Sacituzumab Govitecan in Patients With Metastatic Castration-Resistant Prostate Cancer Progressing on Second Generation AR-Directed Therapy

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A Multi-arm, Phase 2 Study to Evaluate the Safety and Efficacy of Sacituzumab Govitecan in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Progressed on Second Generation AR-Directed Therapy

Prostate Cancer Clinical Trials Consortium, LLC (PCCTC)

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APPROVAL OF PROTOCOL

Title:

A Multi-arm, Phase 2 Study to Evaluate the Safety and Efficacy of Sacituzumab Govitecan in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Progressed on Second Generation AR-Directed Therapy

Sponsor/Sponsor-Investigator Signature: _____

Print: _____

Date: _____

PCCTC Signature: _____

Print: _____

Date: _____

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the University of Wisconsin with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice (GCP) principles, as adopted by applicable laws and regulations, and to abide by the terms of this protocol.

Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

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1. INTRODUCTION

1.1 Study Rationale

Androgen Receptor Signaling Inhibitors (ARSIs) including the CYP-17 inhibitor abiraterone acetate (administered with prednisone) and the next generation anti-androgen enzalutamide have been shown to improve survival in patients with prostate cancer.[1,2] This includes patients with newly diagnosed, metastatic hormone sensitive prostate cancer and those with castration-resistant prostate cancer (CRPC).[3,4] Abiraterone acetate inhibits CYP17 leading to a reduction in androgen biosynthesis but by targeting both the 17-OH and the lyase portion of the enzyme, glucocorticoid production is also reduced and there is unopposed production of mineralocorticoids.[5,6] Prednisone acts centrally to reduce mineralocorticoid production, reducing the side effects of mineralocorticoid excess. Enzalutamide is a next-generation anti-androgen that has greater avidity to the androgen receptor (AR) than first generation compounds, and uniquely inhibits nuclear translocation of the AR to the nucleus, and binding of the receptor complex to DNA.[6]

A review of the post-therapy PSA change patterns seen with these agents can be categorized into three distinct categories: rapid and durable declines consistent with sensitivity, no decline consistent with intrinsic resistance or decline and later progression consistent with acquired resistance.[7] These mechanisms of resistance can be quite diverse, extending from genomic alterations (e.g., AR amplifications/point mutations/rearrangements), transcriptomic alterations (e.g., AR splice variants) and neuroendocrine differentiation among others[8-12]. We are at an early understanding of the frequency of patients with these signatures and the timing during which these resistance mechanisms develop. The clinical and therapeutic impact of these alterations is observed in retrospective studies showing the response to enzalutamide in patients who have been treated with abiraterone acetate plus prednisone,[13,14] and separately, the response to abiraterone acetate plus prednisone in patients previously treated with enzalutamide[15,16] is significantly lower than patients not previously treated with either drug (Table 1). Equally important is that sensitivity to one does not predict sensitivity to the other: some patients show sensitivity or resistance to both, while others respond to one and not the other. Patients progressing on either of these oral agents are faced with the prospect of intravenous cytotoxic chemotherapy using docetaxel or platinum doublets, or the use of Radium 223 in patients with bone only metastases as the next-line treatment. These limited options create a critical need for new therapies that target resistant prostate cancer, including single agent and combination strategies.

This study will investigate the safety and efficacy of Sacituzumab Govitecan in patients progressing on ARSIs. Patients who have progressed while on therapy with combination enzalutamide/abiraterone or ARN-509/abiraterone as part of ongoing clinical trials are allowed and may be enrolled in the study. To better understand the heterogeneity of response and in particular to identify patients likely to benefit, an extensive correlative biomarker program will be included to collect and analyze tumor tissue biopsies, circulating tumor cells (CTCs), and circulating tumor DNA (ctDNA).

A validated predictive biomarker would benefit the individual patient by enabling him to be treated with a safe effective oral drug and avoid one from which he is unlikely to benefit. It is also essential for prostate cancer drug development because the increasing availability of more life-

prolonging therapies is making it more difficult to prove a survival benefit for the next promising agent.

1.2 Prostate Cancer

Prostate cancer is the most common cancer in men, and the second leading cause of cancer deaths in men.[17] In men with early-stage (localized) prostate cancer, currently available local therapies are successful: 8-year freedom from metastatic disease is 97% in men undergoing radical prostatectomy and 93% in men undergoing radiation therapy.[18] However, once prostate cancer has spread beyond the prostate gland or the immediate surrounding tissue, systemic therapy is indicated.

First-line systemic treatment for metastatic disease with androgen deprivation therapy (ADT) has long been shown to lead to a decline in PSA and tumor regression. The addition of abiraterone acetate or docetaxel in men with hormone sensitive, metastatic prostate cancer has been shown to improve survival compared to ADT alone.[3,4,19] Unfortunately, these treatments are not curative and men invariably develop a rise in PSA and tumor growth as a castration resistant tumor (CRPC) which for most men is lethal. Approved therapies shown to confer a survival benefit in men with CRPC include: Sipuleucel-T, abiraterone acetate plus prednisone, enzalutamide, apalutamide, darolutamide, docetaxel, cabazitaxel, and radium-223.[2,20-24] For men with CRPC, abiraterone acetate plus prednisone and enzalutamide are often used as first-line systemic treatment for CRPC, unless abiraterone was used in the hormone sensitive setting. After progression on either one of these agents the likelihood of response to the other is lower than in the first-line setting (**Table 1**). Specifically, PSA response rates (≥50% decline from baseline) to enzalutamide after progression on abiraterone are 21-27% in docetaxel-naïve patients.[15,16] Many patients seek to avoid cytotoxic therapy and, even before the more recently approved drugs became available, a significant proportion of these men did not receive it. The identification of an effective therapy after progression on enzalutamide or abiraterone represents a significant unmet clinical need that would spare patients the toxicity of an intravenous cytotoxic therapy that is similarly less efficacious in the post-AR and AR signaling directed therapy.

Table 1. PSA response rate (≥50% decline) to abiraterone acetate/prednisone, enzalutamide or docetaxel is lower after prior AR targeted treatments

	Response rate first-line [2,20,23]	Response rate second-line [15,16,25-27]	Response rate third- line [13,14,28,29]
Enzalutamide	78%	25%	~20%
Abiraterone	62%	25%	~5%
Docetaxel	48%	35%	NR
Response defined as ≥50% decline in PSA from baseline at any time point			

1.3 Sacituzumab Govitecan Pharmacology, Pre-clinical and Clinical Experience

Sacituzumab Govitecan is a novel Antibody Drug Conjugate (ADC) based on a humanized anti-Trop-2 antibody (hRS7) conjugated to an SN-38 payload. Trop-2 (trophoblastic cell-surface antigen; also known as EGP-1, epithelial glycoprotein-1), is a cell surface, transmembrane calcium signal transducer glycoprotein belonging to the TACSTD gene family that is highly expressed in many epithelial cancers, particularly metastatic sites, with much lower expression in normal tissues. Trop-2 has been implicated as an important antigen in oncogenesis, often being found in

more aggressive tumors.[30] The murine RS7 antibody was initially identified as being specific for epithelial glycoprotein-1 (aka, Trop-2), being found in a number of different epithelial cancers and it was internalized,[31-33] a highly desirable property for an antibody-drug conjugate. While Trop-2 is highly conserved among various species, the hRS7 antibody does not bind to murine Trop-2, but an immunohistology study of monkey tissues showed hRS7 bound to Trop-2 and had a similar distribution as found in humans.[34] Thus, a toxicology study was performed with Sacituzumab Govitecan with the purpose to assess the dose-limiting toxicity and to determine if Trop-2 expressing normal tissues would limit the use of this conjugate. Two doses were administered within one week (3 days apart) at a cumulative amount of 120 and 240 mg/kg (1.92 and 3.84 mg/kg of SN-38; human equivalent dose of the conjugate was 38.7 and 77.4 mg/kg).[34] At 120 mg/kg, there was evidence of myelosuppression, within 3 days, but the decrease in counts did not achieve gradable levels and were completely restored within 10-14 days. No significant change in serum chemistries or tissue pathology was noted. At the 240 mg/kg, severe GI and hematological toxicities occurred, and thus the maximum tolerated dose had been exceeded. Thus, the conjugate displayed a similar toxicity profile as irinotecan itself has major gastrointestinal and hematologic toxicity. Importantly, there were no serious histopathological changes to tissues with known hRS7 binding in the monkey, with the exception of mild to moderate hemorrhage of the endometrium and atrophy of the endometrial glands that were showing recovery at the time the study was terminated. ***(See Investigator Brochure for additional information on Sacituzumab Govitecan)***.

Pharmacokinetic analysis of the clearance of the hRS7 IgG and SN-38 (as free SN-38, total SN-38, and a derived IgG-bound SN-38) in monkeys showed the IgG cleared at what appeared to be an expected rate (e.g., 30% cleared over 1 day, terminal half-life ~5 days). The clearance parameters for the total and IgG-bound SN-38 were very similar, with a half-life of ~13 h, which reflect the clearance of the IgG and the fact that the SN-38 is released from the conjugate at a rate of ~50% every 20 h. As expected, the AUC for the total and IgG-bound SN-38 was nearly 15-times higher than for free SN-38, which had a half-life of ~25 h, similar to the rate reported for SN-38 released from irinotecan. Thus, the conjugate can liberate low concentrations of SN-38 in the serum at a slow and sustained rate. These properties are similar in humans.[35]

The chemotherapy backbone of Sacituzumab Govitecan , SN-38 (the active metabolite of irinotecan) is a topoisomerase-I-inhibiting camptothecin. The SN-38 active moiety of irinotecan, has already been studied in subjects with diverse tumor types and the FDA approved irinotecan as first line therapy for patients with metastatic colorectal cancer in conjunction with 5-FU and leucovorin. The SN-38 moiety of Sacituzumab Govitecan has >100-fold more cytotoxic activity compared to the parent compound, irinotecan, and is therefore hypothesized as being more active against the targeted tumors over-expressing Trop-2 antigen. Further, Sacituzumab Govitecan has a better therapeutic index than irinotecan. This improved therapeutic index and encouraging activity has been corroborated in the phase I trial when Sacituzumab Govitecan was given to subjects with diverse metastatic cancers,[36] including triple-negative breast cancer (TNBC),[37] urothelial cancer,[38] and non-small-cell and small cell lung cancers,[39,40] demonstrating activity and manageable toxicity profiles in subjects with advanced and heavily-pretreated, metastatic diseases.

Since SN-38 is not water soluble, it was derivatized to form the water-soluble irinotecan. However, irinotecan must be enzymatically cleaved to the active SN-38 form for it to have

maximum potency. Unfortunately, at best, only 5% of irinotecan will be converted to the active SN-38 form by esterase activity residing primarily in the liver, albeit there are esterases in the tumor that can cleave irinotecan to SN-38.[41-44] Its rapid catabolism in the liver results in its transport through the bile duct into the intestines, resulting in GI toxicity.

To improve the bioavailability of SN-38, Gilead Sciences, Inc. developed a procedure for coupling SN-38 to an antibody with an average drug:antibody ratio of 7.6 that retains the antibody molecular integrity and specific binding.[45-47] The specific linker being used with the current conjugate was selected from several initial candidates that were susceptible to cleavage in human serum at 37°C, with 50% of the SN-38 released in ~0.5 to >7.0 days.[45,46] In mouse models bearing human tumor xenografts, one particular linker with an SN-38 release half-life of 1.0 to 1.5 days was found to have the best therapeutic response.[45] Since these initial studies were performed with an antibody that did not internalize readily, we believe the conjugate's therapeutic activity benefits from a slow release of SN-38 from the antibody, particularly after it is localized in the tumor. Importantly, significant anti-tumor effects were possible at doses in mice that were completely non-toxic. For example, depending on the tumor cell line, significant therapeutic effects were observed at cumulative doses of 1 to 4 mg (~2 to 6.4 µg SN-38) of the conjugate given over 1 to 4 weeks, yet the maximum tolerated dose was ~60 mg of the conjugate given in 1 week. These results suggested the ADC had a therapeutic window of > 10:1.

The anti-tumor activity of the hRS7-SN-38 conjugate was examined in mice bearing a variety of human epithelial cancer xenografts, where it was shown to have significant anti-tumor effects as compared to free SN-38, irinotecan, or an irrelevant IgG-SN-38 conjugate.[34,47,48] As mentioned above, preclinical studies in mice revealed animals could tolerate as much as 60 mg of the conjugate (3000 mg/kg) given as 2 doses spaced 3 days apart with no evidence of weight loss or appreciable change in blood counts. However, there were significant changes in liver transaminases that were returning to normal levels 2 weeks after treatment.[34]

In the phase I portion of this study (Sacituzumab Govitecan 1),[36] 3 subjects (2 colorectal and 1 pancreatic cancer) were treated at the starting dose of 8 mg/kg, 2 still continuing after 6 cycles without toxicity while one withdrew after 3 cycles due to disease progression, not toxicity. This met the protocol requirement for dose escalation with 0/3 cases of dose-limiting toxicity (DLT) occurring during the first cycle. At 12 mg/kg, 9 subjects received treatments (3 pancreatic, 2 triple-negative breast, 1 non-small -cell lung, 1 urinary bladder, 1 hormone-refractive prostate, 1 ovarian cancer). None encountered DLT, but at the next dose level of 18 mg/kg, 2 of the 3 subjects treated (2 triple-negative breast, 1 esophageal cancer) encountered DLT (severe neutropenia) within the first cycle, thus exceeding the maximum tolerated dose (MTD). In addition, an acceptable dose level was defined as one for which ≥ 2/6 subjects tolerate a full 21-day cycle of treatment without the need for dose delay or reduction or any ≥ Grade 3 toxicity.

Eight of the 9 subjects treated at 12 mg/kg required dose delays and reductions during the first cycle suggesting that the starting dose had exceeded the maximum acceptable dose for further consideration. In contrast, the initial dose level of 8 mg/kg appeared acceptable with 3 additional subjects (2 pancreatic, 1 gastric cancer). To establish an optimal acceptable dose level, a final intermediate dose level of 10 mg/kg was evaluated and considered to be active with an acceptable safety profile. At this dose level severe (Grade 3 or higher) toxicities have primarily

included manageable neutropenia, diarrhea and febrile neutropenia. Adverse events (AEs) of all causalities (all grades and Grade ≥3) are shown in **Table 2** and **Table 3**.

Table 2: Adverse Events Leading to Treatment Interruption in >2% of Patients					
	8 mg/kg	***10 mg/kg***	***12 mg/kg***	***18 mg/kg***	***Any Dose***
Patients, n (%)	*81 (100)*	*327 (100)*	*9 (100)*	*3 (100)*	*420 (100)*
Patients with AEs leading to treatment interruption	43 (53.1)	152 (46.5)	7 (77.8)	3 (100)	205 (48.8)
Blood and lymphatic system disorders	20 (24.7)	70 (21.4)	7 (77.8)	2 (66.7)	99 (23.6)
Neutropenia	17 (21.0)	61 (18.7)	7 (77.8)	2 (66.7)	87 (20.7)
Anemia	5 (6.2)	13 (4.0)	0	0	18 (4.3)
Investigations	5 (6.2)	47 (14.4)	0	0	52 (12.4)
Neutrophil count decreased	3 (3.7)	35 (10.7)	0	0	38 (9.0)
WBC count decreased	4 (4.9)	12 (3.7)	0	0	16 (3.8)
Gastrointestinal disorders	6 (7.4)	28 (8.6)	0	2 (66.7)	36 (8.6)
Nausea	3 (3.7)	10 (3.1)	0	1 (33.3)	14 (3.3)
Vomiting	2 (2.5)	9 (2.8)	0	1 (33.3)	12 (2.9)
General disorders and administration site conditions	12 (14.8)	22 (6.7)	1 (11.1)	1 (33.3)	36 (8.6)
Fatigue	5 (6.2)	10 (3.1)	1 (11.1)	0	16 (3.8)
Pyrexia	5 (6.2)	4 (1.2)	0	0	9 (2.1)
Infections and infestations	7 (8.6)	22 (6.7)			29 (6.9)
Respiratory, thoracic and mediastinal disorders	4 (4.9)	8 (2.4)	0	0	12 (2.9)
Metabolism and nutrition disorders	2 (2.5)	8 (2.4)	0	0	10 (2.4)

Table 3: Adverse Events of ≥ Grade 3 Occurring in >5% of Patients				
	Any grade	≥Grade 3	Grade 4	Grade 5
Patients, n (%)	420 (100.0)			
Patients with at least one AE	419 (99.8)	227 (54.0)	70 (16.7)	20 (4.8)
Gastrointestinal disorders	382 (91.0)	87 (20.7)	0	0
Nausea	283 (67.4)	22 (5.2)	0	0
Diarrhea	261 (62.1)	37 (8.8)	0	0

General disorders and administration. site conditions	316 (75.2)	54 (12.9)	0	5 (1.2)
Fatigue	224 (53.3)	41 (9.8)	0	0
Blood and lymphatic system disorders	277 (66.0)	109 (26.0)	49 (11.7)	0
Anemia	171 (40.7)	47 (11.2)	1 (0.2)	0
Neutropenia	171 (40.7)	75 (17.9)	43 (10.2)	0
Febrile neutropenia	25 (6.0)	18 (4.3)	5 (1.2)	0
Metabolism and nutrition disorders	266 (63.3)	76 (18.1)	8 (1.9)	0
Hypophosphatemia	51 (12.1)	22 (5.2)	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	210 (50.0)	23 (5.5)	6 (1.4)	7 (1.7)
Investigations	204 (48.6)	71 (16.9)	21 (5.0)	0
Neutrophil count decreased	77 (18.3)	41 (9.8)	13 (3.1)	0
WBC count decreased	62 (14.8)	25 (6.0)	9 (2.1)	0
Infections and infestations	179 (42.6)	38 (9.0)	3 (0.7)	2 (0.5)

Responses have been observed in subjects with triple-negative breast cancer (TNBC), small-cell lung cancer, non-small- cell lung cancer, esophageal cancer, urinary bladder, and colorectal cancer.[37-40,49] Disease stabilization has been observed in many subjects. Since the initial results over 465 subjects (including, 32 colorectal, 147 TNBC, 60 SCLC, 46 urothelial cancer, 55 non-small cell lung cancer (NSCLC), and 52 advanced/metastatic breast cancer (Non-TNBC), have been treated with Sacituzumab Govitecan, the majority at 10mg/kg given on days 1 and 8 in a 21-day cycle.

While Sacituzumab Govitecan has not been combined with ARSIs in prior studies, fatigue is the only anticipated overlapping toxicity between these classes of agents. ARSIs have been combined with chemotherapy agents in other studies and found to be feasible. [69,70,71]

Subjects who started treatment prior to IRB approval of amendment 5 will continue at their current dose with the ability to dose reduce per protocol.

1.4 New Biomarkers in Prostate Cancer

1.4.1 Need for predictive biomarkers in the second-line CRPC setting

Abiraterone and enzalutamide are established standards of care for pre- and post-chemotherapy treated CRPC, as well as abiraterone in metastatic hormone sensitive prostate cancer. Both target the AR signaling axis, indicating the importance of this pathway in the pathogenesis of prostate cancer. While response rates have been observed when patients initially treated with one of these agents crossover to receive the contralateral therapy, these response rates and duration of response are significantly lower than untreated men. The optimal sequence of administration of abiraterone and enzalutamide to maximize patient benefit has not been established and it is appropriate

to use either agent in the first-line setting at this time as both have similarly high response rates. It remains unknown if there is a select group of patients that would benefit from continued targeting of the AR signaling axis or transition to a therapy with a distinct mechanism of action. All of these scenarios highlight the choice of agent following progression on the first "next-generation hormonal treatment" as a key decision point in management.

Mechanisms of resistance to AR-targeted therapy

Possible mechanisms of resistance to both abiraterone and enzalutamide and to each one individually have been postulated. In laboratory models and translational studies resistance to these agents has been associated with genomic alterations in the AR and expression of AR variants lacking the ligand binding domain. The F876L somatic point mutation of the *AR* gene converts enzalutamide into a functional agonist of the mutated AR.[50] Early work has identified the presence of this mutation in clinical samples and confirmed its presence as a mechanism of acquired resistance to enzalutamide. Another mechanism identified in tumor models with acquired resistance to enzalutamide is upregulation of the glucocorticoid receptor which in turn acquires the ability to activate a selected series of AR responsive genes, co-opting AR signaling.[51] In this model, dexamethasone conferred resistance to enzalutamide, a finding validated clinically in a post hoc analysis of the phase III AFFIRM trial which showed concomitant use of glucocorticoids was associated with inferior survival.[52] Other mechanisms of resistance include *AR* splice variants,[53,54] truncated forms of the AR that lack a LBD and are constitutively activated to regulate a similar (but not identical) set of genes to those regulated by full-length AR protein. They are more prevalent in CRPC than in hormone-naïve tumors and both preclinical and clinical data have identified them as possible mechanisms of resistance to abiraterone and enzalutamide.[12,55,56] The selection or emergence of neuroendocrine-like cells, termed neuroendocrine differentiation, may also contribute to treatment resistance.[57] Other alterations that may confer resistance include loss of reciprocal feedback inhibition between the PI3K/mTOR pathway, mutation, deletion or epigenetic silencing of *PTEN*, or activating mutations of *PI3KCA* or *AKT.*[58]

Given these findings, biopsies of metastatic sites are now considered standard of care interventions for patients who have progressed on treatment with abiraterone or enzalutamide.[10] Recent studies have identified other genomic and transcriptomic alterations, including AR gene rearrangements and novel splice variants that identify distinct mechanisms of resistance.[11]

Correlative circulating biomarker assays

All of the aforementioned mechanisms of resistance to novel AR targeted therapies point to the need to search for predictive biomarkers of response/resistance to these agents. The practice of *"**Precision Medicine**"* requires the ability to characterize the changing biology of the disease in an individual as it evolves over time. This biology is a reflection of intrinsic properties of the tumor and the prior treatment(s) to which it has been exposed. While some studies suggest that a core set of mutations in primary and metastatic disease are shared, it is now recognized that separate tumor foci with the same

ancestral event (e.g., ERG fusion) can have subclonal secondary events, which suggests continued subclonal acquisition of rearrangements.[59]

Blood based biomarkers including CTCs and ctDNA may overcome this limitation and serve as a source of tumor material that represents multiple metastatic sites and can be easily accessed non- invasively through peripheral blood sampling thereby giving real-time insight to the biologic profile of a tumor at the time treatment is considered. Such information can be used to assess baseline disease characteristics and heterogeneity as well as detecting and following the emergence of treatment resistant cell populations. They may also obviate the need for invasive and costly metastatic biopsies.

1.4.2 Circulating tumor cells

CTCs disseminate from multiple metastatic sites and may provide an ideal source of tumor for real time molecular information about a patient's disease that can be accessed easily by non-invasive means through peripheral blood sampling. Numerous CTC isolation and capture techniques have been reported, but only one assay, CellSearch (Menarini Silicon Biosystems) is analytically validated and FDA-cleared.[60] The assay uses an epithelial cell adhesion molecule (EpCAM) capture method and reports only one CTC subtype - the number of cells that stain for cytokeratin (CK6),[24,56] display a nucleus (40, 6 diamidino 2 phenylindole [DAPI]) which lacks the white blood cell marker CD45. The results provide prognostic information pre- and post-therapy, but are limited by a low sensitivity of detection (5 or more cells are detected in only 1%, 55% and 40% of localized, metastatic castration-sensitive, and metastatic CRPC, respectively).[61-63]

The VERSA (Vertical Exclusion-based Rare Sample Analysis) platform employs a microfluidic technology that performs a highly efficient (up to 90% of tumor cells) and highly sensitive CTC capture (as low as one tumor cell per 20mL of blood) that integrates downstream techniques for intracellular staining of CTCs and nucleic acid extraction.[11,64] The VERSA incorporates a dialysis membrane for in-chip fixation, permeabilization, and intracellular staining within a single cell with essentially no cell loss as there is no direct sample manipulation. This technology is now being used to purify CTCs from patients with prostate cancer followed by quantitative immunocytochemistry and subcellular localization of the AR in CTCs. The VERSA platform further performs total nucleic acid extraction for both genomic and gene expression studies on the same sample, from as few as 1-10 cells. Gene expression analysis for multiple AR variants, AR pathway targets and neuroendocrine markers can be performed.

1.4.3 Circulating tumor DNA (ctDNA)

Non-invasive detection of tumor genotype offers an attractive strategy to monitor response to a targeted therapy, query for resistance mechanisms, and evaluate for residual disease or recurrence after definitive therapy. Recent studies suggest that highly sensitive genotyping assays can detect mutations in cell-free plasma DNA (cfDNA) from cancer patients, potentially representing the biology of a patient's cancer. The underlying concept is that genes from malignant cells dissipate or "leak" into the circulation, where they can be detected and quantified by quantitative and sensitive PCR techniques. This central concept has been convincingly validated in preliminary studies and an analytically valid, clinically feasible, noninvasive assay has been developed for quantitative

measurement of cfDNA genotypes using droplet digital PCR (ddPCR).[65] This technology emulsifies input DNA into ~20,000 droplets so that the proportion carrying mutant versus wild type alleles can be counted using flow cytometry. Unlike prior sensitive genotyping assays, ddPCR is quantitative and so has allowed the development of assays with nearly 100% specificity and 70% sensitivity in patients with advanced progressive NSCLC and melanoma. The method has been used to serially analyze cfDNA from *EGFR* mutant NSCLC patients treated with the EGFR kinase inhibitor erlotinib. Prior to treatment, the *EGFR* activating mutation can be detected from cfDNA and decreases following erlotinib therapy. However, over time both the activating and the drug resistance T790M mutation emerge and can be detected from cfDNA. Data from the lung cancer literature show that the *EGFR* T790M mutation (which confers resistance to EGFR inhibitors erlotinib or gefitinib) is likely present as a subclone of cells at baseline in many patients and estimate that it only confers resistance when present in ≥3.2% of cancer cells.[66] Likewise, the emergence of the *AR* 876L mutation can be detected with these approaches in the context of acquired resistance to enzalutamide.[67] New assays continue to be developed for specific alterations in prostate cancer.

2. OBJECTIVES

2.1 Primary Objective

- To determine the proportion of subjects who have ≥50% PSA decline at or within 9 weeks of starting treatment with Sacituzumab Govitecan.
- To determine the 6-month rPFS rate

2.2 Secondary Objectives

- To determine median rPFS
- To determine radiologic response rate
- To determine OS
- To determine safety and tolerability

2.3 Exploratory Objective

To associate predictive biomarkers with clinical outcomes to Sacituzumab Govitecan in CRPC subjects who have progressed while on enzalutamide, apalutamide, or abiraterone.

3. STUDY POPULATION

Subjects with CRPC who have progressed while on second generation AR-directed therapy (e.g., enzalutamide, darolutamide, apalutamide and/or abiraterone), in either the hormone sensitive or CRPC setting, will be considered. Subjects who have progressed while on therapy with combination enzalutamide/abiraterone or prior ARN-509/abiraterone as part of ongoing clinical trials are allowed. Subjects will continue single agent ARSI and Sacituzumab Govitecan will be added to the treatment regimen as part of this clinical trial protocol. Subjects who started treatment prior to IRB approval of amendment 5 will continue on Sacituzumab Govitecan single therapy.

3.1 Inclusion Criteria

To be included in this study, subjects should complete all screening procedures and meet all of the following criteria:

3.1.1 Documented histological or cytological evidence of adenocarcinoma of the prostate

3.1.2 Documented metastatic disease on bone scan and/or CT scans

3.1.3 Currently receiving enzalutamide, darolutamide, apalutamide and/or abiraterone. Subjects who have received combination enzalutamide/abiraterone or combination apalutamide/abiraterone as part of clinical trials are allowed but will need to be receiving only a single agent ARSI at the time of study enrollment. Subjects who have received any other therapeutic investigational product directed towards the AR or androgen biosynthesis are allowed. Prior treatment with first-generation AR antagonists (i.e., bicalutamide, nilutamide, flutamide) before second generation AR-directed therapy is allowed.

3.1.4 Demonstrated disease progression while on enzalutamide, darolutamide, apalutamide and/or abiraterone. Progressive disease is defined by one or more of the following:

- A rise in PSA on two successive determinations at least one week apart and PSA level ≥2 ng/mL
- Soft-tissue progression defined by RECIST 1.1
- Bone disease progression defined by PCWG2 with ≥2 new lesions on bone scan

3.1.5 A minimum serum PSA level of ≥2 ng/mL that is rising based on the PCWG2 criteria

3.1.6 ≥18 y ears of age

3.1.7 Castrate levels of testosterone (<50 ng/dL [1.74 nmol/L])

3.1.8 Undergone orchiectomy, or have been on LHRH agonists or antagonists, for at least 3 months prior to study treatment start. Subjects on LHRH agonists/antagonists must remain on these agents for the duration of the study

3.1.9 ECOG Performance Status of 0-1 (Appendix A)

3.1.10 Normal organ function with acceptable initial laboratory values within 30 days of study treatment start:

WBC	≥3000/µl
ANC	≥1000/µl
Platelet count	≥100,000/µl
HGB	≥9 g/dL

3.1.11 Adequate hepatic function as evidenced by AST/ALT levels <3X the ULN and bilirubin levels of <2.0 mg/dl.

3.1.12 Adequate renal function as evidenced by serum creatinine of <2.0 mg/dL

3.1.13 Able to provide written informed consent, or have a legal representative provide written informed consent

3.1.14 Subjects must have a previously-acquired biopsy from a metastatic site available

3.1.15 Subjects must be willing and able (in the opinion of the treating physician) to undergo one research biopsy for the investigational component of this study

3.1.16 Subjects who have partners of child-bearing potential must be willing to use at least two forms of effective birth control (one form must be a barrier method) during the treatment period and for 90 days after last dose of Sacituzumab Govitecan . Subjects must also agree to not donate sperm through 90 days following the last dose of Sacituzumab Govitecan.

3.2 Exclusion Criteria

3.2.1 Received prior cytotoxic chemotherapy such as docetaxel, cabazitaxel or platinum chemotherapy for metastatic prostate cancer, castration sensitive or castration resistant, within two years prior to study entry. Neoadjuvant chemotherapy is allowed.

3.2.2 Completed sipuleucel-T (Provenge ®) treatment within 30 days of study treatment start.

3.2.3 Received any therapeutic investigational agent within 2 weeks of study treatment start.

3.2.4 Received palliative radiotherapy within 4 weeks of study treatment start.

3.2.5 Received herbal products or alternative therapies that may decrease PSA levels or that may have hormonal anti-prostate cancer activity (e.g., saw palmetto, PC-SPES, PC-HOPE, St. John's wort, selenium supplements, grape seed extract, etc.) within 4 weeks of study treatment start or plans to initiate treatment with these products/alternative therapies during the entire duration of the study.

3.2.6 Active CNS metastases from prostate cancer. Subjects with treated epidural disease are eligible to enroll. Subjects with treated brain metastases can be included as long as >4 weeks have elapsed since last treatment (radiotherapy or surgery) for brain metastases, the subject is neurologically and radiographically stable, and is not receiving corticosteroids for brain metastases. Subjects with untreated brain metastases are excluded. Brain imaging (CT or MRI) is not required at baseline if brain metastases are not clinically suspected.

3.2.7 A history within the last 3 years of another invasive malignancy (excluding non-melanoma skin cancer).

3.2.8 A QTcF interval of >470 msec on the initial Screening ECG; if the Screening ECG QTcF interval is >470 msec, then it may be repeated two more times, and if the mean QTcF of the 3 ECGs is ≤470 msec, the subject may be enrolled.

3.2.9 A history of clinically significant cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes and second degree or third degree atrioventricular heart block without a permanent pacemaker in place. Subjects with resolved or rate-controlled atrial fibrillation/atrial flutter are allowed.

3.2.10 NYHA Class III or IV congestive heart failure, unstable angina, myocardial infarction/acute coronary syndrome within the preceding 6 months.

3.2.11 Diabetes mellitus with more than 2 episodes of diabetic ketoacidosis in the 12 months preceding study treatment start.

3.2.12 Inadequately controlled hypertension (defined as blood pressure >150mmHg systolic and/or >100 mmHg diastolic despite antihypertensive medication) or any history of hypertensive crisis or hypertensive encephalopathy.

3.2.13 History of loss of consciousness or transient ischemic attack within 12 months before study treatment start.

3.2.14 Known active HIV, Hepatitis B, or Hepatitis C infections.

3.2.15 Any other medical, psychiatric, or social condition, including substance abuse, which in the opinion of the Investigator would preclude safe participation in the study.

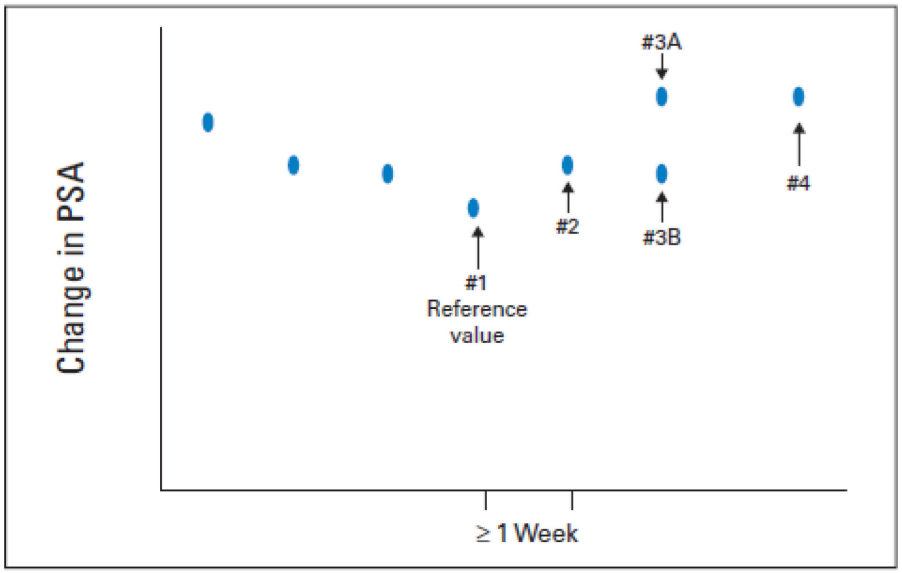
4. ENROLLMENT PLAN

Enrolled Subjects must have CRPC and have demonstrated disease progression (objective or PSA) while on second generation AR-directed therapy and have rising PSA levels immediately prior to enrollment based upon the criteria as defined by the PCWG2. PSA values must exhibit a rise on two occasions of at least a week apart, over a baseline value, with the final value ≥2 ng/ml. A graphical depiction of this is shown in **Figure 1** (PCWG2 Rising PSA Study Eligibility Criteria).[68]

Prior exposure and sensitivity to AR-directed therapy will be recorded and subjects will be considered to have responded (i.e., were sensitive) to the prior agent if there was a ≥50% PSA decline from baseline. Patients will continue on an ARSI and Sacituzumab Govitecan will be added to the treatment regimen as described below. Treatment with Sacituzumab Govitecan can continue until disease progression, unacceptable toxicity, initiation of alternative therapy or withdrawal of consent.

Figure 1. PCWG2 rising PSA study eligibility criteria

The reference value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point 3 (value #3A) is greater than that at point 2, then eligibility has been met. If the PSA is not greater than point 2 (value #3B), but value #4 is, the subject is eligible assuming that other criteria are met. Values 3A or #4 must be 2 ng/mL or higher.[68]



4.1 Number of Subjects

It is planned that up to 55 subjects will be enrolled.

4.2 Eligibility Confirmation

Confirmation of eligibility will be completed centrally by the Prostate Cancer Clinical Trials Consortium (PCCTC) prior to study treatment start. A record of subjects who fail to meet eligibility criteria (i.e., screen failures) will be maintained. **A complete, signed informed consent and HIPAA authorization are required as part of eligibility confirmation.** All subjects must sign an IRB-approved informed consent prior to starting any protocol-specific procedures; however, evaluations performed as part of routine care prior to informed consent can be used for screening and eligibility confirmation.

5. STUDY PROCEDURES

This is an open-label, multicenter, single-arm phase II study in subjects with metastatic CRPC who have progressed while on second generation AR-directed therapy. Subjects enrolled in this study will receive Sacituzumab Govitecan as treatment for CRPC and continue treatment with an ARSI. Subjects who started treatment prior to IRB approval of amendment 5 will continue on Sacituzumab Govitecan single therapy.

The following assessments and procedures will occur during the study. A schedule of assessments is provided in Appendix B.

5.1 Screening Activities

Each subject will undergo a screening period of up to 30 days following the provision of signed informed consent. Screening will include procedures as outlined in the schedule of procedures in Appendix B.

5.1.1 Informed consent and research/HIPAA authorization

No study procedure or alteration of patient care will be undertaken until informed consent has been obtained from the patient or legal representative. However, evaluations performed as part of routine care prior to informed consent can be used for screening and eligibility confirmation. The Investigator will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the patient and/or legally authorized representative. If the patient agrees to participate, the informed consent form will be signed, dated, and witnessed, with a copy given to the subject.

5.2 Study Procedures

5.2.1 Demographics and Medical history

A careful medical history, with particular attention to the subject's history of prostate cancer and prior therapy for prostate cancer, will be obtained during Screening. Treatment history will include treatment response and time to progression for last therapy regimen. Other *pertinent* aspects of the subject's medical history should also be obtained. Medical history that does not impact a subject's prostate cancer, or their expected tolerance of Sacituzumab Govitecan need not be collected. Previous use of anti-androgens and anti-hormonal medications for treatment of prostate cancer should also be obtained. For subjects on this study, the duration of treatment with abiraterone or enzalutamide as well as responses to these therapies (clinical, radiographic and PSA response) should also be recorded. Additionally, it should be noted if the therapies were co-administered with prednisone or other steroids.

5.2.2 Concomitant Medications

Concomitant medications will be recorded from the time of informed consent through the latter of the end of treatment or resolution of any adverse ongoing at the end of treatment.

5.2.3 Physical Examination

A comprehensive physical exam should be performed at Screening and at the End of Treatment Visit. Physical exams conducted at other visits can be brief and targeted on areas known to be abnormal, or driven by clinical findings and/or subject complaints

5.2.4 Vital Signs

Vital signs will consist of blood pressure, pulse, and body temperature. On treatment days, vital signs (blood pressure, pulse) will be collected prior to first infusion and every 15 minutes for the first hour then every 30 minutes until completing IV administration, at completion, and then additionally 30 minutes later. In absence of significant changes, frequency may be reduced with subsequent doses to prior to infusion, at 30 minutes, and then at completion. All time points may be collected ± 5 minutes.

5.2.5 Weight and Height

Weight and height will be obtained with the subject clothed, but without shoes. Height will only be obtained at Screening. Weight will be conducted at each treatment visit prior to study drug administration. Use weight on day 1 of each cycle to determine dose. Dose must be recalculated on day 8 if weight changes (increases or decreases) by > 10% from day 1 weight. Round each dose to nearest one milligram.

5.2.6 ECOG Performance Score

ECOG performance status assessments (Appendix A) are required to assess subject functional status for study eligibility purposes and will be performed throughout the study according to the schedule of procedures.

5.2.7 ECG

A 12-lead ECG will be obtained at screening and at the end of study visit. It is not necessary to do ECGs 5 minutes apart. Additional unscheduled 12-lead ECG may be conducted when necessary at the investigator's discretion.

5.3 Determination of Extent of Metastatic Disease

All subjects will undergo an extent of disease evaluation consisting of bone scintigraphy, CT of the chest, CT of the abdomen and pelvis, and other regions of known/suspected involvement, at Screening unless already conducted within 30 days of Cycle 1, Day 1. CT scans should be performed with contrast unless contraindicated. MRI abdomen and pelvis with contrast may be done in situations where a CT with contrast is equivocal or contraindicated. A non-contrast chest CT should be done for subjects requiring an MRI of the abdomen and pelvis.

Subjects will undergo repeat evaluations of their extent of disease every 9 weeks (± 7 days) if they remain progression- free on study. Imaging modality should remain consistent by lesion throughout the study.

5.4 Laboratory Evaluations

On treatment days, blood samples should be collected prior to infusion. Laboratory tests will be performed by local labs and will include:

5.4.1 CBC

A CBC will consist of determinations of hemoglobin (HGB), hematocrit (HCT), white blood cells (WBC), red blood cells (RBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count. Absolute values are preferred.

5.4.2 Coagulation factors

Partial thromboplastin time (PTT) and prothrombin time (PT) or international normalized ratio (INR) will be obtained according to the schedule of procedures and at any other visit where clinically indicated.

5.4.3 Comprehensive metabolic panel (CMP)

A CMP will consist of determinations of sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), glucose, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, lactate dehydrogenase, total bilirubin, total protein, albumin, serum calcium, magnesium, and phosphorous.

5.4.4 Urinalysis

Urinalysis will include pH, specific gravity, and hemoglobin, glucose, ketones, and protein by dipstick, with microscopic exam if any of the dipstick analytes are 2+ or higher.

5.4.5 PSA

Serum PSA will be obtained per the schedule of procedures. At Screening, the PSA must be increasing in conformance with the requirements of the PCWG2 criteria (Appendix E).

5.4.6 Testosterone

Serum testosterone will be measured to confirm castrate levels <50 ng/dL.

5.5 Correlative biomarker studies

Subjects will have correlative biomarker studies performed at baseline, serially throughout treatment per study schedule and again at time of disease progression in subjects who initially respond. The specific aims of these studies are to:

1) Identify predictive biomarkers of response/resistance to Sacituzumab Govitecan.
2) Assess if early changes in circulating biomarkers can identify impending disease progression in advance of traditional measures such as PSA, radiologic measurements and clinical symptoms.
3) Identify mechanisms of acquired resistance to Sacituzumab Govitecan by re-biopsy of tumor tissue and circulating biomarkers prior to cycle 4.

5.5.1 Tumor Biopsy

Subjects must have an available tumor (including archival material) from a biopsy of a metastatic site performed as standard of care to enroll. No specific timeframe parameters will be applied to the archival material as long as the material is from a metastatic site. Normal tissue (buffy coat of blood) will be collected. The buffy coat and tumor will be sent for DNA sequencing ± RNA expression analysis. The exact methodology for DNA sequencing and RNA expression analysis will be decided at the time of sample analysis, depending on methodologies available at the time because there are continued developments in this field with new technologies and sequencing panels emerging regularly. Biopsy of a soft tissue lesion is preferable over a bone lesion if safe and feasible; however, either will be accepted to meet the enrollment and on-study biopsy requirements. A new biopsy will be performed on Cycle 3 Day 15 (± 7 days) for DNA sequencing and RNA expression analysis. This biopsy should preferably be obtained from the same site as the pre-treatment biopsy. This will provide a unique opportunity to investigate the potential mechanisms of response and resistance to Sacituzumab Govitecan. Biopsy samples will be sent for processing and analysis to Dr. Scott Dehm at the University of Minnesota.

5.5.2 CTCs

Blood will be collected for analysis of CTCs and plasma factors that may include ctDNA and exosomes. Blood sample will be shipped to the University of Wisconsin for analysis and comparison of Trop-2 and EpCAM CTCs. Evaluation of AR splice variants and neuroendocrine signatures will be performed in CTCs. Plasma will be collected and stored for future analysis.

5.6 End of Treatment Evaluation or Unscheduled/Early Termination Visit

Procedures listed in the study schedule will be conducted 30 days (+7 days) after the last dose of study drug or in the event of premature study termination.

The End of Treatment procedures listed in the study schedule will also be performed at the time of progression or initiation of another treatment if the subject discontinued study treatment for other reasons.

5.7 Long-Term Follow-Up

After completing the end of treatment evaluation, follow-up continues for subjects who have not progressed with assessments including PSA, bone scan and/or CT scans performed every 3 months or per standard of care for up to 2 years from initiation of study therapy or until progression of disease or initiation of other treatment. Modalities of disease assessment at baseline will be used at subsequent response evaluations for determination of response and/or disease progression.

Adverse events and concomitant medications reported at any follow-up visits will include outcome of any ongoing unresolved events, new events attributed to the study treatment, deaths, hospitalizations, and infectious episodes requiring prescription or IV anti-infectives or GI toxicity. Follow-up for treatment related toxicities which may include physical exam, CBC and chemistries will be required till resolution or stabilization of the toxicity.

5.8 Criteria for Removal from Protocol Treatment

Every effort should be made to keep subjects on study drug for a minimum of 9 weeks (i.e., 3 cycles) unless withdrawal of informed consent, the presence of significant toxicity, clear progression of neoplastic disease, or any other reason for the removal from study as outlined in this section. Per the PCWG2 guidelines, “in the absence of clinically-compelling indicators of disease progression, early changes (within 9 weeks) in indicators such as serum PSA, patient-reported pain, and radionuclide bone scan should be ignored”. With respect to bone scan changes, 72% of the apparent disease progressions, in the abiraterone acetate plus prednisone vs. placebo plus prednisone registration trial, proved to be responders and were able to continue therapy. In contrast, unequivocal signs of disease progression such as spinal cord compression or pain requiring a change in therapy would require discontinuation of Sacituzumab Govitecan prior to 9 weeks (i.e., before completing Cycle 3).

Subjects who require palliative radiotherapy for focal symptom relief may remain on study as long as the treating investigator feels they are deriving benefit from Sacituzumab Govitecan 2 and the radiotherapy is not to a target or non-target lesion recorded at baseline.

Subjects may be removed from protocol treatment under the following conditions:

- First documentation of progressive disease or symptomatic deterioration indicating treatment failure.
    - Discontinuation is subject to the goal of not removing subjects prior to completing 9 weeks of treatment especially for the lone reason of rising PSA. Subjects with rising PSA may continue on study beyond Cycle 3 at the discretion of the investigator.

- Subjects who want to continue treatment after radiological documentation of progressive disease should notify the physician who will obtain Sponsor approval before treatment continuation.

- Unacceptable toxicity, or any AE, which in the opinion of the investigator precludes further participation in the study.
- Treatment delay for any reason > 3 weeks (Treatment delays of up to 3 weeks will be allowed at the investigator's discretion). If treatment delay is due other than to treatment-related toxicity and a patient is receiving clinical benefit, the subject may be allowed to remain on study after > 3 weeks treatment delay after first obtaining approval from the Sponsor Investigator. The maximum treatment delay allowed even when the subject is receiving clinical benefit is no more than 6 weeks.
- Development of an intercurrent medical condition and need for prohibited concomitant treatment that precludes further participation in the study.
- Subject failure to follow study requirements.
- Physician decision: the investigator removes the patient from the study in the best interest of the patient.
- The subject is lost to follow-up.
- Study termination by the Sponsor.
- Use of prohibited concomitant medications (defined in Section 6.5.1).
- The subject may withdraw from the study at any time for any reason.

If a subject voluntarily withdraws from the study, attempts should be made to contact the subject to determine the reason(s) for discontinuation. All procedures and evaluations required by the End of Treatment Visit should be completed in the event of early withdrawal, regardless of reason. All subjects who discontinue the study due to an AE must be followed until resolution or stabilization of the AE.

6. INVESTIGATIONAL MEDICINAL PRODUCT AND STUDY TREATMENT

6.1 Sacituzumab Govitecan Formulation

hRS7 is a CDR-grafted, humanized monoclonal IgG_1 anti-Trop-2 antibody. The antibody is prepared using cell culture methods by Gilead Sciences, Inc., (Morris Plains, NJ) in accordance with FDA guidelines for the manufacture and testing of monoclonal antibody products for human use. SN-38 (7-ethyl-10-hydroxy-camptothecin) is a small molecule and the active metabolite of the chemotherapeutic agent irinotecan.

Sacituzumab Govitecan is an antibody drug-conjugate prepared by Gilead Sciences, Inc., (Morris Plains, NJ) at an SN-38 to hRS7 ratio of ~7:1 (mol:mol). The conjugation uses a spacer containing a cleavable-carbonate bond to attach SN-38 to reactive cysteine thiols present on the hRS7 antibody. For clinical use, 10 mg/mL Sacituzumab Govitecan is formulated in 25 mM MES, pH 6.5 together with the other excipients (25 mM trehalose, 0.01% Polysorbate 80), which is then lyophilized. Glass vials containing 200 mg Sacituzumab Govitecan as a sterile, non-pyrogenic, lyophilized powder are to be stored under refrigerated conditions (2-8°C) until used. Each vial is labeled "For Investigational Use Only," and identified by study drug name, lot number, and dose. Since the formulated drug product contains no preservative, vials should be used only once.

6.2 Sacituzumab Govitecan Packaging and Storage

All vials of study drug must be stored under refrigeration (monitored at 2-8°C) in a locked room that can be accessed only by the pharmacist, the study Investigator, or another duly designated person. The study medications must not be used outside of the context of this protocol. Under no circumstances should the Investigator or other site personnel supply study drug to other Investigators, subjects, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from Gilead Sciences, Inc..

6.3 Sacituzumab Govitecan Preparation and Administration

For subject dose preparation, Sacituzumab Govitecan is to be reconstituted with normal saline for use, and diluted immediately into infusion bags. Sacituzumab Govitecan is photosensitive and should be protected from light during storage and use per guidance provided below.

Appropriate use of aseptic technique should be employed in preparing the dose. Allow the Sacituzumab Govitecan vials to warm to room temperature to allow faster dissolution. The 200mg lyophilized powder in each vial should only be reconstituted using 20ml 0.9% sterile sodium chloride (normal saline). The reconstituted solution should be gently shaken and allowed to dissolve for up to 15 minutes. Calculate the prescribed dose in mg based on the subject's body weight at the beginning of EACH cycle, or more frequently if the subject experiences a weight change (increase or decrease) >10% at day 8 of the cycle. The appropriate calculated amount should then be withdrawn from the supplied vials of study medication. 21-gauge needle use is recommended. Inject the solution into a glass or plastic infusional container slowly to minimize foaming and do not shake the contents. Adjust the volume in the infusional container as needed with normal saline to obtain a concentration of 1.1-3.4 mg/mL (total volume should not exceed 500 mL). Only normal saline should be used since the stability of the reconstituted product has not been determined with other infusion base solutions. A sample drug preparation chart for a 70-kg subject is provided in **Table 4** with 200 mg/vials, and 250 mL bags of normal saline as the infusion container. Initiate the infusion within 1 hour of reconstitution and dilution. If the infusion is delayed beyond 1 hour, refrigerate at 2-8C. If refrigerated, allow the diluted solution to come to room temperature prior to administration. If infusion does not begin within 4 hours after reconstitution/dilution, dispose of the original preparation and prepare a new infusion bag by reconstitution and dilution from new vials. Discard any unused portion in the vial. The product does not contain a preservative.

Table 2. Sacituzumab Govitecan Preparation for 10 mg/kg Dosing (Assumes 70-kg Subject).

Total Dose Needed	**700 mg (200 mg/vial)**
Vials Required	4
Volume of saline to be used for reconstitution	20 mL
Volume after reconstitution of each vial with USP saline	80 mL
Volume Withdrawn for Scheduled Dose	70 mL
Dilute with Normal Saline.	180 mL
Total Volume Dispensed	250 mL
Final Concentration (mg/mL)	2.8

6.3.1 Sacituzumab Govitecan drug administration

Subjects will take Sacituzumab Govitecan at their assigned dose on days 1 and 8 in a 21-day cycle. The Schedule of Assessments for the various segments of the study is detailed in Appendix B.

Efficacy of Sacituzumab Govitecan will be determined according to the PCWG2 criteria (Appendix E) and response to Sacituzumab Govitecan will be assessed as the maximum change in PSA from baseline as well as the change in PSA from baseline at the 9-week time point. For subjects who have evaluable and/or measurable metastases, the PCWG2 criteria for response and progression in soft tissue and bone will be used.

6.3.2 Prophylactic medications

Pre-medication with acetaminophen, diphenhydramine, corticosteroids, Histamine H2 antagonists (i.e., Pepcid or equivalent) or other drugs is not anticipated; however, it will be employed as clinically indicated to decrease infusion reactions. Subjects with a history of infusional reactions to other antibody therapies or who develop reactions to this study agent may be pre-medicated at the discretion of the treating physician.

6.3.3 Intravenous administration

Do not administer as an IV push or bolus. Sacituzumab Govitecan is administered intravenously as a slow infusion as described below.

Intravenous access must be well established prior to initiating infusion. At the time of dosing, the IV line will be connected to an infusion container containing the prepared volume of Sacituzumab Govitecan. Either gravity or an infusion pump may be used. Only normal saline should be used as the infusion base solution, since the Sponsor has not examined the compatibility of Sacituzumab Govitecan with other infusion diluents.

First infusion: Administer infusion over approximately 3 hours. Subjects should be observed during the infusion and for at least 30 minutes following the initial dose for fever, chills or other infusion-related reactions.

Second infusion: Administer infusion over approximately 2 hours if the prior infusion was tolerated. Subjects should be observed during the infusion and for at least 30 minutes after infusion.

Subsequent infusions: Administer infusion over approximately 1-2 hours if prior infusions were tolerated. Subjects should be observed during the infusion.

Following completion, the intravenous line should be flushed slowly with 20 mL normal saline and the end of infusion time recorded. In the event of infusion reactions or vital sign changes, the infusion rate may be slowed, interrupted or terminated, as considered appropriate by the managing physician.

6.3.4 Managing infusion-related reactions

Gilead Sciences, Inc. should be notified within 24 hours of awareness; in the event of any serious infusion reaction.

NCI CTCAE version 4.0 is used to grade all AEs and to provide management guidelines for infusion related reactions.

For a serious infusion reaction considered severe or life threatening (NCI toxicity Grade 3 or higher) an infusion must be permanently terminated.

- Examples of such events include: serious or clinically significant cardiopulmonary events, severe allergic (symptomatic bronchospasm) or anaphylactic reactions, or other severe reactions.
- The occurrence of Grade 3 infusion-related reactions (e.g., Prolonged infusion related reactions-not rapidly responsive to symptomatic medication and/or brief interruption of infusion) also require the infusion to be permanently terminated.

Otherwise, for moderate infusion related toxicity (Grade 2 events), the infusion should be temporarily stopped for at least 15 minutes or until symptoms resolve, and then resumed at the slowed infusion rate, if the subject is stable.

Recommended actions for mild toxicity (Grade 1 events) include slowing the remaining infusion rate.

Any infusion related reaction must have resolved to ≤ Grade 1 prior to a subject receiving the next scheduled infusion.

Table 5 provides a systematic approach to infusion reactions based upon criteria developed by the National Cancer Institute (NCI) for classifying drug toxicity according to increasing levels of severity: mild (Grade 1), moderate (Grade 2), severe (Grade 3) or life-threatening (Grade 4). Management guidelines and examples of qualifying toxicity are also included.

Table 5. Management Guidelines for Infusion Related Reaction			
Severity	**IV Actions**	**Medical Support Actions**	**Examples of Qualifying Events (NCI Toxicity Criteria*)**
Mild	Slow remaining infusion rate. Monitor closely for other adverse events.	None required	Transient hypotension; palpitations; mild hypertension; asymptomatic arrhythmias (none requiring treatment); mild allergic reaction (transient rash, drug fever < 38°C), or isolated fever ≤ 39°C; other mild reactions: flushing, rigors, chills, diaphoresis, pruritus, cough, pain, nausea, vomiting, etc.
Moderate	Stop infusion for 15 minutes. Monitor. If stable, resume infusion at slower rate.	For hypotension, IV fluid Replacement. For chills or rigors, pain control, moderate narcotic analgesic (e.g., 25 mg Demerol p.o. or equivalent). For dyspnea, initiate O_2, with bronchodilators for subjects with underlying compromised pulmonary function. For general or other allergic reaction, antihistamines (25-50 mg diphenhydramine or equivalent, p.o. or IV, 20 mg Pepcid, p.o. or equivalent) or steroids (50 mg hydrocortisone or equivalent, p.o. or IV)	Infusion-related reaction responding promptly to symptomatic treatment and requiring prophylactic medication ≤ 24 hours; Hypotension requiring fluid replacement; advanced hypertension or symptomatic arrhythmias requiring non-urgent medical attention; moderate allergic reaction (urticaria, dyspnea, drug fever ≥38°C) or isolated fever 39.1 to 40°C; frequent or drenching diaphoresis; controlled intense or widespread pruritus; other moderate reactions: pain, GI, skin, etc.
Severe	Discontinue infusion. Permanently remove from treatment.	If actions above for moderate severity are unsuccessful, initiate emergency resuscitative medications as per institutional protocol (O_2, IM or SC epinephrine, IV fluids, bronchodilators, antiarrhythmics, antihypertensives, etc)	Prolonged (not rapidly responsive to symptomatic medication and/or brief interruption of infusion) infusion- related reaction involving recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae; Congestive heart failure/LVEF < 40-20%, hypotension requiring sustained ≥ 24hrs therapy, hypertension requiring more than one drug or arrhythmias symptomatic and incompletely controlled medically or controlled with device, severe allergic reaction (symptomatic bronchospasm requiring parenteral medications, with or without urticaria, allergy-related edema/angioedema and hypotension), rigors/chills unresponsive to narcotics; laryngeal edema with stridor and respiratory distress, other severe pain, GI or skin symptoms, etc.
Life Threatening	Discontinue infusion. Permanently remove from treatment.	Initiate emergency resuscitative medications as per institutional protocol (O_2, airway support, IV epinephrine, IV fluids, bronchodilators, antiarrhythmics, antihypertensives, etc)	Infusion-relation reaction which is life-threatening and requiring pressor or ventilator support. Acute myocardial infarction, tamponade, hypertensive crisis, life-threatening arrhythmia (e.g., associated with CHF, hypotension, shock), anaphylaxis, renal failure requiring chronic dialysis or renal transplant, other life-threatening or disabling reactions.

*Partial list of examples. Refer to NCI CTC Version 4.0 for complete list and exact definitions.
†Additional medical support as per Investigator judgment.

Additional Medications

Subjects may be medicated during treatment as indicated in the judgment of the treating physician to control potential infusion or hypersensitivity responses. For anaphylactic reactions, appropriate medical measures (e.g., epinephrine, antihistamines, hydrocortisone, and IV fluids) should be taken. Such a subject should not receive additional study drug and should be discontinued from the study.

Nausea, Vomiting and Diarrhea

Gastrointestinal toxicity may be dose limiting with this study agent. Hospital or institutional guidelines may exist and should be consulted for recommended treatment of these conditions in subjects received cancer therapy. Several major oncology organizations have also provided comprehensive guidelines for optimal medical management of nausea, vomiting and diarrhea with cancer treatment. As of this writing, guidelines from these organizations are not stratified by toxicity grade. A partial list of the major medications is provided below, but the hospital/institution guidelines or the references below should be consulted for more detailed information as to management of these conditions. Subjects who exhibit an excessive cholinergic response to Sacituzumab Govitecan treatment (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g. Atropine) for subsequent treatments.

Table 6. Recommended Medications for Nausea, Vomiting and Diarrhea

Agent	Dose/Frequency	Route of administration
For Prevention of Acute Emesis:		
Palonosetron	0.075mg	
Decadron	10-20 mg	PO or IV
	10 mg every 12 hours	PO or IV
Granisetron	1 mg or 0.01 mg/kg	IV
	1-2 mg daily	PO
Ondansetron	8 mg or 0.15 mg/kg	IV
	16-24 mg daily	PO
Lorazepam	0.5-2 mg every 4-6 hours	PO or sublingual
Alprazolam	0.5-2 mg every 4-6 hours	PO or sublingual
For Delayed Emesis:		
Aprepitant	125 mg on Day 1 followed by 80 mg on Days 2 & 3	PO
Fosaprepitant	115 mg day 1 only	IV
For Diarrhea:		
Loperamide	4 mg initially followed by 2 mg with every episode for a maximum of 16 mg daily. Discontinue 12 hours after diarrhea resolves and normal diet is resumed.	PO
Octreotide	100-150 mcg three times daily	Subcutaneously
Fluoroquinolones (diarrhea persisting > 24 hrs, ANC < 500 or fever with diarrhea)	(e.g., ciprofloxacin 250-750 mg every 12 hours for 7 days)	PO
Based on NCCN Anti-emesis Guidelines v1.2011; Benson et al (2004) Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 22:2918-26; Kris et al (2006) American Society of Clinical Oncology guidelines for anti-emetics in oncology: Update 2006. J Clin Oncol 24:2932-47.		

6.4 Dose modification of Sacituzumab Govitecan

The current established dose schedule for Sacituzumab Govitecan is 10 mg/kg on days 1 and 8 repeated every 21 days given as an intravenous infusion at the rates described in Section 6.3.3. There should be a minimum of 14 days between the day 8 infusion and the day 1 infusion of the next cycle in the absence of progression of disease or unacceptable toxicity. Planned deviations in treatment schedule are allowable up to 7 days due to holidays, vacations or personal reasons. The protocol allows aggressive medical management of patients in order to avoid dose reduction and dose delay as much as possible. Growth factors should be initiated once the ANC starts decreasing and may be used prophylactically as clinically indicated. In patients who would be considered high risk for neutropenia (those who experienced febrile neutropenia or Grade 3-4 neutropenia with prior treatments), use of growth factors should be initiated early on and used prophylactically as early as Cycle 1. Growth factors are required at cycle 1 for all patients $\geq$ 65 years old.

6.4.1 Dose reduction and termination guidelines

The most likely toxicities of Sacituzumab Govitecan are expected to be gastrointestinal symptoms and hematologic suppression. All subjects are closely monitored over the course of their treatment. NCI CTCAE v4.0 is used to grade all AEs and to provide the following dose reduction, delay or cessation guidelines in the event of treatment-related toxicity.

In this phase II study, subjects will receive 10 mg/kg Sacituzumab Govitecan once weekly for 2 consecutive weeks followed by 1 week rest in cycles of 21 days, with treatment continued in the absence of progression or unacceptable toxicity. Neutropenia, GI toxicity, fatigue and alopecia were the most common toxicities in phase I testing. All subjects will be closely monitored over the course of their treatment, with NCI CTCAE v4.0 used to grade all AEs and to provide dose reduction, delay or cessation guidelines in the event of toxicity.

On the first treatment day (Cycle 1 Day 1), if a subject experiences ANC <1000/µl or ≥ Grade 2 GI toxicity (disease related or from prior treatments), treatment initiation should be withheld until resolved to ≤ Grade 1 or baseline level. It is recommended that growth factor support prophylaxis be administered to subjects who receive treatment and whose Cycle 1 Day 1 ANC is <1500/ul and $\geq$1000/ul.

If recovery to ≤ Grade 1 or baseline level requires more than three-week delay, the subject should be withdrawn from the study.

Treatment will be permanently discontinued for a subject in the event of any ≥ Grade 3 infusion reactions or for any Grade 2 immediate-type allergic/hypersensitivity infusion reactions (e.g., generalized urticaria, wheezing, hypoxia, dyspnea), which occur after pre-medication with antihistamines, H2 blockers and steroids.

Patients with grade 4 non-hematologic toxicity deemed at least possibly related must permanently discontinue the study drug except for the following situations:

a. Chloride, bicarbonate, magnesium, phosphate or glucose abnormalities that last <72 hours, if not clinically complicated, and resolve spontaneously or respond to conventional medical interventions
b. Amylase or lipase elevations that are not associated with symptoms or clinical manifestations of pancreatitis.

Treatment should be permanently discontinued if:

a. ALT or AST >8x ULN
b. ALT or AST>5x ULN for more than 2 weeks
c. ALT or AST>3x ULN and total bilirubin >2x ULN or INR >1.5

Patients with life threatening, grade 3 non-hematologic toxicity regardless of relationship to study drug should discontinue study treatment permanently. Examples include myocardial infarction or stroke.

In the event of other Grade 3 treatment-related toxicity at the time of a scheduled treatment day, the dose will be held and subjects will be assessed at least weekly. If recovery to ≤ Grade 1 delays the next dose by only one week, treatment may resume then without dose reduction. If recovery to ≤ Grade 1 delays the next dose by 2 or 3 weeks, treatment must be resumed at a reduced dose (Table 7). If treatment on day 8 of a cycle is held, the dose should be skipped and treatment resumed with day 1 of the following cycle. If treatment on day 1 is delayed, the entire cycle should be delayed, maintaining the same cycle number. The use of prophylactic G-CSF in subsequent cycles is recommended to prevent recurrence of neutropenia that would require a dose reduction. If recovery to ≤ Grade 1 requires more than a three-week delay, treatment must be permanently discontinued.

After **cycle 1 day 1** treatment initiation should be withheld until ANC is ≥ 1000 /uL. If day 8 is held for ANC < 1000 /uL, that dose will be missed. Resume dosing with next cycle. If delay more than 4 weeks, discontinue treatment. GCSF prophylaxis prior to cycle 2 is recommended if clinically appropriate.

For grade ≥ 3 neutropenia (ANC <1000 /uL) after cycle 1 day 1 or after day 1 of subsequent cycles, hold day 8, initiate growth factor support and administer prophylactic growth factors with each subsequent cycle. Resume dosing with the next cycle only if toxicity resolves. **In subsequent treatment cycles**, treatment initiation for Day 1 of the cycle should be withheld until ANC > 1000 /uL and GROWTH FACTORS should be used as clinically indicated. Patient will be assessed weekly for grade 3 ANC (ANC <1000 /uL to 500 /uL) and bi-weekly for grade 4 ANC (ANC <500 /uL). If delay more than 3 weeks, discontinue. Resume dosing at the next cycle if toxicity recovers to ≤ grade 2 within 3 weeks. All subsequent cycles should be administered with growth factor support.

In the event of neutropenia **grade ≥ 3** at the time of scheduled treatment day **despite growth factor prophylaxis**, resume treatment if the toxicity recovers to ≤ grade 2 within 2 or 3 weeks with a 25% dose reduction for the first event (7.5mg/kg for a starting dose

of 10mg/kg). For subjects whose starting dose was 10mg/kg there will be a 50% dose reduction (5 mg/kg) for the second event that occurs while the patient is receiving prophylactic growth factors. Subjects will discontinue treatment for the 3rd occurrence while on growth factor support. NO DOSE REDUCTION IS REQUIRED IF TOXICITY RESOLVES WITHIN 1 WEEK.

Table 7. Dose Reduction Requirements for Severe Treatment-Related Toxicity

Event	Occurrence	Study Drug Dose
Grade 4 hematologic toxicity ≥ 7 days OR Grade 3 febrile neutropenia (ANC < 1000/mm^3, fever ≥ 38.5°C), OR Grade 3 thrombocytopenia with clinically relevant bleeding OR Grade 4 thrombocytopenia, regardless of duration	First	7.5 mg/kg
OR Any Grade 3 nausea, vomiting or diarrhea due to treatment, or other Grade 3 non-hematologic toxicity persisting > 48 hours despite optimal medical management. OR At time of scheduled treatment, Grade 3 hematologic or Grade 3 non- hematologic toxicity which delays dose by 2 or 3 weeks for recovery to ≤ Grade 2 or baseline.	Second	5 mg/kg
	Third	Study drug will be discontinued
Hematologic toxicity: ≤ Grade 1 (ANC ≥ 1500/mm^{3}or baseline level, Platelets ≥ 75,000/mm^3, or Hgb ≥ 10.0 g/dL or baseline level); Grade 2 (ANC ≥ 1000/mm3, Platelets ≥50,000/mm3, or Hgb ≥ 8 g/dL); Grade 3 (ANC < 1000/mm^3, Platelets < 50,000/mm^3, or Hgb < 8.0 g/dL); Grade 4 (ANC < 500/mm^3, Platelets < 25,000/mm^3, or Hgb < 6.5 g/dL).		
Note: In the event of adverse effects unrelated to study drug administration (both hematological and non-hematological adverse events), decision to dose delay or dose reduce is investigator discretion, based on the tolerability of the toxicities.		

The development of any of the severe toxicities noted in table 7 due to treatment requires permanent dose reduction for that subject by 25% of the assigned dose for first occurrence, 50% of the initial assigned dose for second occurrence. Subjects whose starting dose was 10mg/kg will discontinue treatment entirely in the event of a third occurrence (Table 7).

Do not re-escalate the Sacituzumab Govitecan dose after a dose reduction for toxicity has been made.

The dose guidelines will be followed with a goal of being able to give the first cycle without requiring dose reduction, delay, or discontinuation or cytokine support at the time the second cycle is given.

6.5 Concomitant Therapy

Patients will continue on the most recent ARSI on which documented progression was observed. For example, a patient with PSA progression on abiraterone would continue abiraterone and enroll on this trial. For patients that have stopped the most recent ARSI and been treated with another anti-cancer therapy (i.e., progression on abiraterone and then treatment with radium-223), the patient should resume treatment with an ARSI and show documented progression on that treatment before enrolling on this trial. For patients that have stopped an ARSI and then resumed as part of standard of care prior to this trial, a rising PSA is sufficient for eligibility. ARSI's are FDA approved for the treatment of metastatic prostate cancer and will be administered per institutional standards in this study.

All intercurrent medical conditions should be treated by the investigator according to current community standards of care. Subjects may also receive medications for symptomatic relief, such as analgesics, laxatives, anti-emetics, etc.

Subjects who require palliative radiotherapy for focal symptom relief may remain on study as long as the treating investigator feels they are deriving benefit from Sacituzumab Govitecan and the radiotherapy is not to a target or non-target lesion recorded at baseline.

Complementary/alternative therapies which may lower PSA or have an anti-hormonal effect (e.g., saw palmetto, selenium supplements, grape seed extract, etc.) are prohibited.

All medications used during the study and taken within 30 days of the screening visit will be recorded.

6.5.1 Prohibited medications/treatments

Any investigational therapies other than Sacituzumab Govitecan.

Any other systemic therapy intended for the treatment of prostate cancer other than Sacituzumab Govitecan, ARSI used on study, and LHRH agonists or antagonists, which the subject must have started at least 3 months prior to study entry if the subject has not undergone orchiectomy.

6.6 Drug Accountability

Sacituzumab Govitecan will be supplied by Gilead Sciences, Inc. The investigator acknowledges that the drug supplies are investigational and, as such, must be used strictly in accordance with the protocol and only under the supervision of the investigator or sub-investigators. No study medication will be sent to the study site until all required regulatory documents, including IRB approval, are received by the sponsor or its representatives.

Adequate records documenting receipt, use, return, loss, or other disposition of study drug vials must be kept. A complete drug accountability record, supplied by Gilead Sciences, Inc. (or its designee or NCI drug accountability forms), or computer records used by the pharmacy at the investigational site, can be used to provide drug accountability. In all cases, information describing study medication supplies and their disposition, subject-by-subject, must be provided and signed by the Investigator (or the pharmacist or other person who dispensed the drug) and collected by the Study Monitor. Requisite data include relevant dates, quantities, batches or code numbers, and subject identification for subjects who received trial product.

The investigator and investigational site staff are responsible for maintaining an accurate inventory and accounting of investigational drug. Receipt and use of Sacituzumab Govitecan will be recorded on an Investigational Drug Inventory Form provided by the sponsor, or site-required form if approved by the sponsor. The investigator will record the following information:

- Date and quantity of Sacituzumab Govitecan received by the site
- Subject number for each subject receiving Sacituzumab Govitecan
- Date and quantity of Sacituzumab Govitecan dispensed to each subject
- Date and quantity of Sacituzumab Govitecan returned to inventory from each subject
- The name of the person dispensing investigational drug
- Each shipment of Sacituzumab Govitecan will be accompanied by an invoice describing the amount of drug shipped to the site. The information on the invoice must be verified against the actual amount of Gilead Sciences, Inc. drug received by the site; the investigator or the investigator's designee will then sign the invoice and place it in the investigator's file.

At each monitoring visit, the monitor will reconcile the information on the Investigational Drug Inventory Form with the actual amount of Sacituzumab Govitecan remaining at each site. At the conclusion of the study, all unused drug supplies must be returned to the sponsor or its designee, or destroyed according to institutional operating standards. Drug accountability will be performed on site by the clinical monitor before destruction, unless approval is given to destroy prior to monitoring. A record of the destruction will be placed in the investigator's file.

Unused investigational product must not be discarded or used for any purpose other than the present study. Investigational product which has been dispensed to a subject and returned unused must not be re-dispensed to a different subject, but may be dispensed to the same subject.

At the end of the study, following authorization by study management, study medication may be destroyed at the site as dictated by the appropriate standard operating procedures at the participating institutions. Destruction must be documented. Alternatively, after notification, all unused products will be collected by the Study Monitor and returned to Gilead Sciences, Inc..

7. SAFETY EVALUATION

7.1 Definitions

7.1.1 Adverse event (AE)

All subjects must be carefully monitored for AEs, including clinical laboratory tests. AEs should be assessed in terms of their seriousness, intensity, and relationship to the study drug. For consistency, events are to be graded using the CTCAE version 4.0.

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

AEs include the following:

1. An exacerbation, or an unexpected increase in frequency or intensity of a pre-existing condition (other than condition under investigation), including intermittent or episodic conditions.
2. Significant or unexpected worsening or exacerbation of the condition/indication under investigation.
3. A suspected drug interaction.
4. An intercurrent illness.
5. Any clinical significant laboratory abnormality.

An AE does <u>not</u> include:

1. Anticipated day-to-day fluctuations of any pre-existing conditions, including the disease under study.
2. Signs and symptoms of the disease under study that do not represent a significant worsening or exacerbation.
3. Expected progression of the disease under investigation.

7.1.2 Adverse drug reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADRs). The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Causality assessment is required for all clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs.

7.1.3 Unexpected adverse drug reaction

An unexpected ADR is an AE where the nature or severity of which is not consistent with the applicable product information (e.g., Investigational Brochure, study protocol or ICF). The following documents or circumstances will be used to determine whether an AE/ADR is expected:

- For a medicinal product not yet approved for marketing in a country, a company's Investigational Brochure, study protocol or ICF will serve as the source document in that country.
- Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigational Brochure would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a subsequent report of fulminant hepatitis.

7.1.4 Serious Adverse Event (SAE)

A *serious adverse event* (SAE) or reaction is any untoward medical occurrence that at any dose:

- Is life-threatening (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Results in death.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly or birth defect.
- Disabling/incapacitating
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. The term "severe" is often used to describe the intensity (severity) of an event; the event itself may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.
- An SAE does <u>not</u> include: Progression of the underlying disease or hospitalization for a routine clinical procedure as stipulated by the protocol and hospitalization for elective or pre-planned procedure not associated with a precipitating event or non-medical reasons (i.e., social admissions, hospitalizations for social, convenience or respite care.

7.1.5 *Exposure During Pregnancy*

Pregnancy occurring in female partners of male subjects while the male partner is receiving study drug within 120 days after the final dose should be reported within 24 hours of becoming aware of the event.

The investigator should counsel the subject, and in the case of a male subject, the subject's partner, regarding the risks of continuing with the pregnancy and the possible effects on the fetus. If the female partner of a male subject becomes pregnant, the investigator should obtain informed consent of the pregnant partner, if allowable per

local policy, prior to monitoring the pregnancy. Monitoring of the pregnancy in the female partner of the male subject should continue to the conclusion of the pregnancy. The outcome of all pregnancies (including normal births) must be reported. Follow-up information on the status of the infant should be collected and reported until 90 days post-partum, including anomalies diagnosed at birth or within 90 days post-partum, and condition at birth, neonatal illnesses, hospitalizations, and drug therapies. Complications of pregnancy, such as abortion (spontaneous or induced), premature birth, or congenital anomaly are considered SAEs.

The Sponsor must be notified of any subject's partner becoming pregnant during the study or of any spontaneous abortion or of any therapeutic abortion and any pregnancy must be followed until completion or termination of pregnancy, if allowable per local policy. The notification should be performed on the pregnancy form and handled in the same manner as for SAEs. In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth. The "normality" of an aborted fetus can be assessed by gross visual inspection unless pre-abortion laboratory findings are suggestive of a congenital anomaly.

All pregnancies of any subject's partner, from the time of treatment/ allocation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy must be reported by the investigator.

7.2 Documenting Adverse Events

The investigator should elicit information regarding the occurrence of AEs through open-ended questioning of the subject, physical examination and review of laboratory results.

All AEs, whether serious or not, will be described in the source documents and the AE page of the electronic case report form (eCRF). AEs will be reported from the time of signing of informed consent, however AEs captured prior to the initial administration of Sacituzumab Govitecan will not be considered related to study drug. All new events, as well as those that worsen in intensity or frequency relative to baseline, which occur after administration of study drug through the period of protocol-specified follow-up, must be captured. AEs occurring for 30 days after the last dose of study drug must be reported. SAEs, felt by the investigator to be related to study drug, however, must be reported any time the investigator becomes aware of such an event, even if this occurrence is more than 30 days after the last dose of study drug.

Abnormal laboratory values per se need not be reported as AEs. Abnormal laboratory values that result in clinical sequelae, that require intervention, that are deemed clinically significant by the investigator or investigator's designee, that are SAEs, that result in a change in protocol treatment, or that result in study discontinuation should be reported as AEs.

Information to be reported in the description of each AE includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded).
- The date of onset of the event or whether it is ongoing.

- Whether the event is serious or not.
- Action taken in response to the event.
- Action taken with study drug.
- Outcome.

7.3 Reporting of Adverse Events and Serious Adverse Events

The Investigator is to report all AEs directly observed or spontaneously reported by subjects using concise medical terminology. Each subject will be questioned about AEs at each clinic or evaluation visit, asking, for example, "Since your last clinic visit have you had any health problems?"

The AE reporting period begins with informed consent and ends with the last scheduled study evaluation or until all drug related toxicities and ongoing SAEs have resolved, whichever is later. All AEs must be reported in the eCRF, whether or not considered related to study medication using the appropriate forms/procedure.

7.3.1 Reporting serious adverse events

All SAEs, events determined to be medically significant by the treating Investigator, and unknown reactions or unexpected events should be reported to the PCCTC within 24 hours of knowledge of the event using the contact information below. The initial report should include the following information at a minimum:

- protocol # and title
- subject identification number, sex, age at event
- date the event occurred
- description of the SAE
- causal relationship to the study treatment(s)

The MedWatch Form will be used for reporting each SAE and should be submitted to the PCCTC Project Coordinator with the minimum information within 24 hours. The PCCTC will facilitate all SAE report form submissions to the Sponsor-Investigator (UW PI).

Grade, relationship, action taken, concomitant medications, outcome, etc. should be reported to the PCCTC as soon as possible.

Follow-up of adverse events should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator.

SAE contact information for the PCCTC is listed below.

PCCTC:
Prostate Cancer Clinical Trials Consortium
Email: pcctc@mskcc.org

For SAEs, the PCCTC is to be notified by the Investigator, using the designated form, **within 24 hours of the event**. The initial report is to be followed by submission of more detailed SAE information within 5 calendar days of the initial report.

The PCCTC will facilitate the notification of SAEs to Gilead Sciences, Inc. All SAEs and pregnancies should be reported to: Email: sacituzumab_govitecan_SO@iqvia.com

7.3.2 Other reporting requirements

University of Wisconsin Carbone Cancer Center (UWCCC) site: SAEs that occur at UWCCC require reporting to the PCCTC within 24 hours, so submission to the UWCCC DSMC via an email to saenotify@uwcarbone.wisc.edu must be done within that same 24 hour period. The OnCore SAE Details Report must be submitted along with other report materials as applicable (UWCCC SAE Routing Form, Sponsor-Investigator Determination Form for FDA Reporting of Safety Events, FDA Medwatch Form #3500A, supporting documentation). Follow-up information for the SAE must be submitted to saenotify@uwcarbone.wisc.edu within 5 calendar days of the initial report.

Non-UWCCC participating sites: For SAEs occurring at non-UWCCC sites, the site will submit FDA Medwatch form 3500A and other protocol-specific SAE reporting to the PCCTC (pcctc@mskcc.org) within 24 hours of the site being made aware of the event. The PCCTC will then forward the SAE information to the UWCCC study team (uwcccgu@medicine.wisc.edu). . The UWCCC study team will complete the UWCCC Sponsor-Investigator Determination Form for FDA Reporting of Safety Events.

SAE information will be entered and tracked in the UWCCC secure, password protected computer network.

Reporting to the FDA

Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor-investigator must be reported to the FDA by UWCCC within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

Sponsor-Investigator Responsibilities for SAE Review

The Sponsor-Investigator (i.e., the individual who holds the IND) assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 312.32. In this capacity, the Sponsor-Investigator reviews all reports of serious adverse events occurring on the study at the UWCCC and other participating sites and makes a determination of 1) **suspectedness** (i.e., whether there is a reasonable possibility that the drug caused the SAE); and 2) **unexpectedness** (the event is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed) in the context of this study.

Expedited Reporting

SAEs with suspected causality to study drug and deemed unexpected are reported as IND Safety Reports by the Sponsor-Investigator to FDA, all PIs participating on the study at other sites, and the external global sponsor (if applicable) within 15 calendar days. All fatal or life-threatening SAEs that are unexpected and have suspected causality to the study drug will be reported by the sponsor-investigator to FDA, all PIs participating on the study at other sites, and the external global sponsor (if applicable) within 7 calendar days.

7.4 Grading and Relatedness of Adverse Events

7.4.1 Grading of severity of an AE

The severity of each AE will be graded using the NCI CTCAE Version 4.0, which may be found at http://ctep.cancer.gov/reporting/ctc.html. In most cases AE terms will be listed in the CTCAE, with grading criteria specific to that term. If the AE is not specifically defined in the CTCAE, it is to be reported using the "Other, specify" term under the appropriate system organ class and graded according to the general CTCAE severity guidelines.

For each event, the highest severity grade should be reported. If a CTCAE criterion does not exist, the Investigator should use the grade or adjectives as described in **Table 8**.

Table 8. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Does not interfere with subject's usual function
Grade 2	Moderate	Interferes to some extent with subject's usual function
Grade 3	Severe	Interferes significantly with subject's usual function
Grade 4	Life-Threatening	Results in a threat to life or in an incapacitating disability

A severe reaction (e.g., a severe headache) would not be classified as serious unless it met one of the criteria for SAE(s) listed above.

7.4.2 Relatedness to study drug

The investigator must attempt to determine if an AE is in some way related to the use of the study drug. This relationship should be described as follows:

Unrelated: The event has no temporal relationship to study drug administration (too early or late or study drug not taken), or there is a reasonable causal relationship between the AE and another drug, concurrent disease or circumstance.

Unlikely: The event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Possible: The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug *BUT* the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug *or* the event could be the effect of a concomitant medication.

Definite: The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

Reporting requirements for AEs are summarized in *Table 9*:

Table 9. Reporting Requirements for Adverse Events

	Reporting Time	Type of Report
SERIOUS	Within 24 hours	Initial report on designated SAE form
	Within 5 calendar days of initial report	Follow-up/Final report on designated form
NON-SERIOUS	Per CRF submission procedure	Appropriate CRF pages

7.4.3 Recording information on AEs

All AEs, whether observed by the Investigator, elicited from, or volunteered by the subject, will be recorded including: duration, severity, relationship to the study medication, treatment, action taken with respect to the study medication and outcome. When possible, all events should be reported in diagnostic terms or the most acceptable medical terms in order to interpret safety information accurately.

The investigator must review all laboratory test data and record any AEs. The same format will be used as for other AEs, regardless whether related to study therapy or not, including event severity grading, attribution, and resolution. A summary listing of all AEs occurring during the past year on this study will be provided in progress reports reported to regulatory authorities.

7.5 Follow-up of Unresolved Adverse Events

All AEs should be followed until they are resolved or the Investigator assesses them as chronic or stable or the subject's participation in the trial ends (i.e., until a final report is completed for that subject). Instructions for reporting changes in an ongoing AE during a subject's participation in the trial are provided in the instructions that accompany the AE CRFs.

In addition, all SAEs and those non-SAEs assessed by the Investigator as possibly related to the investigational medication/product should continue to be followed even after the subject's participation in the trial is over. Such events should be followed until they resolve or until the Investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the appropriate CRF.

8. STATISTICAL CONSIDERATIONS

8.1 Data Management

Data from the study will be entered into eCRFs. Data may only be entered by authorized personnel. The data will be periodically monitored by the clinical monitor; in addition, programmatic edit checks will review the data for correctness, logic and consistency. Based on the monitoring findings and the edit checks, queries may be issued to the clinical site for data clarification. The results of all original entries, as well as any corrections, will be maintained by the data management system. The principal investigator will review and approve all data entries with electronic signature on the eCRF.

8.2 Study Design

A multi-arm, multi-institutional phase II study design will be used to assess the efficacy of Sacituzumab Govitecan in subjects with metastatic CRPC progressing on an ARSI. Patients will continue treatment on the ARSI and enroll on this trial. Prior exposure and sensitivity to second generation AR-directed therapy will be recorded and subjects will be considered to have responded (i.e., were sensitive) to the prior agent if there was a ≥50% PSA decline from baseline.

Treatments can continue until radiographic disease progression, unacceptable toxicity, initiation of alternative therapy or withdrawal of consent.

8.3 Determination of Sample Size

The primary endpoints for the study are (1) PSA response rate, which is defined as the proportion of subjects achieving a ≥50% decline in PSA at or within 9 weeks of starting Sacituzumab Govitecan. Prior published data from retrospective studies report PSA response rates (≥50% decline) in 20-30% of subjects on 2nd line AR directed therapy after progression on a 1st line agent in the pre-docetaxel setting (3-8), (2) and the 6-month rPFS rate. The response rate appears higher with cytotoxic chemotherapy. Although data are limited in the pre-docetaxel setting, retrospective studies in the post-docetaxel setting suggest patients with prior response to abiraterone are more likely to respond to second line enzalutamide (9-11). The familywise type I error for the two primary endpoints of the study is one-sided 0.05 and a Bonforreni adjustment for evaluating two primary endpoints will be applied that each endpoint will be tested at the one-sided 0.025 (0.05/2) significance level. A PSA response rate of 20% or less will be considered as unacceptably low. A PSA response rate of 40% or more, on the other hand, will be considered sufficient evidence to consider further clinical trial investigation. Hence, the null hypothesis that the PSA response rate is 20% will be tested against the alternative hypothesis that the PSA response rate is 40%. A sample size of 45 evaluable subjects for PSA response (defined as subjects who received at least 1 dose of Sacituzumab Govitecan and have at least 1 post-dose assessment of PSA) is required to detect an increase in the PSA response rate from 20% to 40% with 87% power at the one-sided exact test with a significance level of 0.025 . Analogously, a 6-month rPFS rate of 20% or less will be considered as unacceptably low and 40% or more considered sufficient evidence. Again a sample size of 45 evaluable subjects (for assessing 6-month PFS rate) is required to detect an increase in the 6-month rPFS rate from 20% to 40% with 87% power at the one-sided 0.025 significance level. The following table shows the probabilities for rejecting the null hypothesis with a sample size of 45 evaluable subjects, assuming that the true PSA response/6-month rPFS rates range between 35-50%.

Table 10. Attainable power levels with a sample size of 45 evaluable subjects

True PSA response/6-months PFS rate	Probability of rejecting null hypothesis
35%	68%
40%	87%
45%	96%
50%	>99%

Hence, a sample size of 45 evaluable subjects will provide between 68-99% power to detect a true PSA response rate or 6-month rPFS rate between 35-50% at the one-sided 0.025 significance level.

A sample size of 45 subjects will also be adequate for estimating toxicity rates with sufficient accuracy. Specifically, toxicity rates will be estimated with a standard error of less than 8% and the corresponding 95% confidence intervals will be no wider than 30%.

In order to account for unevaluable (for assessing PSA response or 6-month rPFS rate) subjects, 55 subjects in total will be enrolled.

8.4 Analysis Plan

8.4.1 Baseline and Demographic Analysis

The disposition of all subjects (number of subjects enrolled, treated, completed, discontinued and replaced) will be presented. Demographic and baseline subject characteristics will be summarized (e.g., age, race, ethnicity, ECOG Performance Score, prior medical history, prior therapy and response to prior therapy).

8.4.2 Safety Analysis

The Safety Analysis Set will consist of all subjects who received at least 1 dose of Sacituzumab Govitecan.

Safety parameters will include results of AE reporting, physical exam findings, vital signs, safety laboratory determinations and ECGs. AEs will be listed according to the MedDRA coding dictionary by system organ class, preferred term and high level terms. All AEs will be classified by type, severity, and causality. In addition to all AEs, SAEs, drug-related AEs, Grade 3 or higher AEs, drug-related Grade 3 or higher AEs, and AEs leading to discontinuation or death will be described. A customized drug dictionary will be used to classify concomitant medications by therapeutic class and preferred term.

Changes from baseline assessments (e.g., laboratory parameters, vital signs and ECG parameters) will be presented using descriptive statistics. The distribution of the maximum observed grade of each AE will be tabulated. Toxicities will be summarized by type and severity in tabular format. Toxicity rates (Grade 2, Grade 3, Grade 4, Grade ≥ 2, Grade ≥ 3, etc.) will be calculated and reported along the corresponding 95% confidence intervals. The 95% confidence intervals will be constructed using the Wilson score method.

The safety analyses will be stratified by subjects who continued single agent ARSI in combination with Sacituzumab Govitecan and patients who discontinued single agent ARSI before starting Sacituzumab Govitecan.

8.4.3 Efficacy Analysis

The Efficacy Analysis Set will consist of all subjects who receive at least 1 dose of Sacituzumab Govitecan and have at least 1 post-dose assessment of PSA; and/or 1 post-dose radiographic assessment for subjects with evaluable and/or measurable metastases at screening, 1 post-dose assessment of metastatic disease will be required. Subjects who

discontinue study participation early so they do not meet criteria for inclusion in the efficacy analysis set can be replaced.

Changes in PSA will be compared to baseline and maximal change from baseline and change at Week 9 (e.g., end of Cycle 3) will also be determined, as will duration of response. Maximum change in soft tissue lesions as seen on CT or MRI of the chest, abdomen and pelvis, as well as changes on bone scintigraphy according to the PCWG2 criteria will also be compared to baseline, and summarized.

A subgroup efficacy analysis will be conducted in the group of patients who continued single agent ARSI in combination with Sacituzumab Govitecan.

Definition and analysis of primary efficacy endpoint:

PSA response rate: Subjects who achieve ≥50% PSA decline at or before 9 weeks of therapy with Sacituzumab Govitecan are considered to have responded. PSA responses will be analyzed by descriptive statistics and summarized in tabular format (frequency tables). The overall PSA response rate will be reported along with the corresponding 95% confidence interval which will be constructed using the Wilson score method.

6-month rPFS rate: Proportion of subjects remaining alive and progression free (using PCWG2 criteria) 6 months from time of starting treatment as estimated by the Kaplan-Meier method. The point estimate of the 6-month rPFS rate will be reported along with the corresponding two-sided 95% confidence interval.

Definition and analysis of secondary efficacy endpoints:

i. *Median rPFS*. The probability distribution of PFS will be estimated using the Kaplan-Meier method. The median will be estimated from this distribution. Subjects who have not died or progressed (using PCWG2 criteria) will be censored at the date of last assessment.

ii. *Median OS*. OS is the duration from start of treatment until death from any cause. The probability distribution of OS will be estimated using the Kaplan-Meier method. The median will be estimated from this distribution. Subjects who have not died will be censored at the date of last contact.

Response. The number and frequencies of subjects with progressive disease, stable disease, partial response and complete response will be summarized in tabular format. The overall response rate will be reported along with the corresponding 95% confidence interval which will be constructed using the Wilson score method.

8.5 Correlative Biomarker Analysis

An exploratory endpoint of the study is to evaluate the predictive accuracy of potential biomarkers for the PSA response and rPFS endpoints. Other exploratory objectives include assessment of mechanisms of resistance to Sacituzumab Govitecan via biomarker analysis of post-

progression tumor tissue. These analyses will be mostly descriptive for future references. All exploratory endpoints will be summarized using standard descriptive statistics, stratified by assessment time point. Longitudinal changes will be evaluated using a linear or generalized linear mixed effects model.

A Cox proportional hazards regression model (for the rPFS endpoint) and a logistic regression model (for the PSA response endpoint) will be used to assess the prognostic significance of baseline factors both alone and in combination with other biomarkers (e.g., clinical parameters, LDH, Hb). For each regression model, the c-index will be used to quantify the predictive accuracy of these biomarkers.

9. ADMINISTRATIVE PROCEDURES

9.1 Pre-Study Documentation

Prior to initiating the study, the Investigator will provide to the sponsor the following documents:

- A signed FDA Form 1572
- A current curriculum vitae for the principal investigator and each sub-investigator listed on the FDA Form 1572
- A copy of the current medical license for the investigator
- A letter from the IRB stipulating approval of the protocol, the informed consent document and any other material provided to potential study participants with information about the study (e.g., advertisements)
- A copy of the IRB-approved informed consent document
- The current IRB membership list for the reviewing IRB, or the multiple project assurance number from the Federal Wide Assurance program (www.ohrp.osophs.dhhs.gov).
- A fully signed Investigator Protocol Agreement
- A completed financial disclosure form for the investigator and all sub-investigators
- Current laboratory certification for the reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory

9.2 Source Documents

The investigator will maintain records separate from the eCRFs in the forms of clinic charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The investigator will document in the clinic chart or medical record the date on which the subject signed informed consent prior to the subject's participation in the study. Source documents must completely reflect the nature and extent of the subject's medical care, and must be available for source document verification against entries in the eCRFs when the sponsor's monitor visits the investigational site. All information obtained from source documents will be kept in strict confidentiality.

9.3 Study Ethics

9.3.1 Ethics statement

The study will be performed according to the principles of the Declaration of Helsinki (Appendix D), the International Conference on Harmonization Guidance on Good Clinical Practice, as adopted by applicable laws and regulations, and the requirements of the FDA regarding the conduct of human clinical studies. This study is planned to be conducted both in the North America.

The Institutional Review Board (IRB) and/or the Institutional Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The Investigator is responsible for providing their IRB/IEC with any required study documents, progress reports and safety updates and is responsible for notifying the IRB/IEC promptly of all SAEs occurring at the site, in accordance with IRB/IEC policies.

All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Gilead Sciences, Inc. or the designee.

9.3.2 Informed consent

It is the responsibility of the Investigator to give each subject (or the subject's legal representative) full and adequate verbal and written information regarding the objective and procedures of the trial including the possible risks and benefits involved. Written subject information, approved by the IRB/IEC must be given to each subject before any trial-related procedure is undertaken. During the consent process, the subject must be informed about their right to withdraw from the trial at any time. The subject must also be given ample time to read the written informed consent form and have all study-related questions answered to the satisfaction of the subject (or the subject's legally acceptable representative). It is the responsibility of the Investigator to obtain a signature from each subject, the subject's legally acceptable representative if applicable, and from the persons conducting the informed consent discussion prior to undertaking any trial-related procedure. The subject (or the subject's legally acceptable representative) must be given a copy of the signed and dated informed consent form.

The Investigator is also responsible for providing the subject (or the subject's legally acceptable representative) with any clinical trial updates that may affect the subject's willingness to continue participation in the study. The informed consent process must be documented in the subject's medical or source chart.

The written subject information must not be changed without prior approval by Gilead Sciences, Inc. and the IRB/IEC.

Per ICH E6 4.3.3, it is recommended that the Investigator notify the subject's primary care physician of the subject's participation in the trial if the subject agrees to the Investigator informing the primary care physician.

No study related procedures will be performed until a subject or a subject's legal representative has given written informed consent. The sponsor will provide to the investigator a sample informed consent document that includes all the requirements for informed consent according to U.S. FDA guidelines (21 CFR 50). However, it is up to the investigator to provide a final informed consent that may include additional elements required by the investigator's institution. The informed consent document must clearly describe the potential risks and benefits of the study, and each prospective participant must be given adequate time to discuss the study with the investigator or site staff and to decide whether or not to participate. Each subject who agrees to participate in the study and who signs the informed consent will be given a copy of the signed, dated and witnessed document. The provision of informed consent will be documented in the medical record.

9.3.3 Investigational Review Board approval

The study will not be initiated until there is approval of the protocol, informed consent document and any other material used to inform the subject about the nature of the study by the IRB. The IRB should be duly constituted according to regulatory requirements. Approval must be in the form of a letter signed by the Chairperson of the IRB or the Chairperson's designee, must be on IRB or IEC stationary and must include the protocol by name and/or by designated number. If an investigator is a member of the IRB, the approval letter must stipulate that the investigator did not participate in the final vote, although the investigator may participate in the discussion of the study. The investigator will also inform the IRB of any SAEs that the sponsor reports to regulatory authorities, will report on the progress of the trial at least yearly (or more frequently if required by local regulation or guidance) and will provide to the IRB a final summary of the results of the study at the conclusion of the study.

9.4 Data and Safety Monitoring

9.4.1 Data and safety monitoring plan

UWCCC site: This protocol undergoes review of subject safety at regularly scheduled Disease Oriented Team (DOT) meetings where the following are discussed as applicable: number of subjects enrolled, subject treatments given, dose holds/modifications, significant toxicities, and response to treatment. These discussions will be documented in the DOT meeting minutes.

<u>UWCCC Data and Safety Monitoring Committee (DSMC) Study Progress Review</u>

The following information enables the UWCCC DSMC to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. In the event that there is a significant risk warranting study suspension or closure, the UWCCC DSMC will notify the sponsor-investigator of the findings and ensure the appropriate action is taken for the study. The UWCCC ensures that the Sponsor-Investigator reports any temporary or permanent suspension of the clinical trial to the appropriate parties.

UWCCC site: Based on the risk level of the study, Protocol Summary Reports (PSRs) must be submitted to the UWCCC DSMC twice yearly.

Non-UWCCC participating sites: The PCCTC will prepare summary information as noted below in section 9.4.2 UWCCC Data and Safety Monitoring Committee (DSMC) Oversight, which will also be submitted to the UWCCC DSMC by the UWCCC study team at the time of the PSRs.

PCCTC oversight activities include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Notify Sponsor-Investigator of adverse events requiring expedited reporting at Safety_FC@gilead.com within 24 hours of the Investigator's awareness.
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator

9.4.2 *UWCCC Data and Safety Monitoring Committee (DSMC) oversight*

The UWCCC DSMC will review this clinical trial for subject safety, protocol compliance, and data integrity. This is achieved by their twice yearly review of the following:

- Study accrual patterns
- Cumulative summary report of all Serious Adverse Events (SAEs)
- Cumulative summary report of all responses to treatment
- Cumulative summary report of all non-compliance, unanticipated problems, and other IRB reportable events

The UWCCC DSMC will review UWCCC PSRs and participating site summary information twice yearly. Documentation of these reviews and the UWCCC DSMC recommendation (e.g., protocol continuation, protocol continuation with modifications, protocol suspension, or discontinue protocol or treatment arm) will be provided to the Sponsor-Investigator and the PCCTC (pcctc@mskcc.org). Issues of immediate concern will be brought to the attention of the Sponsor-Investigator and other regulatory bodies as appropriate. The Sponsor-Investigator will work with the PCCTC to address these concerns.

9.4.3 *Review and oversight requirements*

UWCCC DSMC Review of Auditing and/or Monitoring Reports

Reports created through the auditing and/or monitoring activities of the PCCTC are submitted in real-time by the PCCTC to the UWCCC DSMC via an email to DSMC@uwcarbone.wisc.edu. Following UWCCC DSMC review of these reports, the committee may issue a request for corrective and/or preventive action(s), protocol suspension, or for-cause audit(s).

UWCCC DSMC Review of Non-compliance, Unanticipated Problems, and Other IRB Reportable Events

Reports of non-compliance, unanticipated problems, and other IRB reportable events are submitted to the IRB of record for the site at which the event occurred and to the PCCTC

simultaneously. The PCCTC will then forward the event information to the Sponsor-Investigator within 24 hours of receipt. The Sponsor-Investigator, or designee, will submit the event information to the UWCCC DSMC within 24 hours of receipt from the PCCTC.

Real-time UWCCC DSMC Review of SAEs
The UWCCC DSMC Chair, or designee, will review SAE information and determine if immediate action is required.

UWCCC site: The Principal Investigator (PI), or designee, notifies the following individuals/entities of SAEs as applicable:

- Other investigators involved with the study at the UWCCC
- IRB of record for the study conducted at the UWCCC
- UWCCC DSMC (see section 7.3.2 – Other reporting requirements)
- PCCTC

Non-UWCCC participating sites: The site PI, or designee, notifies the following individuals/entities of SAEs as applicable:

- Other investigators involved with the study at the site
- IRB of record for the study conducted at the site
- PCCTC

9.5 Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all subjects participating in the study and all of their medical information is maintained. eCRFs and other documents submitted to the sponsor must never contain the name of a study subject. All subjects in the study will be identified by a unique identifier which will be used on all CRFs and any other material submitted to the sponsor. All study documents and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the study.

Personal medical information may be reviewed by representatives of the sponsor, of the IRB or the FDA in the course of monitoring the progress of the study. Every reasonable effort will be made to maintain such information as confidential.

The results of the study may be presented in reports, at scientific meetings or published in scientific journals; however, subject names will never be used in such reports, presentations or publications.

9.6 Protocol Amendments

The protocol will only be amended with the consent of the sponsor and the IRB. Changes to the protocol must be in the form of a written amendment; changes other than those of a simple administrative nature (e.g., a new telephone number for a medical monitor) must be submitted by the investigator to the IRB and such amendments will only be implemented after approval of the requisite IRB. All amendments will also be submitted by the sponsor to the FDA.

Protocol changes to eliminate an immediate hazard to a study subject may be implemented by the investigator immediately. The investigator must then immediately inform the local IRB or IEC and the sponsor will immediately notify local regulatory authorities.

All protocol amendments will be submitted to local regulatory authorities by the sponsor as required by local regulation.

9.7 Protocol Compliance

The Investigator will conduct the study in compliance with the protocol and given approval by the IRB/IEC and the appropriate regulatory authorities.

Modifications to the protocol should not be made without agreement of both the Sponsor-Investigator and Gilead Sciences, Inc. Changes to the protocol will require written IRB/IEC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to the subjects. The IRB/IEC may provide, if applicable, regulatory authorities permit, expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB/IEC. University of Wisconsin or its designee, the PCCTC, will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the PCCTC, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the subject's CRF and source documentation.

9.8 Site Monitoring and On-Site Audits

A clinical monitor will make regularly scheduled trips to the investigational site to review the progress of the study. The actual frequency of monitoring trips will depend on the enrollment rate and performance at each site. As required by federal regulations, the investigator will allow access to all pertinent medical records in order to allow for the verification of data gathered in the eCRFs and for the review of the data collection process. At each visit, the monitor will review various aspects of the study including, but not limited to: screening and enrollment logs; compliance with the protocol and with the principles of Good Clinical Practice; completion of eCRFs; source data verification; study drug accountability and storage; facilities and staff. It is expected that eCRFs are completed within the timeframe outlined in the CRF completion guidelines.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the study, make necessary corrections to eCRF entries, respond to data clarification requests and respond to any other study-related inquiries of the monitor.

The clinical monitor has the obligation to follow the study closely. In addition to site visits the monitor will maintain necessary telephone, e-mail, and letter contacts as well as ongoing data review and query resolution.

In addition to the above, representatives of local or foreign health authorities may review the conduct or results of the study at the investigational site. The investigator must promptly inform the PCCTC of any audit requests by health authorities, and will provide Gilead Sciences, Inc. with the results of any such audits and with copies of any regulatory documents related to such audits.

As applicable, in accordance with HIPAA, a patient authorization to use personally identifiable health information may be required from each subject before research activities. This

Authorization document must clearly specify what parties will have access to a subject's personal health information, for what purpose, and for how long.

Monitoring and auditing procedures developed by the Sponsor or its designee will be followed, in order to comply with GCP guidelines. On-site review of subject's CRFs for completeness and clarity, cross-checking with source documents, and review of regulatory documents will be performed. All available source documents should be obtained by the Investigator and provided to the Sponsor or designee at each monitoring visit.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications.

Regulatory authorities, the IRB/IEC, University of Wisconsin, the PCCTC, and/or Gilead Sciences, Inc. clinical quality assurance group or designee may request access to all source documents, subject's CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

9.9 Patient Data Protection

Privacy Act Compliance. Information collected in this clinical trial is subject to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) as described in 45 CFR 160 and 45 CFR 164. The study Investigator is responsible for informing subjects of their rights under HIPAA, and obtaining any necessary HIPAA authorizations. In compliance with the provisions of that policy, Gilead Sciences, Inc. or designee will not collect any protected health information, and will only collect de-identified health information. Any clinical study information referred to in this section is understood to be compliant with the provisions of the Privacy Act.

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. Information obtained during the conduct of this study will be used by Gilead Sciences, Inc. or designee in connection with the development of the study drug. The study Investigator is obliged to provide Gilead Sciences, Inc. or designee with complete test results and all data developed in this study. This information may be disclosed to other physicians participating in the study, to the FDA, or to national and local health authorities. To ensure compliance with all current Federal Regulations and the ICH/GCP guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, Gilead Sciences, Inc., designee, and the IRB/EC for each study site.

9.10 Financial Disclosure

In accordance with 21 CFR Part 54, FDA requires that certain financial interests and arrangements between sponsors of clinical investigations be disclosed in marketing applications. Since the results of this study may eventually be used in a marketing application, compliance with this Federal statute is essential. In order to comply with the provisions of this regulation, Gilead Sciences, Inc. requests that every Investigator and sub-Investigator mentioned on FDA Form 1572 fill out a financial disclosure form. Under the provisions of 21 CFR Part 54, the term clinical Investigator includes the spouse and each dependent child of the Investigator.

The provisions of 21 CFR Part 54 specify disclosure of significant equity interests in the Sponsor that exceed $50,000, or significant payments of other sorts made by the Sponsor to the Investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies (e.g., grants to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation), during the time the clinical Investigator is carrying out the study or for 1 year following the completion of the study. If a change in financial interest occurs throughout the study, the Investigator is obligated to notify Gilead Sciences, Inc.

To assist Gilead Sciences, Inc. in providing the FDA with the required information, please complete the financial disclosure form and return the original signed copy. All information provided in the financial disclosure form will be regarded as strictly confidential and will only be disclosed to the FDA.

9.11 Discontinuation Criteria

Gilead Sciences, Inc. reserves the right to discontinue the trial prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating subjects within a time period set by the Sponsor-Investigator and Gilead Sciences, Inc. As directed by the Sponsor-Investigator, all study materials will be collected and all CRFs completed to the greatest extent possible.

10. DISSEMINATION AND PUBLICATION OF RESULTS

The dissemination and publication of the trial results will be a joint decision between Investigators of participating institutions and Gilead Sciences, Inc.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: STUDY CALENDAR

Cycle = 21 days	Screening	Cycle 1		Cycle 2		Cycle 3			Cycle 4+		End of Treatment /Progression	Follow-up[7]
	Within 30 days prior to C1D1	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 8 (±3)	Day 15 (±7)	Day 1 (±3)	Day 8 (±3)	30 days from last treatment (+7)	Every 3 months (±7)
Assessments												
Medical History & Comorbidities	X	X		X		X			X			
Consent	X											
Physical exam and ECOG PS	X	X		X		X			X		X	
Toxicity assessment		X	X	X	X	X	X		X	X	X	
Concomitant medications	X	X	X	X	X	X	X		X	X	X	
Vital signs, height, weight[1]	X	X	X	X	X	X	X		X	X	X	
ECG	X										X	
Laboratory Evaluations												
PSA	X	X	X	X		X			X		X	X
Testosterone	X											
CTCs & plasma	X	X	X	X		X			X[2]		X	
Buffy coat	X											
CBC with differential[9]	X	X	X	X	X	X	X		X	X	X	
CMP[3]	X	X	X	X	X	X	X		X	X	X	
PT/INR and PTT	X						X					
Urinalysis[4]	X											
Treatment-Experimental Interventions												
Sacituzumab Govitecan		X	X	X	X	X	X		X	X		

Metastatic Biopsy[5]	X							X				
Imaging studies												
^{99m}Tc-MDP bone scan[6]	X								X[2]		X[8]	X
CT Chest; CT or MRI Abdomen/ Pelvis[6]	X								X[2]		X[8]	X

[1]Height is only required during screening. BP and pulse prior to first infusion, every 15 for the first hour and then every 30 minutes until completing IV administration, at completion, and then additionally 30 minutes later. In absence of significant changes, frequency may be reduced with subsequent doses to prior to infusion, at 30 minutes, and then at completion. All time points may be collected ±5 minutes.

[2]Every 3 cycles (cycle 7, cycle 10, etc.) or every 9 weeks; if a cycle is delayed, procedures should still be performed every 9 weeks.

[3]Sodium, potassium, chloride, bicarbonate, BUN, glucose, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase, total bilirubin, total protein, albumin, serum calcium, magnesium, and phosphorous

[4]To include pH, specific gravity and hemoglobin, glucose, ketones, and protein by dipstick, with microscopic exam if any of the dipstick analytes are 2+ or higher.

[5]Fresh or Archived tumor from standard of care biopsy from metastatic site required for enrollment. On study biopsy at cycle 3 day 15 should be performed, regardless of treatment delays, to be performed in line with CT and bone scans.

[6]Window extended to ±10 days for scans.

[7]All subjects should have adverse events evaluated at least 30 days from the last dose of study drug. Follow-up for progression will be performed every 3 months or per standard of care for up to 2 years from initiation of study therapy if subjects discontinue study treatment prior to progression. For subjects coming off-treatment due to progression, follow-up is complete once AEs have been evaluated at least 30 days after the last dose of the study drug.

[8]If not performed within 30 days of End of Treatment/Progression

[9] If lab values are not within normal range on day 1 or day 8, consider repeat CBC with differential on day 15, as per MD discretion. In the case of a Grade 3 ANC subjects should be assessed weekly and for grade 4 ANC subjects should be assessed bi-weekly as per section 6.4.1.

APPENDIX C: ELEMENTS OF INFORMED CONSENT

Signed studies items: informed consent will be obtained from all subjects participating in clinical research or the subject's legally authorized representative. This consent must include the following:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and identification of any procedures that are experimental; and the expected duration of the subject's participation.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others that may reasonably be expected from the research. If the subject is to be paid for participating in the study, the consent form must state the amount he/she will receive and the schedule of payment (to assure neither coercion nor undue influence).
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that regulatory agencies, the IRB, or an authorized contract research organization (CRO) may inspect the records.
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of, or where further information may be obtained.
- An explanation of whom to contact, including the appropriate telephone number, for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject. (NOTE: In some cases it may be necessary to identify some person other than the investigator as the contact. The guidance of the IRB may be required.)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject
- A copy of the consent form given to the subject.
- A statement of consent, e.g. "I agree to participate."
- A place for signature and date of signature for the research subject.
- A statement that the particular treatment or procedures may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable.
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- Any additional costs to the subject that may result from participation in the research.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject.
- The approximate number of subjects involved in the study.

APPENDIX D: THE DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Patients

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 198948th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human patients, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human patients to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human patients. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human patients, the well-being of the individual research patient must take precedence over all other interests.
7. The primary purpose of medical research involving human patients is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is patient to ethical standards that promote respect for all human patients and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human patients in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients.
2. Medical research involving human patients must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
3. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
4. The design and performance of each research study involving human patients must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for patients and provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study patients to interventions identified as beneficial in the study or access to other appropriate care or benefits.
5. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any SAEs. No change to the protocol may be made without consideration and approval by the committee.
6. Medical research involving human patients must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research patients must always rest with the physician or other health care professional and never the research patients, even though they have given consent.
7. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
8. Every medical research study involving human patients must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

9. Every clinical study must be registered in a publicly accessible database before recruitment of the first patient.
10. Physicians may not participate in a research study involving human patients unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
11. Medical research involving human patients may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research patients.
12. Participation by competent individuals as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
13. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
14. In medical research involving competent human patients, each potential patient must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential patient must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information. After ensuring that the potential patient has understood the information, the physician or another appropriately qualified individual must then seek the potential patient's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
15. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
16. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential patient is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
17. For a potential research patient who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential patient, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
18. When a potential research patient who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential patient's dissent should be respected.
19. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the

study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the patient or a legally authorized representative.

20. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human patients and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FORMEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.
2. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    a. The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    b. Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be patient to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
3. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
4. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

APPENDIX E: PROSTATE CANCER WORKING GROUP 2 (PCWG2) REPONSE CRITERIA

The effects of Sacituzumab Govitecan will be assessed using both "control/ relieve/ eliminate" endpoints as well as "prevent/ delay" endpoints as outlined in the PCWG2 response criteria summarized in the table below.

Variable	PCWG2 (2007)
PSA	Recognize that a favorable effect on PSA may be delayed for 9 weeks or more, even for a cytotoxic drug Monitor PSA by cycle but plan to continue through early rises for a minimum of 9 weeks unless other evidence of progression Ignore early rises (prior to 9 weeks) in determining PSA response **For control/relieve/eliminate endpoints:** Record the percent change from baseline (rise or fall) at 9 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot **For prevent/ delay (progression): Decline from baseline:** Record time from start of therapy to first PSA increase that is > 25% and > 2 ng/ml above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend). **No decline from baseline:** PSA progression > 25% and > 2 ng/ml after 9 weeks
Soft-tissue lesions	**For control/relieve/ eliminate endpoints: Use RECIST with caveats:** Only report changes in lymph nodes that were > 2 cm in diameter at baseline Record changes in nodal and visceral soft tissue sites separately Record complete elimination of disease at any site separately Confirm favorable change with second scan Record changes using waterfall plot **For prevent/ delay endpoints (progression):** Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. Note that for some treatments, a lesion may increase in size before it decreases
Bone	**For control/relieve/ eliminate endpoints:** Record outcome as new lesions or no new lesions First scheduled re-assessment: **No new lesions**: continue therapy; **New lesions**: perform a confirmatory scan 6 or more weeks later **Confirmatory scan:** No new lesions: continue therapy; **Additional new lesions:** progression **Subsequent scheduled re-assessments:** No new bone lesions: continue; **New lesions:** progression **For prevent/ delay endpoints (progression):** The appearance of > 2 new lesions, and for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions. The date of progression is the date of the first scan that shows the change.
Symptoms	Consider independently of other outcome measures; Document pain and analgesia at entry with a lead in period and measure repeatedly at 3- to 4- week intervals; Perform serial assessments of global changes in HRQOL, urinary or bowel compromise, pain management, additional anticancer therapy; Ignore early changes (< 9 weeks)in pain or HRQOL in absence of compelling evidence of disease progression; Confirm response or progression of pain or HRQOL end points > 3 weeks later

** Adapted from Scher et al, 2008*

APPENDIX F: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ACTH	adrenocorticotrophic hormone
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
AR	androgen receptor
ARSI	Androgen Receptor Signaling Inhibitors
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CBR	clinical benefit rate (%OR+SD)
CDR	complementarity-determining region
CFR	Code of Federal Regulation
CMP	comprehensive medical panel
CNS	central nervous system
CR	complete response
CRF	case report form
CRPC	castration-resistant prostate cancer
CT	computerized tomography
CTC	circulating tumor cells
CTCAE	common terminology criteria for adverse events
ctDNA	circulating DNA
CYP17	cytochrome P450
D	day
DHEA-S	dehydroepiandrosterone-sulfate
17A1 DHEA	dehydroepiandrosterone
dL	deciliter
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DT	dose titration
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
GCP	good clinical practice
GLP	good laboratory practice

GR	glucocorticoid receptor
HAHA	human anti-human antibodies
HCT	hematocrit
HDPE	high density polyethylene
hERG	human Ether-a-go-go-related gene
HGB	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Committee on Harmonization
IC50	half–maximal inhibitory concentration
ICF	informed consent form
IEC	independent ethics committee
IgG	immunoglobulin G
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board
IULN	institutional upper limit of normal
HIV	human immunodeficiency virus
K	potassium
Kg	kilogram
L	Liter
LDH	lactate dehydrogenase
LHRH	luteinizing hormone–releasing hormone
mAb	monoclonal antibody
mEq	milliequivalent
mg	milligram
mL	milliliter
µl	microliter
MRI	magnetic resonance Imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ng	naogram
NSAE	non-serious adverse event
NSAID	non-steroidal anti-inflammatory drug
NOAEL	No-observed –adverse –effect level
NOEL	no-observed–effect level
NYHA	New York Heart Association
OR	Objective Response, OR = CR + PR
OS	overall survival
PCWG2	prostate cancer working group 2
PD	pharmacodynamics
PFS	progression free survival
PK	pharmacokinetics
PR	partial response

PSA	prostate specific antigen
PT	prothrombin time
PTT	partial prothrombin time
QD	once a day
QTcF	QT interval corrected by Fredericia correction formula
RBC	red blood cell
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
rPFS	radiological progression free survival
SAE	serious adverse event
SOP	standard operating procedure
TTP	time to progression
WBC	white blood cell
ULN	upper limit of normal
US	United States of America
UWCCC	University of Wisconsin Carbone Cancer Center