will be recommended for the therapeutic management of neutropenia and as clinically indicated. For participants with homozygous *UGT1A1**28 alleles (or other allows associated with reduced UGT1A1 expression

and/or enzymatic activity) or with high risks as per ASCO guidelines, G-CSF support may be used as primary prophylaxis.

4.2.3 Transfusion Support

In prior clinical trials with SG, anemia occurred in 71% of participants (18% with Grade 3-4 anemia), and thrombocytopenia occurred in 25% of participants (2% with Grade 3-4 thrombocytopenia). Packed red blood cell (PRBC) transfusion will be allowed for the therapeutic management of symptomatic anemia and/or hemoglobin level below 9g/dL, as well as management of acute bleeding episodes. Diagnostic workup of anemia is detailed in Section **3.2.1.1.2**. In case of iron deficiency anemia, repletion with oral iron repletion is permitted. Intravenous iron repletion is also permitted if there is a contraindication to oral repletion or actual or anticipated intolerance to iron repletion. Platelet transfusion will be allowed for bleeding prophylaxis.

4.2.4 Antiemetic Support

SG is considered to be moderately emetogenic; in TROPHY-U-01 (IMMU-132-06), 64% of participants receiving SG monotherapy experienced nausea (all grades) and 35% of participants experienced vomiting (all grades). Premedicate with a two or three drug combination antiemetic regimen according to institutional practice standards and/or national guidelines. Intravenous fluids (IV fluids)/electrolyte repletion may be administered to support rehydration at the discretion of the treating investigator. See Section **3.2.1.1.1.1** / **Table 2** regarding dose modifications in the setting of persistent nausea/vomiting.

4.2.5 Antidiarrheal Support

SG monotherapy in TROPHY-U-01 (IMMU-132-06), 64% of participants experienced diarrhea (all grades), with 11% experiencing Grade 3 diarrhea. Subjects who exhibit acute onset diarrhea (within 24 hours of treatment) and/or an excessive cholinergic response to treatment with SG (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive subcutaneous atropine or other appropriate medication for subsequent treatments. Infectious causes of the diarrhea will be evaluated and if negative, loperamide will be administered at the onset of treatment-related Grade 1 or Grade 2 diarrhea, at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine. Consider adding octreotide 100-150 mcg subcutaneous (SC) three times per day if diarrhea persists. IV fluids/electrolyte repletion may be administered to support rehydration at the discretion of the treating investigator.

See Section **3.2.1.1.1.2** / **Table 2** regarding dose modifications in the setting of persistent diarrhea potentially attributable to SG.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

5.1.1 Sample Collection Table

Test/assay	Type of tube[a] and volume	Collection point	Location of specimen analysis[b]
Blood Samples			
Circulating tumor DNA (ctDNA)	2x10mL Streck Tube	C1D1(prior to treatment), C1D8 & C3D1 (within 48 hours after the SG dose), EOT/at progression	Biospecimen Processing Core (BPC)
Circulating tumor cells (CTC)	1x10 mL Streck Tube	C1D1(prior to treatment), C1D8 & C3D1 (within 48 hours after the SG dose), EOT/at progression	DTB Clinical Translational Unit
γH2AX expression	2x8 mL CPT blue/black tube	C1D1(prior to treatment), C1D8 & C3D1 (within 48 hours after the SG dose), EOT/at progression	
UGT1A1 genotyping	1x6 mL Lavender-top tube (K2EDTA)	C1D1 (prior to treatment)	BPC
Tumor Samples			
TROP2 IHC	FFPE , 1 core	Archival FFPE tissue if available, C1D1 (prior to treatment, mandatory except as noted in Section 5.1.3), EOT/at progression (optional)[c]	BPC/LP
Evaluation of DNA damage repair and other pathway genes (Next gene sequencing, whole genome sequencing and RNAseq)	FFPE/fresh frozen tissues, 3 cores		BPC/fee-for-service Core lab
TSO500	Archival, 10 unstained slides or tissue block	Archival FFPE tissues, C1D1 (prior to treatment)	LP

a. Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.
b. The location of specimen analysis may be adjusted at the time the analyses are performed
c. Biopsies may be not performed on the specific dates and times due to the following reasons, including but not limited to, delayed recovery of hematologic toxicities, delayed clinic schedule, or national holidays

5.1.2 Blood samples

Blood samples will be collected and processed according to validated standard operating procedures (SOPs) to maintain sample quality and participant confidentiality. All biospecimens will be collected during visits to NIH.

5.1.3 Tumor tissues

Baseline research tumor biopsies are mandatory for every subject who is deemed safely able to be biopsied by Interventional Radiologist review. Biopsies at progression are optional. If a biopsy is

done for clinical reasons, samples will also be collected for research at that time, if feasible. No more than 2 biopsies per subject will be done for research during the study.

Research biopsies will be performed under local anesthesia. General anesthesia may be provided as clinically indicated.

Pretreatment tumor biopsies will be obtained by minimally invasive methods such as CT guided percutaneous biopsies. The biopsy site will be determined by a discussion between an interventional radiologist and the study PI or AI.

Attempts will be made to obtain up to five cores if safe and feasible, which will be frozen for research studies. These tumor core biopsies will be obtained percutaneously or per vagina through interventional radiology as long as considered minimal surgical risk. Two 3-millimeter punch biopsies of skin will be acceptable in lieu of 18-gauge core biopsies for participants with skin involvement. Inability to get tissue with a reasonable attempt will not preclude treatment and the participant will remain eligible for all other translational components.

The use of imaging to facilitate biopsies will be decided upon by members of the interventional radiology team. Should CT scans be needed for biopsy, a limit of 2 scans for each procedure will be observed to minimize radiation exposure to the participant.

The schedule for the biopsies will be made with Special Procedures (e.g., Dr. Brad Wood). Members of the Biospecimen Procession Core (BPC) will be on call to receive and embed biopsies.

- One core biopsy will be sent to the LP to confirm the diagnosis and for TROP2 immunohistochemical staining (see Section **5.2.2.1**)
- The remaining core biopsies from pretreatment biopsy are to be immediately embedded, frozen, and stored, barcoded, in the BPC at -80^{o}C until use. At least one tissue core will be paraffin-embedded, barcoded, and stored in the BPC until use.

Any required consent for optional biopsies will be documented via procedure consents presented to the participants at the time of the procedure.

5.2 PLANNED ANALYSES

Note: Platforms and procedures may be adjusted based upon current technology and/or collaborations in place at the time of actual analyses.

5.2.1 *UGT1A1* Genotyping

Results from prior SG studies indicate that the frequency of some exposure related adverse events (i.e., anemia, neutropenia and febrile neutropenia) may be higher in subjects homozygous for the *UGT1A1**28 allele; however, the frequencies of neutrophil count decreased and other treatment-related adverse events, notably diarrhea, did not differ among the subgroups.

*UGT1A1**28 allele status will be evaluated as a possible marker of toxicity. Blood sample will be collected to analyze the genomic DNA and assess genotype of the most relevant drug metabolizing enzymes and transporters. DNA will be analyzed on a PharmacoScan™ (ThermoFisher) genotyping platform that tests for 4,527 genetic variations in 1,191 drug disposition genes, including CYP (phase I metabolism) genes, non-CYP (phase I metabolism) genes, phase II metabolizing genes (including UGTs), transporters, genes involved in facilitation of drug transporters, genes involved in global regulation of drug metabolizing/transporting proteins, drug binding proteins, and drug targets.

The genes encoding the drug metabolizing enzyme UGT1A1 will be evaluated. Since PharmacoScan does not test the (TA)8 repeat in rs3064744, a fragment analysis assay to test *UGT1A1* genotype was developed by the Clinical Pharmacology Program (CPP) [98]. This assay will be used by CPP to test this allele.

5.2.1.1 Analysis of circulating tumor cells (CTC)

CTCs will be assessed using ferrofluidic enrichment and multiparameter flow cytometric detection. CTCs will be identified as viable, nucleated cells, that positively express one or more epithelial or tumor markers and are negative for expression of hematopoietic markers. CTCs will be further characterized for marker expression, including TROP2.

5.2.1.2 γH2AX-staining

Peripheral blood mononuclear cells (PBMCs) will be assessed for γH2AX expression using multiparameter flow cytometry along with other markers.

5.2.2 Tumor studies

5.2.2.1 TROP2 IHC

TROP2 expression will be assessed by IHC to evaluate concordance (or discordance) between archival tumor tissues and fresh pretreatment biopsy samples. TROP2 IHC will be performed in one representative FFPE tumor section and evaluated independently by two pathologists at CCR/Laboratory of Pathology (LP).

In previous studies, membranous expression is clinically relevant in breast and gynecologic cancers for prognosis and the use of ADC [77, 79, 91, 99, 100]. Therefore, TROP2 expression will be evaluated for membranous expression. Appropriate negative and positive controls will be performed with each case. Protein expression will be quantified using H-score calculated as follows: (1 × percentage of weak staining) + (2 × percentage of moderate staining) + (3 × percentage of strong staining) within the target region, ranging from 0 to 300 [79, 91, 99]. The final immunoreactivity score will be then classified into four ordinal categories: H score 0–9, 10–99, 100–199, and 200–300 groups [79, 91, 99]. For the case where the H scores by two pathologists fall in different H-score groups, the two pathologists review the case together and get a consensus.

Please email to Dr. Sun A. Kim, MD PhD at suna.kim@nih.gov as soon as the participant is scheduled for biopsy.

5.2.2.2 DNA damage repair pathways

mRNA levels of key molecules of DNA damage response pathways (i.e., ATM, ATR, CCNE1 or RPA1) and/or specific mutations of genes will be assessed via Next gene sequencing/ whole genome sequencing/RNAseq along with γH2AX levels. This will be performed in an exploratory fashion. Results gleaned from the preliminary laboratory data in PI's lab and findings from the latest literature may modify the other endpoints of DNA damage response pathways.

5.2.3 Genomic studies

5.2.3.1 Circulating tumor DNA (ctDNA)

ctDNA can provide a noninvasive means of monitoring both longitudinal changes in tumor burden and participants' mutational profiles. The effects of ADCs on ctDNA and associations with

response are not fully elucidated. ctDNA will be sequenced along with tumor sequencing and will be further characterized for other mutations including *TROP2* gene.

5.2.3.2 Next gene sequencing, whole genome sequencing and RNAseq

Coded, linked samples will be provided to a collaborator or core lab/company for a fee-for-service for the next generation sequencing, RNAseq, or whole genome sequencing. Gene expressions of DNA repair/replication stress response and other survival pathways will be assessed using RNAseq analyses on freshly obtained tumor biopsy and correlated with clinical outcomes. Whole genome sequencing will be performed to identify *TROP2* mutations or other gene alterations and correlated with clinical outcome.

5.2.3.3 TSO500

TSO500 will be performed on archival tissue samples by the laboratory of pathology to complement the findings from RNAseq and/or whole genome sequencing. This will be a hypothesis-generating and research only test. Note that participants will not be informed of these results as they are research only.

5.3 Storage, Use, and Sharing of Specimens and Data (Including for Secondary Research)

5.3.1 Sample Tracking and Processing

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.

5.3.1.1 Biospecimen Processing Core (BPC)

Samples sent to the BPC will be placed immediately on wet ice and refrigerated. The date and exact time of each blood draw should be recorded on the sample tube

Please e-mail at 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 BPC number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

Upon arrival in the BPC, samples will be centrifuged and the plasma transferred into cryovials for storage at -80 C until the time of analysis.

5.3.1.2 DTB Clinical Translational Unit

As soon as the participant is scheduled, please send an email notification to the DTB Clinical Translational Unit. As soon as the sample is drawn, please call the lab at 240-760-6330 to communicate that the sample is ready, where the sample is located, and a lab member will pick up the sample.

Immediately after collection, invert the blood tubes 8-10 times. Blood samples must be kept at room temperature. The blood samples will be picked up by a member of the DTB Clinical Translational Unit.

5.3.2 Sample Storage and Disposition

Barcoded samples are stored in barcoded boxes according to stability requirements. Access to stored clinical samples is restricted. Unless other permission obtained, samples are only to be used for research purposes associated with this trial (as per the IRB-approved protocol) by investigators named on the protocol. It is the responsibility of the Principal Investigator to ensure that samples are being used in a manner consistent with IRB approval.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of a sample tracking database (e.g., Labmatrix). It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, to correlate results with sample characteristics.

5.3.3 Protocol Completion/Secondary Use/Sample Destruction

Any specimens remaining at the completion of the protocol will be stored indefinitely in the conditions described above. The study will remain open so long as sample or data analysis continues. All samples and data from consenting participants will be stored in identifiable format until they are no longer of scientific value or if a participant withdraws consent for their continued use, at which time they will be destroyed.

If, at any time, a participant 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 participant, if so requested. The participant's samples and data will be excluded from future distributions, but those which have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

through a code available to the study team, will be stored indefinitely and used for secondary research, including genetic research. Furthermore, the data and/or specimens, may be shared with other investigators in identifiable or coded (code key not available to recipient) format for secondary research. Any investigator conducting secondary research in human subjects will seek either additional regulatory approval or exemption for research as appropriate.

Data will also be shared in public database per the study's data sharing plan in compliance with NIH policies.

In addition, specimens/data may be anonymized and further research, including genetic research, conducted at the site or other institutions without participant consent. Participants will be informed that the possibility for this type of research exists.

5.4 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.4.1 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 will be performed on tumor samples collected pre-treatment, on-treatment and/or post-progression. Genetic/genomic analysis will be performed by the core lab/company for a fee-for-service.

5.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized.

Initially the samples of each participant will be barcoded. At no time will participant's names be used on the blood and tissue samples. Sometimes, because a group collaboration or journal policy requires it, a subject's genetic data will be deposited in a database such as dbGaP. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.4.3 Management of Results

Whole genome/exome sequencing on this study is limited to tumor samples. No germline whole genome sequencing is performed; therefore, it is not feasible to return secondary findings. If we encounter a medically significant incidental finding, we may coordinate with the IRB, the ethics consult service, and the genetic consult service to explore on a case-by-case basis.

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. 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.

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

Document AEs from the first study intervention, Study Day 1 through 30 days after the subject received the last product administration. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

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 participant's outcome.

The PI (or designee) evaluation of each AE not captured in the clinical database determining that it meets the criteria above will be documented in the source documents. Note: the investigator

performing the assessment must be a clinician licensed to diagnose and listed on the FDA Form 1572.

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

6.2 PUBLICATION AND DATA SHARING POLICY

6.2.1 NIH Data Management and Sharing Policy and NIH Genomic Data Sharing Policy Compliance

This study will comply with the NIH Data Management and Sharing (DMS) Policy, which applies to all new and ongoing NIH-funded research in the IRP, as of January 25, 2023, that is associated with a ZIA, with a clinical protocol that undergoes scientific review and/or will involve genomic data sharing.

This study will comply with the NIH Genomic Data Sharing (GDS) Policy, which applies to all new and ongoing NIH IRP-funded research, as of January 25, 2015, that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

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

6.2.2 NIH Public Access Policy Compliance

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

6.3 RESPONSE CRITERIA

For the purposes of this study, participants should be re-evaluated for response as noted in Section **3.1**. In addition to a baseline scan, confirmatory scans should also be obtained within 8 weeks (not less than 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) [101]. 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:

- By chest x-ray: ≥20 mm;
- By CT scan:
    - Scan slice thickness 5 mm or under: as ≥10 mm
    - Scan slice thickness >5 mm: double the slice thickness

- 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 participant, 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 participant 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[102, 103]. 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 [104].

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:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. 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.

c. 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).

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 participant 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.

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).

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 participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants 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	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*

* *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: Participants 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.

6.3.4 Duration of Response (DOR)

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)

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

6.3.6 Overall survival (OS)

OS is defined as the length of time from start of treatment until death from any cause.

6.3.7 Response Review

Tumor measurements will be performed by the CCR radiologist.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant 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/hrpp-policy-guidelines/.

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/hrpp-policy-guidelines/. Note: Only IND Safety Reports that meet the definition of an unanticipated problem or present new information that might affect the willingness of participants to enroll or remain on the study 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/hrpp-policy-guidelines/.

7.2.3 NCI Clinical Director Reporting

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director; 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 should 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 to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.3 NIH Required Data and Safety Monitoring Plan

7.3.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (weekly) 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 PI or a lead AI. Events meeting requirements for expedited reporting as described in Section **7.2.1** will be submitted within the appropriate timelines.

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

8 SPONSOR PROTOCOL/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 Section **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.

8.2 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 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 principal investigator or sub-investigator.

With the exception of any listed in Section **8.4**, reporting is required for all serious adverse events occurring from the first study intervention, Study Day 1, through 30 days after the subject received the last product administration. After 30 days, only adverse events which are serious and related to the study investigational agent need to be reported.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria 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** .

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://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI

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 disease progression and death are part of the study objectives (OS, 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

Reporting will be per the collaborative agreement.

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://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI

8.6.1 Maternal exposure

Participants should refrain from becoming pregnant during the study and for 6 months after the last dose of SG.

If a participant 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 becomes known.

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

The outcome of all pregnancies occurring from the date of the first dose of study therapy until 6 months after the last dose of study therapy should be followed up and documented.

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 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

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) 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, 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

10 STATISTICAL CONSIDERATIONS

10.1 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the ORR of SG in participants with recurrent gynecological malignancies, calculated for each individual tumor histology by RECIST v1.1	ORR (RECIST v1.1) assessed by radiographical evaluation i.e., CT/MRI every 9 weeks (+/- 1 week) for the first year and then every 12 weeks (+/-1 week) until PD or up to 5 years and at EOT which occurs within 14 days after the end of therapy.	Standard endpoint for phase 2 cancer clinical trials. Success of regimens will be determined by these endpoints.
Secondary		
To determine the safety of SG	Identify adverse events (AE) per CTCAE v5.0, by type and grade of toxicity on Days 1, 8, and 15 of each cycle, at EOT which occurs within 14 days after the end of therapy, and 30 days after the end of treatment. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention will be assessed.	Safety is a standard endpoint for clinical trials (collecting information on all major organ function and observed toxicity, if any, to determine prominent toxicity to advise safety).
To determine the PFS of participants receiving SG	Participants will be assessed for PFS by CT CAP at every restaging every 9 weeks for the first year and then every 12 weeks until PD or up to 5 years and at EOT which occurs within 14 days after the end of therapy.	Standard endpoints for correlative studies. These endpoints will explore changes within timepoints as stipulated within the protocol to understand the effect of SG.
To determine the OS of participants receiving SG	Participants will be assessed for OS from start of treatment. OS will be collected on Days 1, 8, and 15 of each cycle for up to 5 years, at EOT which occurs within 14 days after the end of therapy, 30-day safety visit and every 6 months during follow up for up to 10 years.	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To determine the median DoR of SG	Participants will be followed until progression after completion of study therapy and assessed by CT CAP very 9 weeks for the first year and then every 12 weeks until PD or up to 5 years and at EOT which occurs within 14 days after the end of therapy.	
Exploratory		
To evaluate *UGT1A1**28 allele as a predictive marker for gastrointestinal and hematologic toxicities	*UGT1A1* allele genotype will be measured at baseline.	*UGT1A1* genotype influences the rate of metabolism of SN38 and has been shown to correlate with toxicity in prior trials of SG. This data can guide management of toxicity for participants in this study and future clinical trials.
To evaluate the concordance (or discordance) of TROP2 expression between archival tissues and pretreatment fresh biopsies	The concordance of TROP2 protein expression levels by IHC (median H-scores) between archival tissue samples and fresh pretreatment biopsy	Preclinical data suggest TROP2 expression may change (either decrease or increase) over time but most clinical trials use archival tissue samples to assess TROP2 expression. Our data on the concordance (or discordance) of TROP2 expression between archival and pretreatment samples can help understand SG's biology in participants.
To identify mutations of TROP2 gene (*TACSTD2*) in tumors with resistance against SG	TROP2 surface protein expression from tumor tissue will be measured at baseline (i.e., prior to study treatment)	Correlates of TROP2 expression, specific transcriptomic, and/or mutational profiles and response can guide appropriate selection of participants in future study if the primary objective is met.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To investigate systemic pharmacodynamic biomarkers before and after SG treatment (i.e., ctDNA, CTC, and γH2AX expression)	Potential PD or predictive biomarker endpoints of DNA damage response pathways from blood will be measured at baseline, C1D8, C3D1, and EOT which occurs within 14 days after the end of therapy and from tumor tissue at baseline and EOT which occurs within 14 days after the end of therapy.	Determine baseline and treatment expression of biomarkers of response.

10.2 Statistical Hypothesis

Treatment with SG will result in a higher ORR than standard-of-chemotherapy regimen (> 15% ORR).

10.3 Sample Size Determination

The sample size calculation is determined based on the same calculations for each of the three cohorts separately. In participants with recurrent/metastatic ovarian cancer, endometrial cancer, and cervical cancer, previous studies suggest that response ranges from approximately 10-15% using single agent chemotherapy [25, 26], which is what we aim to improve upon.

For each of cohorts 1, 2, and 3, we will conduct separate phase II studies. For each cohort, the objective is to rule out an unacceptably low ORR (CR + PR) of 15% (p0 = 0.15) in favor of an improved ORR (CR + PR) of 35% (p1 = 0.35). Using a Simon two-stage minimax design, assuming a power of 80% and a type 1 error rate (one-sided) of 10%, the first stage will enroll 10 participants. If during the first stage, 0 or 1 of the first 10 participants have a response, the cohort will stop early for futility. If 2 or more of the first 10 participants have a response, 12 additional participants will be enrolled in the cohort, for a total of 22 participants in that cohort.

In order to ensure that enrollment to the second stage is warranted, a temporary pause may be employed after accrual to the first stage if additional follow-up time is needed to assess the number of responses. If after the second stage, there are 6 or more participants with a response out of 22 (6/22= 27.3%) participants, the treatment would be deemed interesting for further study in later trials. If 2 to 5 out of 22 participants have a response, then further investigation of the treatment would not be warranted.

The trial may accrue up to 22 + 22 + 22 = 66 evaluable participants if all three cohorts proceed to the second stage. To allow for a small number of inevaluable participants (9) and screen failures (20), the accrual ceiling will be set at 95. It is anticipated that up to 2-3 participants per month may be enrolled on this trial. Accrual is therefore expected to be completed within 3 years.

10.4 Population for Analysis

10.4.1 Evaluable for toxicity

Any participant receiving at least one dose of either agent will be evaluable for toxicity.

10.4.2 Evaluable for objective response

Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated at the restaging scans will be

considered evaluable for response. These participants will have their response classified according to the definitions stated in Section **6.3**. (Note: Participants who exhibit objective disease progression before their scheduled first restaging scans may be considered evaluable).

10.5 STATISTICAL ANALYSES

10.5.1 General approach

ORR will be reported by disease cohort along with a confidence interval.

Toxicities will be reported by grade and type; PFS, and OS will be reported by cohort along with a confidence interval.

10.5.2 Analysis of the Primary Endpoint

ORR (the fraction of PR or CR) will be calculated along with a 95% confidence interval for each cohort.

The proportion of participants who achieve a response will be reported separately for each cohort, along with 95% confidence intervals (Clopper-Pearson).

10.5.3 Analysis of the Secondary Endpoints

10.5.3.1 Safety

Safety will be reported by describing AE per CTCAE v5.0, by type and grade of toxicity, as detailed in Section **6.3**.

10.5.3.2 Clinical Efficacy

The assessment of clinical activity as determined by:

- DOR will be calculated by the Kaplan-Meier method, starting at date response was identified until progression or the response is declared to have ended, if the participants have a PR or CR. The median DOR will be reported along with a 95% confidence interval by cohort.
- PFS will be calculated from on-study date until date of progression or death without progression, using the Kaplan-Meier method by cohort. The median PFS will be reported along with a 95% confidence interval by cohort.
- OS will be calculated from on-study date until date of 10-year follow-up, using the Kaplan-Meier method by cohort. The ten-year OS rate, which is the percentage of people in a study or treatment group who are alive ten years after their initiation of the study treatment. The median OS will be reported along with a 95% confidence interval by cohort.

10.5.4 Safety Analyses

To assess safety in previously treated ovarian, endometrial, and cervical cancer participants, the toxicity grade and type will be reported for all participants treated in the three cohorts or separately by cohort.

10.5.5 Baseline Descriptive Statistics

Baseline demographic characteristics will be reported, separately by disease cohort.

10.5.6 Planned Interim Analyses

Interim analyses for efficacy will be performed after the first stage of the two-stage design as appropriate.

Separately for each cohort, after the first restaging scan of the last evaluable participant 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 to document the number of responses in the first stage. The memo will be provided to 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.

10.5.7 Sub-Group Analyses

Analyses will be reported by cohort. Results presented in an exploratory fashion.

10.5.8 Exploratory Analyses

Planned exploratory analyses are detailed in Section **5**.

Each of these will be done using descriptive methods only and reported as exploratory results. If any statistical tests are performed in these analyses, the results will be presented without adjustment for multiple comparisons but reported in the context of the number of tests performed.

11 COLLABORATIVE AGREEMENTS

11.1 Cooperative Research and Development Agreement (CRADA)

This study will receive SG under a CRADA with Gilead Sciences, LLC (CRADA # C-098-2024*)*.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale For Subject Selection

Participants with relapsed/refractory ovarian, endometrial, and cervical carcinomas will be evaluated for participation in this study. Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the participant's medical status.

Pregnant participants are excluded from this study because SG is an investigational agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with SG*,* nursing should be discontinued or not started until 1 month after the last dose of study drug.

12.2 Participation of Children

Because no dosing adverse event data are currently available on the use of SG in subjects <18 years of age, children are excluded from this study.

12.3 Risk/Benefit Assessment

12.3.1 Known Potential Risks

12.3.1.1 Study drug

Please refer to the risks outlined in Section **13.1.2**.

12.3.1.2 Study procedures

12.3.1.2.1 Blood draws

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting. Up to 83 mL of research blood may be collected at any visit but no more than 211 ml in an 8-week period.

12.3.1.2.2 Urine collection

No physical risks are associated with urine collection.

12.3.1.2.3 Electrocardiogram (EKG)

Some skin irritation can occur where the EKG electrodes are placed. The test is completely painless, and generally takes less than a minute to perform.

12.3.1.2.4 Tumor biopsy

Needle biopsy is minimally invasive and is typically a very safe procedure. Depending upon the site being biopsied and the type of biopsy being performed, risks can include infection of the biopsy site, development of a hematoma, and bleeding. Rarely more significant complications can occur when structures near the biopsy target are entered with the needle (e.g., puncture of lung or bowel). Surgical procedures for biopsy specimens will not be conducted for the sole purpose of research specimen collection, although when surgical biopsies are performed for clinical or protocol requirements, samples may be requested as part of participation on this trial. In this instance, no added risk is incurred. In addition, as the biopsies may be collected under CT guidance, subjects in this study may be exposed to radiation as discussed below.

12.3.1.2.5 Local anesthesia

Biopsies may be done under local anesthesia. Potential side effects of local anesthesia include drowsiness, headaches, blurred vision, twitching muscles or shivering, continuing numbness, weakness or pins and needles sensation.

12.3.1.2.6 General anesthesia

Risks of general anesthesia include temporary confusion and memory loss, although this is more common in the elderly, dizziness, difficulty passing urine, bruising or soreness from the IV drip, nausea and vomiting, shivering and feeling cold, sore throat due to the breathing tube.

12.3.1.2.7 CT Imaging

In addition to the radiation risks discussed below, CT scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heart rate and swelling.

12.3.1.2.8 MR imaging

Participants undergoing gadolinium enhanced MRIs may also be at risk for kidney damage. MRIs include the additional risk of damage to hearing.

12.3.1.2.9 Exposure to radiation

On this study, participants may receive up to 3 CT-guided biopsies and up to 7 CT scans/year. The total radiation dose for research purposes will be approximately 12.5 rem. The risk of getting cancer from the radiation exposure in this study is 1.3% and of getting a fatal cancer is 0.6%.

12.3.2 Known Potential Benefits

The potential benefit to a participant that goes onto study is a reduction in the bulk of their tumor which may or may not have favorable impact on symptoms and/or survival. Long range potential benefits of this study will build on knowledge and the science used to develop therapies for future cancer participants.

12.3.3 Assessment of Potential Risks and Benefits

Participants who have relapsed/refractory ovarian, endometrial, and cervical carcinomas may benefit from receiving SG monotherapy, which they would otherwise not obtain in a standard of care setting. Immediate potential benefits include potential response to tumor progression, palliation of symptoms, and improved outcomes. A number of clinically appropriate strategies to minimize risk to participants have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines. Overall, the potential benefits of SG for this group of participants outweigh the risks associated with the proposed entry into this protocol.

12.4 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant 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 site 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. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant 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). 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://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.REGULATORY AND OPERATIONAL CONSIDERATIONS

12.5 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) 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/or Food and Drug Administration (FDA).

12.6 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 for 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.

12.7 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 NIH 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.

12.8 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. 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 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 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 sites will be secured and password protected. At the end of the study, all study databases will be archived at the NIH Clinical Center.

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.

13 PHARMACEUTICAL INFORMATION

13.1 SACITUZUMAB GOVITECAN (IMMU-132; TRODELVY) (IND # 166593)

13.1.1 Source/Acquisition and Accountability

Commercial stock of SG is manufactured and provided by Gilead Sciences. The commercial supply will be delivered directly to the NIH Pharmacy. Expired or unused product will be returned to the manufacturer or disposed of according to standard site procedures based on agreement between the manufacturer and the site.

13.1.2 Toxicity

Per the investigator brochure, the most common adverse reactions (incidence > 25%) occurring with SG are decreased leukocyte count, decreased neutrophil count, thrombocytopenia, decreased hemoglobin, diarrhea, nausea, fatigue, vomiting, alopecia, anemia, constipation, decreased appetite, increased glucose, decreased albumin, decreased creatinine clearance, increased alkaline phosphatase, decreased magnesium, decreased potassium, and decreased sodium. Serious reactions include diarrhea and neutropenia.

Please see package insert for additional information.

13.1.3 Formulation and Preparation

Please see package insert.

13.1.4 Stability and Storage

Please see package insert.

13.1.5 Administration Procedures

SG will be administered on this study as described in Section **3.2**.

SG should be administered in a setting that allows for immediate access to an intensive care unit and administration of therapy for anaphylaxis.

Do not administer as an IV push or bolus. Do not co-administer other drugs through the same intravenous line.

13.1.6 Incompatibilities

Please see package insert.

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15 LIST OF ABBREVIATIONS

Abbreviation	Term
ADC	Antibody-drug conjugate
AE	Adverse Event/Adverse Experience
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATR	Ataxia telangiectasia and RAD3-Related
ATRi	Ataxia telangiectasia and RAD3-Related inhibitor
BPC	Biospecimen Processing Core
BRCA mut	BReast CAncer gene mutant
BRCA wt	BReast CAncer gene wild-type
CAP	Chest, abdomen, and pelvis
CBC	Complete blood count
CBR	Clinical benefit rate
CCR	Center for Cancer Research
CCTV	Clinical Center TV
CFR	Code of Federal Regulations
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COV	Close-out Visit
CPP	Clinical Pharmacology Program
CR	Complete Response
CRADA	Cooperative Research and Development Agreement
CRIS	Clinical research information system
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTEP	Cancer Therapy Evaluation Program
DMS	Data Management and Sharing
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
EoT	End of treatment
FDA	Food and Drug Administration

Abbreviation	Term
FDG	Fluorodeoxyglucose
FFPE	Formalin fixed paraffin embedded
FU	Follow-up
GCP	Good Clinical Practice
G-CSF	Granulocyte – Colony Stimulating Factor
GDS	Genomic Data Sharing
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-wide association studies
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
Hgb	Hemoglobin
HGSOC	High grade serous ovarian cancer
HHS	Health and Human Services
HIV	Human immunodeficiency virus
HRD	Homologous repair deficiencies
HRPP	Human Research Protection Program
ICH	International Council for Harmonisation
ICI	Immune checkpoint inhibitor
IHC	Immunohistochemistry
IMV	Interim Monitoring Visit
IND	Investigational New Drug
INR	International Normalized Ratio
IOCBP	Individuals of child-bearing potential
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LP	Laboratory of Pathology
LVSI	Lymphovascular space invasion
MCV	Mean corpuscular volume
MMR	Mismatch repair
MOP	Manual of Operational Procedures
MRI	Magnetic Resonance Imaging
MSI-H	Microsatellite instability high
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCT	National Clinical Trial (number)
NIH	National Institutes of Health

Abbreviation	**Term**
NK	Neurokinin 1
NSMP	Non-specific molecular profile
OHSRP	Office for Human Subjects Research Protections
OPR	Office of Patient Recruitment
ORR	Objective Response Rate
OS	Overall survival
OSRO	Office of Sponsor and Regulatory Oversight
PARPi	Poly-ADP-Ribose Polymerase inhibitor
PBMC	Peripheral blood mononuclear cell
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PDTS	Protocol Deviation Tracking System
PET	Positron Emission Tomography
PFS	Progression-free survival
PI	Principal Investigator
PO	Per Os
POLEmut	Polymerase ε ultramutated
PR	Partial Response
PRBC	Packed red blood cell
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
RBC	Red blood cell
RDW	Red cell distribution width
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RR	Response rate
SAE	Serious Adverse Event/Serious Adverse Experience
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAV	Site Assessment Visit
SC	Subcutaneous
SCC	Squamous cell carcinoma
SD	Stable disease
SEC	Serous endometrial cancer
SG	Sacituzumab govitecan
SGO	Society of Gynecologic Oncology
SIV	Site Initiation Visit
SNP	Single nucleotide polymorphisms
SOP	Standard Operating Procedure
SROS	Sponsor Regulatory Oversight Support
TNBC	Triple negative breast cancer

Abbreviation	**Term**
TOP1	Topoisomerase 1
TOP1i	Topoisomerase 1 inhibitor
TRAE	Treatment-related adverse events
TROP2	Trophoblastic cell surface antigen 2
TSH	Thyroid Stimulating Hormone
UGT1A1	Uridine diphosphate-glucuronosyltransferase 1A1
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VL	Viral load
WBC	White blood cells
WMB	Women's Malignancies Branch

16 APPENDICES

16.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

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

16.2 APPENDIX B: ANAPHYLAXIS PRECAUTIONS

16.2.1 Equipment needed

- Monitoring devices: EKG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

16.2.2 Procedures

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous EKG and pulse oximetry monitoring, if possible.
5. Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.
7. Draw serum/plasma samples for immunogenicity testing.
8. Ask participant to return for washout immunogenicity sample if appropriate.