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Technical Note

Phase I study of the PARP inhibitor talazoparib with radiation therapy for locally recurrent gynecologic cancers

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SUMMARY

PARP inhibitors have been shown to radiosensitize tumor cells in both in vitro and in vivo studies. This is a phase I study that aims to determine the safety, tolerability, and maximally tolerated dose of talazoparib, a PARP inhibitor, when delivered concurrently with radiotherapy in women with recurrent gynecologic cancers.
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1. Background

Gynecologic cancer is the third leading cause of cancer-related deaths for women in the United States [1]. Ovarian cancer results in an estimated 13,980 deaths a year in the United States, and remains a malignancy with one of the poorest prognoses, a 5-year survival of approximately 35% [1,2]. Uterine cancers, while faring more favorably overall, are estimated to result in 12,160 deaths a year and those with advanced staged or recurrent disease have a 5-year survival of 17% [1,3]. Furthermore, uterine malignancy remains one of the few cancers with an increasing incidence rate and overall mortality [4,5]. Thus, although innovative therapies have arisen, including targeted agents and immunotherapy, novel strategies for women with unresectable, recurrent gynecologic malignancy remain urgently needed.

The role of radiotherapy in the management of recurrent ovarian and endometrial cancer has expanded in the last decade, with several retrospective studies documenting its effectiveness in nodal or isolated recurrences of gynecologic cancers, including isolated relapse of ovarian cancer [6–10]. While radiotherapy has shown improved outcomes, likely due to the ability to deliver escalated doses with techniques such as intensity-modulated radiotherapy or volume-modulated arc therapy, additional adverse side effects have arisen from the high-doses needed to eradicate gross disease, including severe grade 3 or 4 late-bowel and rectal complications which was observed in 21.7% of patients in a series by Rome et al. [8]. Furthermore, the rates of local control of 70% at 5 years leave room for improvement. Accordingly, a radiosensitizer in conjunction with radiotherapy could be utilized to widen the therapeutic ratio by shifting the tumor control probability curve leftward while mitigating complications; one class of such agent includes the poly-ADP-ribose-polymerase (PARP) inhibitors.

PARP is a superfamily of nuclear enzymes with a wide variety of functions, most prominently repair of single-stranded DNA breaks [11]. As ionizing radiation induces both single- and double-stranded DNA breaks, inhibition of PARP enzymes should lead to an increased accumulation of DNA damage and enhanced cytotoxicity. PARP-inhibitors have already been shown to potentiate the effects of both radiation and chemotherapy in xenograft models of lung, colorectal, glioblastoma, and high-grade serous ovarian cancer [12–15]. Moreover, many gynecologic cancers are inherently prone to increased DNA damage due to defective homologous repair mechanisms, including *BRCA* and *PTEN* mutations, among others [16,17]. In one preclinical study of high-grade serous

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ovarian carcinomas, the PARP inhibitor olaparib was found to radiosensitize BRCA1-deficient cells more effectively than BRCA1-proficient cells, although both showed some radiosensitization [15]. Similar findings have been observed in preclinical studies of cervical cancer cells, in which exposure to PARP-inhibitors potentiated radiation responses [18].

Talazoparib (also known as MDV3800 or BMN 673) is a novel, potent inhibitor of PARP. It is particularly notable among other PARP-inhibitors due to the lower concentrations needed to generate antitumor cell responses and its best-in-class in-vitro trapping of PARP-DNA complexes [19–22]. Preclinical work has confirmed that talazoparib monotherapy had remarkable antitumor activity and can sensitize a variety of tumor types to radiation or chemotherapy, including *BRCA1* mutant MX-1 breast cancer xenografts [23], pediatric cell lines such as Ewing sarcoma [24], BRCA deficient osteosarcoma cell lines [25], and glioblastoma stem-cells [14]. Clinical studies of patients with locally-advanced and metastatic breast cancer, including a phase III trial reported in 2018, have shown talazoparib to have low toxicity (primarily transient, reversible cytopenias) and to produce significant improvement in progression-free survival over standard chemotherapy in women with germline *BRCA1/2* mutations [26,27]. Other studies have found talazoparib to be tolerable among patients with gynecologic cancer; one phase I dose escalation study of talazoparib monotherapy observed a response rate of 42% (5/12) in *BRCA*-mutated ovarian cancer patients [27,28]. Overall, these findings suggest that talazoparib is most potent in combination with factors that undermine genomic stability. Thus, because radiation has well-known DNA-damaging effects and gynecologic cancer is prone to DNA-repair deficiencies, talazoparib has auspicious potential for combination with radiation therapy for gynecologic cancer.

In this phase I study we aim to determine the safety, tolerability, and maximally tolerated dose (MTD) of talazoparib when delivered concurrently with radiotherapy in women with recurrent gynecologic cancers, including ovarian, primary peritoneal, fallopian tube, endometrial, vaginal, or cervical cancer.

2. Methods and study design

2.1. Overall study design

This a phase I, open-label, dose escalation study to determine the maximum tolerated dose (MTD) of talazoparib in combination with fractionated radiotherapy for recurrent gynecologic cancers. This study is to be performed at MD Anderson Cancer Center with a total accrual of approximately 24 patients.

Study duration is a total of 3 years. Patients will have had no prior radiotherapy or chemotherapy within 4 weeks of talazoparib initiation and fulfill the inclusion/exclusion criteria outlined below. All patients will have an initial run in of talazoparib alone for 7–10 days prior to 6–7 weeks of concurrent talazoparib/radiotherapy and three years of follow up (Fig. 1). Two cohorts of patients based on radiotherapy field size will be enrolled: large-field (pelvic fields, pelvis/groin, or para-aortic only) and limited-field (hemi-pelvic, ipsilateral pelvis/groin, or localized field).

2.2. Staging and treatment

All patients will undergo standard of care staging including PET-CT, CT, or MRI imaging followed by CT based simulation. Radiotherapy will be administered with standard fractionation, 5 fractions delivered per week in 1.8–2.0 Gy daily fractions, with either photon (intensity modulated radiation therapy or volumetric arc therapy) or proton therapy, for a total of 60–66 Gy over 6–7 weeks. A simultaneous integrated boost with 2 Gy fraction to the gross disease and 1.8 Gy fraction to subclinical disease may be used followed by a sequential boost to treat the gross disease to a total dose of 60–66 Gy depending on normal tissue tolerance. For patients with recurrent ovarian cancer, the field will include the tumor or tumor bed plus a margin (using daily image-guidance with kilovoltage imaging with or without cone beam CT imaging) for a total of 60–66 Gy in 1.8–2 Gy daily fractions. For women with recurrent endometrial, cervical, or vaginal cancer, the initial field may include the regional nodal distribution (i.e. pelvis, para-aortic region, and/or inguinal region) to a dose of 45–50 Gy (with or without a simultaneous integrated boost) followed by a boost to a total dose of 60–66 Gy (1.8–2.3 Gy per fraction for boost). Dose constraints to critical structures are as follows:

- Small bowel: volume receiving 35 Gy <30%; volume receiving 45 Gy <65%; maximum point dose 65 Gy; and no more than 10% to receive >50 Gy.
- Duodenum (if within 2 cm of the planning target volume) <15 cm^3 to <55 Gy
- Femurs: volume receiving 35 Gy <15%
- Spinal cord: maximum dose point 45 Gy.
- Kidneys: No more than 50% of each kidney to receive >18 Gy; mean dose <18 Gy; if one kidney is present, no more than 15% of that kidney to receive >18 Gy.
- Liver: Mean dose $\leq$25 Gy.
- Pelvic bone marrow: V_{20} <76%

Talazoparib will be administered orally and taken approximately 2 hours prior to radiotherapy.

Talazoparib dose escalation is detailed in Table 1. While recommended starting dose of talazoparib is 1 mg daily [29], this trial will begin at 0.25 mg in concordance with other concurrent PARP inhibitor/radiation studies which have observed toxicities at low doses when combined with radiation [30]. Dose escalation will follow a modified time to event Bayesian Optimal Interval design (TITE-BOIN).

2.3. Key inclusion criteria

- Life expectancy $\geq$16 weeks
- Histologically-confirmed recurrent epithelial ovarian, fallopian tube, primary peritoneal cancer, endometrial, vaginal, or cervical cancer in the abdomen or pelvis

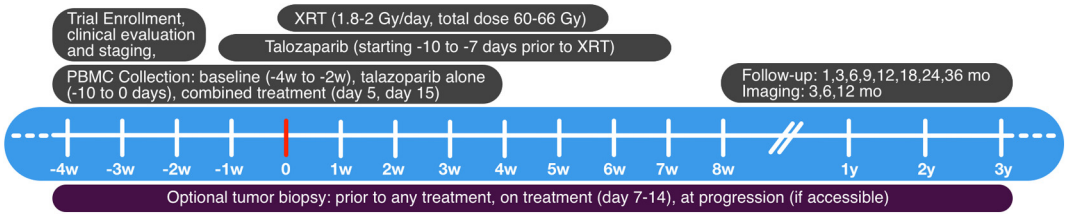

Fig. 1. Study design. Abbreviations: XRT, radiation therapy; w, week; mo, month; y; year; PBMC, peripheral blood mononuclear cells.

Table 1
Dose escalation.

Dose level	Talazoparib
−1	0.25 mg once a week (plus run-in)
1	0.25 mg twice a week (mon and wed plus run-in)
2	0.25 mg Mon-Fri daily during initial 5 weeks of radiotherapy (plus run-in)
3	0.50 mg Mon-Fri daily during initial 5 weeks of radiotherapy (plus run-in)

Run-in: talazoparib monotherapy for 7–10 days prior to radiation therapy.

- At least one lesion, not previously irradiated, with a baseline dimension ≥10 mm in the longest diameter
- Subjects with Stage IV disease are eligible as long as disease elsewhere (other than the site(s) to receive RT) is undetectable or stable (≥3 months) and immediate chemotherapy is not required; No limits to prior lines of therapy as long as therapy is stopped at least three weeks prior to start of investigational therapy

2.4. Key exclusion criteria

- Ascites, peritoneal carcinomatosis, hepatic metastases
- Prior radiotherapy in the region of planned radiotherapy
- Concomitant use of known CYP3A4 inhibitors, P-gp inhibitors, P-gp inducers, or BRCP inhibitors
- Persistent toxicities (≥CTCAE grade 2) with the exception of alopecia
- Resting ECG with QTc >470 ms or family history of long QT syndrome
- Major surgery within 14 days of starting study treatment and patients must have recovered from any effects of any major surgery
- Patients requiring pelvic and para-aortic radiotherapy (defined as levels L1/T12)

2.5. Study objectives

The overall hypothesis is that combining talazoparib with radiotherapy will result in enhanced radiosensitization and improve tumor response rates in patients with recurrent gynecologic cancers. The primary objective is to determine the safety profile and MTD of talazoparib in combination with fractionated radiotherapy; secondary objectives include efficacy (response per the Response Evaluation Criteria in Solid Tumors [RECIST] 1.1), local control rate, time to progression, time to subsequent therapy, progression-free survival, and overall survival. The exploratory objective of this study is to examine the potential feasibility of using biomarkers in tumor tissue, whole blood, or serum to predict treatment response.

2.6. Toxicity

Toxicity will be scored using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.03. Any toxicity observed during the course of the study will be managed by interruption and/or dose reduction if deemed appropriate by the investigator. Repeat dose interruption are allowed as required for a maximum of 14 days per occasion. Talazoparib must be interrupted until the patient recovers completely or if the toxicity returns to CTCAE grade 1 or less. If toxicity reoccurs following re-challenge and further dose interruptions are considered inadequate, the patient will be considered for dose reduction or permanent discontinuation. Treatment must be interrupted if CTCAE grade 3 or 4 adverse events occur. Acute dose-limiting toxicities (those occurring from the start of RT, i.e. the beginning of concurrent treatment, until 1 month afterward) include any grade 4 hematologic toxicity (i.e., absolute granulocyte count $<0.5 \times 10^9$/L that lasted more than 6 days; absolute neutrophil count $<1.0 \times 10^9$/L with fever >38.5 °C; platelet count $<25 \times 10^9$/L; or bleeding thought to be due to grade ≥3 thrombocytopenia). Acute non-hematologic DLTs include any grade ≥3 events thought to be treatment-related; grade ≥3 diarrhea; or missing 5 or more consecutive RT fractions or 3 or more talazoparib doses. Late DLTs (those occurring 1–5 months after treatment completion or initiation of subsequent therapy, whichever came first) include the development of myelodysplastic anemia or acute myeloid leukemia; grade ≥4 fistula; or grade ≥3 bowel obstruction.

2.7. Trial analysis plan

This is a phase I dose finding trial utilizing a time-to-event Bayesian Optimal Interval design (TITE-BOIN). This design grants several advantages including added flexibility (allowing dose assignment decisions to be made for new patients while some enrolled patients' toxicity data are still pending), shortened trial duration, and reduced logistical difficulties caused by repeatedly suspending accrual. In addition to using the number of patients with dose-limiting toxicities (DLTs) when evaluating dose assignment, the TITE-BOIN uses Bayesian multiple imputation to predict DLT outcomes for patients whose data are pending based on their follow-up time. Dose cohorts are detailed below (Table 1). Tables 2 and 3 show the operating characteristics (OC) of this design under various toxicity scenarios including one scenario in which all doses have DLT rates less than 30% and one in which all doses have DLT rates greater than 30%. Table 2 shows the OCs for escalation within the large-field radiotherapy cohort and Table 3 shows the OCs for the limited-field radiotherapy cohort. In particular, they show (a) the probability of a dose being selected, (b) the average number of patients treated at a particular dose, (c) the average number of patients treated in an arm, (d) the probability of stopping enrolment into an arm early because of toxicity, and (e) the average duration of the study under the trial arm.

2.8. Biomarker analysis

This study will also have an optional, exploratory component where tumor samples will be evaluated for biomarkers of response, gene mutation, and transcriptome analysis using targeted capture massively parallel sequencing of genes assessing relevant homologous recombination pathway genes including BRCA1/2, Rad51, and γ-H2AX, among others. Tumor biopsies will be harvested prior to any treatment, after 7–14 days of combined talazoparib/radiotherapy treatment, and at disease progression (if accessible). Analysis will involve well established pipelines including GATK [31], MuTect [32], and Indelocator [33] to evaluate single nucleotide variant and indels, Nexus Copy Number (Nexus Biodiscovery™) and Sequenza [34] for copy number analysis, reverse protein phase arrays (RPPA) for protein expression analysis, as well as whole exome sequencing, should targeted sequencing fail to identify novel mutations. We will also collect peripheral blood mononuclear cells (PBMC) at 4 timepoints (Fig. 1). We will examine the extent of PARP inhibition in PBMCs using a validated chemiluminescent PAR immunoassay and look at associations between DNA damage and clinical tumor response. These are exploratory analyses given the limited patient numbers, but may inform the design of future studies.

Table 2
Operating characteristics for large-field radiotherapy arms.

	Dose Level*				Number of Patients	% Early Stopping	Duration (months)
	−1	1	2	3			
Scenario 1: All doses lower than MTD							
True DLT Rate	0.03	0.06	0.12	0.18			28.2
Selection %	0.3	5.2	15.7	79.0		0.0	
# Patients Treated	0.4	3.6	4.4	9.6	18.00		
Scenario 2: MTD @ Dose 3							
True DLT Rate	0.05	0.10	0.20	0.30			26.5
Selection %	1.6	14.8	36.4	47.3		0.1	
# Patients Treated	0.8	4.9	5.9	6.4	17.99		
Scenario 3: MTD @ Dose 2							
True DLT Rate	0.05	0.15	0.30	0.50			23.6
Selection %	3.6	33.8	50.7	11.8		2.9	
# Patients Treated	1.4	6.8	6.6	3.2	17.83		
Scenario 4: MTD @ Dose 1							
True DLT Rate	0.15	0.30	0.45	0.60			29.3
Selection %	27.7	49.3	17.8	1.8		3.5	
# Patients Treated	4.5	8.0	4.0	1.2	17.80		
Scenario 5: MTD @ Dose −1							
True DLT Rate	0.30	0.45	0.60	0.70			22.0
Selection %	50.0	22.4	2.3	0.1		25.3	
# Patients Treated	7.8	6.3	1.8	0.3	16.21		
Scenario 6: All doses too toxic							
True DLT Rate	0.45	0.60	0.70	0.80			18.1
Selection %	29.2	4.1	0.3	0.0		66.6	
# Patients Treated	7.9	4.2	0.7	0.0	12.86		

Abbreviations: MTD, maximum tolerated dose; DLT, dose limiting toxicities.
* Dose levels detailed in Table 1.

Table 3
Operating characteristics for limited-field radiotherapy arm.

	Dose Level**			Number of Patients	% Early Stopping	Duration (months)
	−1	1	2			
Scenario 1: All doses less than MTD						
True DLT Rate	0.05	0.10	0.20			17.9
Selection %	6.5	23.0	69.7		0.9	
# Patients Treated	0.4	2.9	2.7	6		
Scenario 2: MTD @ Dose 2						
True DLT Rate	0.05	0.15	0.30			17.6
Selection %	10.9	36.0	52.3		1.0	
# Patients Treated	0.6	3.2	2.2	6		
Scenario 3: MTD @ Dose 1						
True DLT Rate	0.15	0.30	0.50			17.1
Selection %	32.8	37.3	21.7		8.3	
# Patients Treated	1.3	3.4	1.3	6		
Scenario 4: MTD @ Dose −1						
True DLT Rate	0.30	0.45	0.55			17.0
Selection %	40.9	25.4	9.3		24.5	
# Patients Treated	2.0	3.2	0.8	6		
Scenario 5: All doses too toxic						
True DLT Rate	0.45	0.55	0.65			16.8
Selection %	33.2	15.2	4.0		47.7	
# Patients Treated	2.6	2.9	0.5	6		

Abbreviations: MTD, maximum tolerated dose; DLT, dose limiting toxicities.
** To be determined based upon results in large-field cohort.

3. Discussion

This is a phase I study aimed at assessing the safety, tolerability, and maximum tolerated dose of talazoparib when used concurrently with radiotherapy for recurrent gynecologic cancers. While the mainstay of treatment for recurrent gynecological cancers remains systemic chemotherapy, a new era of radiation use in nodal or isolated recurrent gynecologic cancers is emerging as the ability to safely deliver escalated doses is possible with intensity modulated radiotherapy, volumetric arc radiotherapy, and proton beam radiotherapy coupled with appropriate daily image guidance [35]. Although the use of salvage radiotherapy for recurrent disease has been borne out in several retrospective studies [6–10] given the modest local control rates and persistent concerns for toxicity, the need to improve the therapeutic window to enhance treatment outcomes and decrease toxicity remains. While there is no standard chemotherapeutic agent when delivered with radiotherapy in the recurrent setting for gynecologic cancers, the

regimen that is most frequently used in our clinic is concurrent weekly cisplatin 40 mg/m^2, which is extrapolated from the multiple phase III clinical trials that have demonstrated improved locoregional control and overall survival with concurrent platinum-based chemotherapy for women with locally advanced cervical cancer [36].

PARP-inhibitors have long been known to have chemo- and radiosensitization effects [12–15]. For talazoparib in particular this has been noted in several pre-clinical studies [14,23–25,37], as well as clinical trials demonstrating tolerability and efficacy in a variety of sites as described above [26–28]. One study has shown tolerability of combined PARP-inhibition (veliparib) when combined with low-dose fractionated whole abdominal radiation in patients with peritoneal carcinomatosis in ovarian and fallopian cancer patients [38]. In a phase I study of olaparib concurrent with cetuximab and radiotherapy for locally advanced head and neck cancer, the maximally tolerated dose was identified to be 50 mg twice daily, though the recommended phase II dose was deemed to be 25 mg by mouth twice daily [30]. Overall, the regimen was found to be tolerable with the most common treatment related side effects being grade 3–4 mucositis and dermatitis (38% and 69%, respectively). Response rates were promising with 2-year overall survival, progression free survival, local control, and distal control rates of 72%, 63%, 72%, and 79%, respectively. Due to the low dose that was identified to be the recommended phase II dose with this combination, we are starting our clinical trial of talazoparib with radiotherapy at the lowest oral pill available 0.25 mg and have altered the frequency for the primary and dose level −1 cohorts as outlined in Table 1. Because this is a phase I study and the primary objective is to determine the safety and maximally tolerated dose of talazoparib when administered concurrently with fractionated radiotherapy, we are including all gynecologic cancer types including ovarian, fallopian tube, and primary peritoneal cancers. While these historically are treated with systemic chemotherapy in the recurrent setting, for patients with isolated recurrences limited to the abdomen or pelvis or when other systemic disease if present is well-controlled, primary radiotherapy may be an option. While reports of radiotherapy and PARP inhibitor combination studies have been limited, there are multiple ongoing clinical trials of PARP inhibitors in combination with radiotherapy.

Talazoparib has been shown to potentiate the effects of radiation and chemotherapy in vivo in a variety of cancers including lung, colorectal, glioblastoma, and serous ovarian cancer xenografts [12,13,15]. Regarding glioblastoma specificially, one study found talazoparib to have greater radio-sensitization effects in stem cells, as compared to other PARP inhibitors including olaparib and AG14361, even when used at lower concentrations [14]. Nevertheless, the overall response rate to PARP-inhibitors ranges from 30 to 50% [39], suggesting that a large population of patients have either de novo resistance or later develop drug resistance. While work has been done on developing biomarkers of response and resistance, these studies remain inconclusive and include a small number of patients [40]. To address this gap, this study will also aim to explore signatures of response and resistance using patient tumor biopsies to identify potential biomarkers for more accurate precision medicine. We will obtain tumor biopsies and collect peripheral blood mononuclear cells (PBMC) at multiple timepoints (Fig. 1) to examine the extent of PARP inhibition and explore whether there are any associations between DNA damage in PBMCs and clinical tumor response. Tumor samples will be tested for defects in homologous recombination repair and in patients for whom a second biopsy is available, we will determine whether the combination of radiotherapy and PARP inhibitor increases the mutational burden.

Should talazoparib concurrent with radiotherapy be well tolerated with objective response rates better than historical rates with radiotherapy alone or with radiosensitizing chemotherapy, we will be better positioned to design and statistically justify a subsequent phase II study, allowing us to further our long-term goal to improve relapse free and overall survival in women who have locally recurrent gynecologic malignancies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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