Targeting immune modulation in high grade serous carcinoma: combined effects of chemotherapy and atorvastatin

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PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1	02.05.2026	Initial version	
2	7.17.2026	Updated background, synopsis, statistical	Updated to reflect comments from PRMS committee

Version	Date	Description of Change	Brief Rationale
		considerations and endpoints.	

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The Principal Investigator (PI), Nicole Marjon is conducting the study and is acting as the sponsor. As the Sponsor-Investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), as applicable.

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Principal Investigator: _____
Print/Type Name

Signature: _____ **Date:** _____

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BMI	Body Mass Index
Cis	Cisplatin

CNS	Central Nervous System
CTCAE	Common Terminology Criteria for Adverse Events
DSM	Data Safety Monitoring
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EOC	Epithelial Ovarian Cancer
GCIG	Gynecological Cancer InterGroup
GI	Gastrointestinal
GTFB	Gynecologic Tumor and Fluid Bank
HDL	High Density Lipoprotein
HGSC	High Grade Serous Carcinoma
HR	Hazard Ratio
LDL	Low Density Lipoprotein
mIHC	Multispectral Immunohistochemistry
NK	Natural Killer
NCI	National Cancer Institute
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
RCT	Randomized Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumors
Ros	Rosuvastatin
SAE	Serious Adverse Event
SEM	Standard Error of the Mean
SOC	Standard of Care
TAM	Tumor associated macrophage
TCGA	The Cancer Genome Atlas
TIME	Tumor Immune Microenvironment
UAP	Unanticipated Problems
ULN	Upper Limit of Normal
WHO	World Health Organization

PARTICIPATING SITES

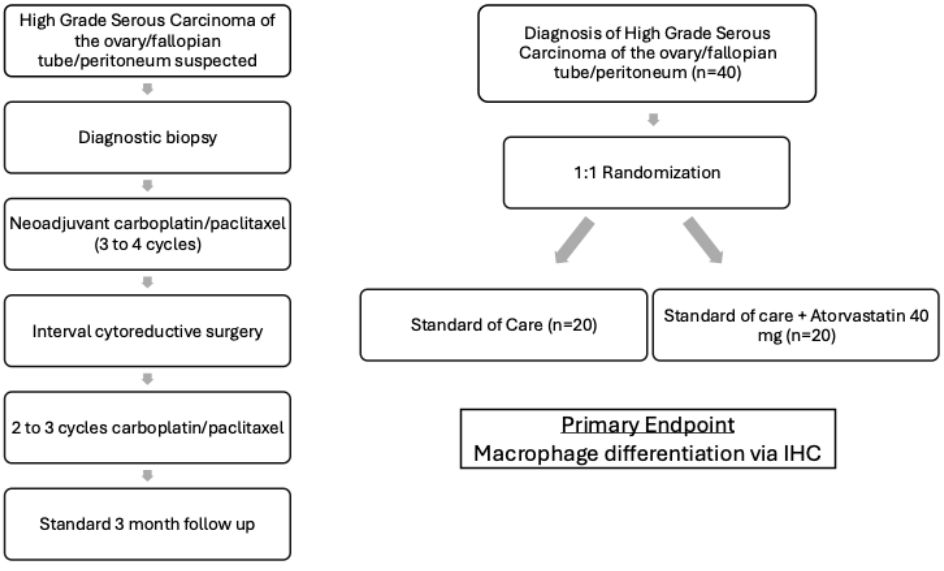
University of Colorado Cancer Center

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title:	Targeting immune modulation in high grade serous carcinoma: combined effects of chemotherapy and atorvastatin
Population:	High Grade Serous Carcinoma of the ovary, fallopian tube, or peritoneum
Sample size:	Maximum number of participants that can be enrolled is 50 (allow for screen failures), plan for 40, 20 per arm
Phase:	Window-of-opportunity
Participating Sites:	University of Colorado
Description of Study Intervention:	Atorvastatin
Study Duration:	Enrollment is expected at 3 patients per month, enrollment is expected to take 8-14 months. Total study duration is expected to be 5 years
Participant Duration:	Expected duration of treatment is 6 months with 90 day follow-up. Charts will be reviewed for PFS and OS for 4 years

1.2 STUDY SCHEMA



1.3 SCHEDULE OF EVENTS

Study Visits	**Screening**	**Cycle 1-3 or 4**	**Interval Surgery**	**Cycle 4 or 5-6**	**Post-therapy follow-up**	**Post progression follow-up**
	Day -28 to Day 0	*Day 0- Day 63*	*Day 63 - Day 107*	*Day 107 – 170*	*Day 260*	*12 months (+/- 30 days)*
Procedures						
Informed consent	X					
Confirm eligibility (inclusion/exclusion criteria)	X					
Medical History	X					
Tumor Collection	X (core needle biopsy)		X (surgery)			
Concomitant Medications and Procedures	X	X	X	X	X	
Toxicity/AE assessment		X		X	X	
Physical Exam[1]	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	
Height/weight[2]	X	X	X	X	X	
Vital Signs [3]	X	X	X	X	X	
CBC/CMP	X	X	X	X	X	
Lipid profile	X		X			
Serum pregnancy[4]	As needed	As needed	As needed	As needed	As needed	
Study treatment provided		X		X		
Medication adherence and modification	X	X		X		
CT imaging chest/abdomen/pelvis	X		X		As needed	
CA 125	X	X	X	X	X	

Survival status[5]						X

[1]Physical exam to include at minimum cardiac, lung, and abdominal exam. [2]Height only required to be measured at enrollment visit, weight at all indicated visits. [3]Vital signs to include temperature, pulse, blood pressure, respiratory rate. [4]For women of childbearing potential (≤ 3 days prior to start of every cycle. Women who have undergone surgical or natural menopause excluded. [5]Conducted by phone or medical record review on annual basis for survival data.

2 INTRODUCTION

2.1 STUDY RATIONALE

Epithelial ovarian cancer (EOC) is a leading cause of death in gynecological cancers and an estimated 14,000 patients die of this disease in the United States annually [1]. High-grade serous carcinomas (HGSC) of the fallopian tube, ovary and peritoneum are the most common and aggressive histological subtype of EOC [2]. Despite initial responses in 75% of patients with advanced HGSC to the standard-of-care (SOC) platinum-based chemotherapy, up to 85% patients experience relapse, resulting in a 5-year survival rate below 50% [3, 4]. This high mortality is largely attributed to the advanced stage (III/IV) at diagnosis and the rapid emergence of chemoresistance, which severely limits treatment options [5, 6].

Chemoresistance has traditionally been understood in the context of tumor cell intrinsic mechanisms [7]. We now understand that there is a complex interplay between treatment, cancer cells, and the tumor microenvironment (TME) which directly contributes to recurrence and chemoresistance [8]. Strategies to alter the TME and improve outcomes in HGSC are urgently needed.

Unique among solid tumors, HGSC spread primarily through the transcoelomic route, relying on anchorage-independent survival and dynamic crosstalk within the TIME [9]. Notably, the omentum, a preferential peritoneal metastatic site for HGSC, and ascitic fluid found in advanced diseases, are both enriched in lipids, including cholesterol [10]. Such findings indicate that lipid metabolism plays a critical role in HGSC pathophysiology [11, 12] Aberrant cholesterol metabolism has been implicated in tumor cell survival, chemoresistance, and immune evasion across in various cancer types [13-18]. In addition to its effects on tumor cells, cholesterol also contributes to the immunosuppressive (TME), particularly polarizing macrophages toward a pro-tumor, M2-like phenotype [19]. Hence, in HGSC, where the TIME is uniquely rich in adipocytes and cholesterol, targeting cholesterol metabolism present an exciting avenue to prevent disease progression and chemoresistance [20-22]. Retrospective cohort studies of EOC outcomes have shown a correlation between statins, an FDA-approved treatment for hypercholesterolemia, and improved outcomes in ovarian cancer [23, 24]. However, no prospective studies have been completed to further evaluate the role of statins in treatment for EOC.

Thus, we propose a single-site randomized control trial to evaluate macrophage polarization in the TIME in HGSC patients treated with standard of care (SOC) with atorvastatin. versus standard of care alone. We hypothesize that *combining statins with chemotherapy will attenuate tumor-promoting M2-like macrophage differentiation.* The primary endpoint will be

macrophage polarization. This pilot study examines macrophage polarization as a primary endpoint given the scope of this trial, however secondary endpoints of PFS and OS will allow us to assess if changes in M2 polarization correlate with clinical outcomes. We also plan exploratory analyses evaluating associations between changes in TAM polarization and CA-125 response, PFS, and OS.

Upon review of our clinical patients, we identified 18% of our current patients with ovarian cancer population are on prescribed statin therapy, with about half of those with a clinical indication of hypercholesterolemia. The administered statin doses range from 10-40 mg. Patients receiving both statin and chemotherapies had no reported lipid or renal toxicities. We noted no significant adverse events with statin use among the current patient population when combined with chemotherapy; therefore, we predict that the addition of a statin to chemotherapy for patients without hypercholesterolemia will be safe. We propose using atorvastatin, a lipophilic statin at 40mg daily, a dose commonly used for patients. The choice of atorvastatin is based on the data demonstrating that lipophilic statins have better penetration into cell membranes [25].

2.2 BACKGROUND

In HGSC, our group and others have published that chemotherapy changes the TME in ways that potentially contribute to both therapeutic response and disease recurrence [26-28]. Macrophages make up a large portion of the TME in HGSC [29, 30]. Macrophages are immune cells of the myeloid lineage [31]. They are phagocytic and mainly function to "eat" and break down foreign antigens, cellular debris, and native cells undergoing necrosis or apoptosis [32]. Macrophages are commonly described as being M1-like or M2-like with regards to their transcriptional state and the markers they express, but this polarization is a spectrum [33]. The polarization of macrophages is highly dependent on the metabolic microenvironment [34]. M1-like macrophages are pro-inflammatory and tumor-suppressing. M2-like macrophages are anti-inflammatory and tumor-promoting. In our data, patients with HGSC more M2-like macrophages convey a worse overall survival (Hazard Ratio [HR]: 1.25, p=0.0039), however M1-like macrophages convey an improved overall survival (HR: 0.816, p=0.0006). In the TCGA dataset higher M1-like macrophages are associated with longer disease-free survival (DFS) (**Fig 1A)** and higher proportion of M2 macrophages is associated with shorter DFS (**Fig 1B**). Notably, M2-like macrophages undergo metabolic reprogramming and become more dependent on fatty acid oxidation as a source of energy (ATP) production [35]

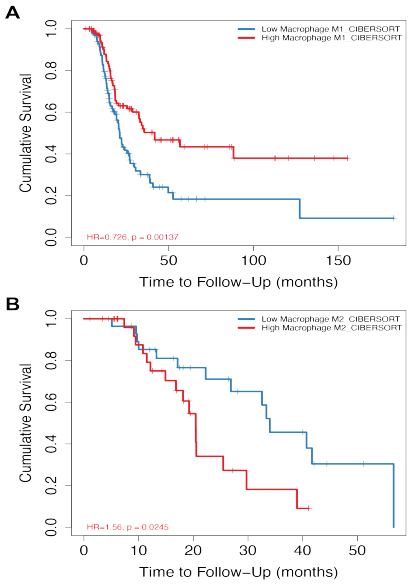


Figure 1: Higher M-2 like macrophages are associated with shorter DFS. A) DFS analysis of M1 high and low based on median expression B) DFS analysis of M2 high and low based on median expression Source:TCGA

In a syngeneic mouse model for HGSC (**Fig 2A)** we combined statin with platinum chemotherapy. In this study we observed that chemotherapy significantly induced M2-like macrophages and that this induction was significantly blunted when combined with statin (**Fig 2C)**. Using patient samples from our Gynecologic Tumor and Fluid Bank (GTFB, IRB #07-935), we compared cytokines in ascites in HGSC patients receiving SOC who use statins (n=7) and those who did not (n=17). Statin use significantly correlated to lower IL-1b, IL-4, IL-6, and IL-12 (**Fig 3A**). Higher than median IL-6 correlated with a significantly shorter time to recurrence (p = 0.028, HR: 2.12, **Fig. 3B**), consistent with current literature [36]. IL-6 signaling promotes chemoresistance and recruitment of macrophages into the TME [37-39]. Using a tissue microarray (TMA) [26, 40] and multispectral IHC (mIHC) on these human tissue samples we found that statin use correlated with decreased macrophage infiltration (**Fig. 3C**).

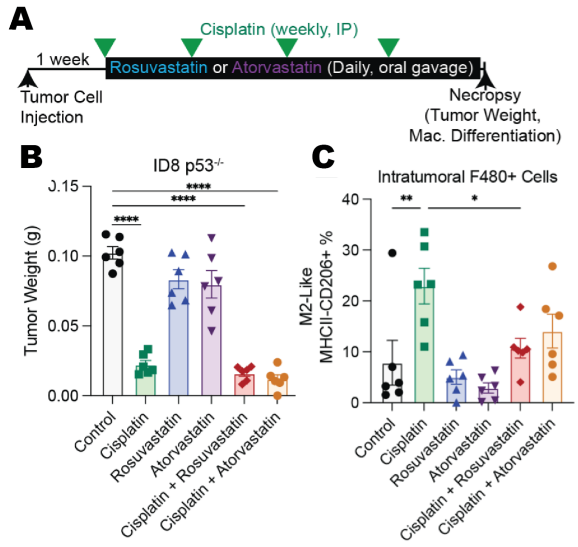


Figure 2. Statins attenuates intratumoral chemotherapy-inducedM2-like macrophages. ID8 Trp53-/- HGSC model treated with cisplatin (1 mg/kg, IP, weekly) and rosuvastatin or atorvastatin (20 mg/kg, daily, oral gavage)**. A)** Study design. **B)** At 28 days, cisplatin decreased tumor burden, there was no significant effect of statins alone or in combination with cisplatin. Flow cytometry of digested omental tumors. **C)**F480+MHCII-CD206+ % of cells (M2-Like macrophages). Error bars, SEM. Stat. test, one-way ANOVA Tukey multi-comp.*p<0.05, ***p<0.001,*** p<0.0001. Error bars, SEM

A growing body of literature describes the anti-tumor properties of statins in preclinical models. In vitro statins have been shown to increase apoptosis in ovarian cancer cell lines [41-44]. Additionally, it has been shown to reduce cell adhesion and invasion[44], In our own lab we have demonstrated that rosuvastatin increased sensitivity to cisplatin in ovarian cancer cell lines. Supplementation of cholesterol alongside rosuvastatin rescued this effect (**Fig 4A),** suggesting that inhibition of cholesterol metabolism is the primary driver of rosuvastatin-mediated cisplatin sensitization. Our hypothesis that inhibiting cholesterol synthesis with statins will prevent HGSC tumor proliferation and progression (i.e.

spread) primarily through the impact on the TIME, however these data also indicate there may be contribution due to effects of statins directly on the tumor cell proliferation.

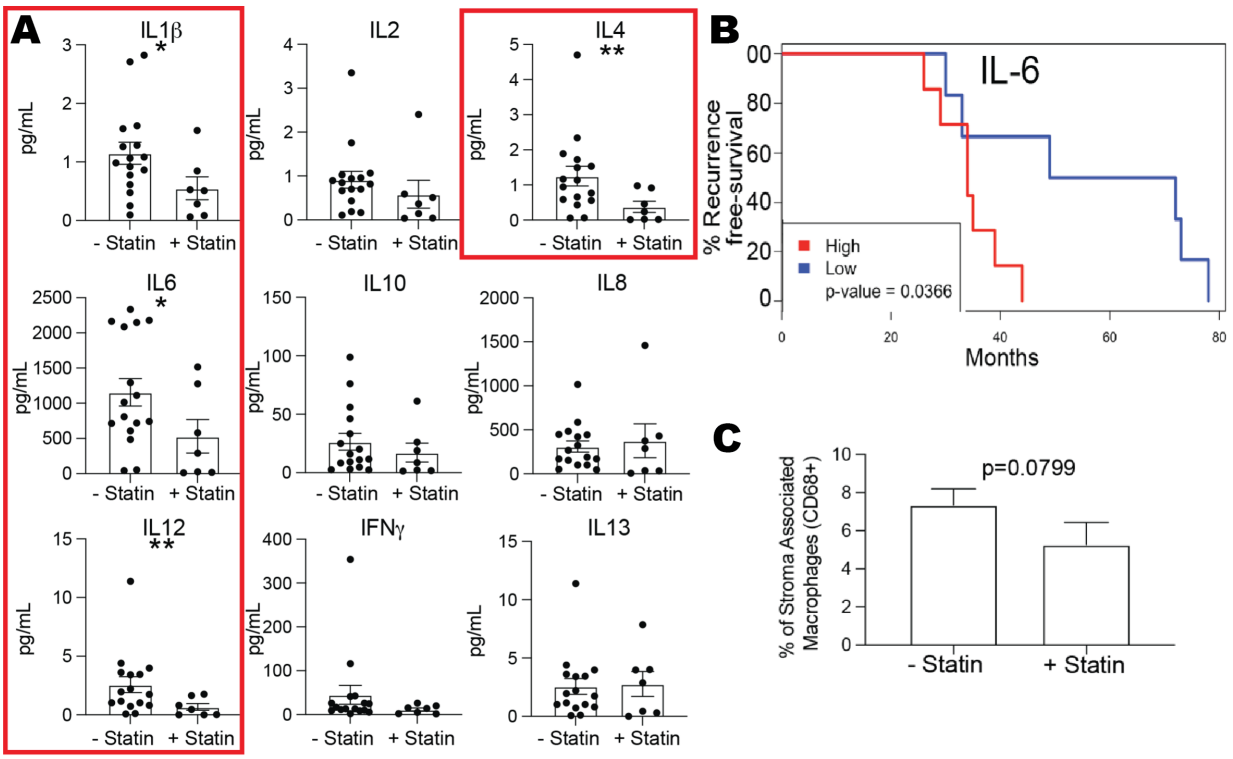


Figure 3. Lower IL-6 in patients being treated with statins, IL-6 correlates to recurrence-free survival and elevated macrophage infiltration. A) Multiplex ELISA from ascites of 24 HGSC patients. Red boxes – significant differences **B)** Kaplan-Meier based on median IL-6 levels. **D)** Mac. (CD68+) infiltration of HGSC tumors with or without statins on-board. Error bars, SEM. Statistical test, unpaired t-test. *p<0.05, **p<0.01.

Taken together, these data in primary HGSC tumors and *in vivo* models demonstrate a strong connection between statin use, an inflammatory TME, and macrophage differentiation. We hypothesize that *combining statins with chemotherapy will attenuate tumor-promoting M2-like macrophage differentiation.* As an immunoinhibitory TME, in part due to increased M2-like macrophages, is associated with worse OS in our GTFB data and in TCGA samples [45] we hypothesize that this is a contributor to the improved outcomes seen in observational studies of statins with chemotherapy. While we recognize that evaluation of macrophage polarization is an unconventional primary endpoint, several other window-of-opportunity and early phase trials have evaluated changes in immune cell populations as a primary endpoint. In a study of a Colony-Stimulating Factor-1 Receptor inhibitor, immune response analysis was the primary endpoint with changes in cell populations being assessed via flow cytometry, in this case, changes in percentages of T cell subset populations [46]. Similarly, a window of opportunity trial of breast cancer patients compared cancer stem cells at

baseline and after treatment with an inhibitor of CXCR1 (a receptor for IL-8 present on cancer stem cells) measured via IHC and flow cytometry as a primary endpoint [47]. No published studies have demonstrated differences in macrophage polarization or presence in HGSC, but a study of premalignant human lung adenocarcinoma found that statin use was associated with reduced protumorigentic macrophages [48].

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Statins are FDA-approved for several indications including hypercholesterolemia. Overall, statins are safe medications with rare risks of muscle injury/rhabdomyolysis at <0.1%, hepatotoxicity , and statin-induced diabetes mellitus at about 0.2%/year of use[49]. A meta-analysis of RCTs involving statins + chemotherapy found no significant incidence in grade 3-5 adverse events [50].

In addition to the above mentioned risks, there are risks Cyp3A4 mediated drug interactions, however atorvastatin does not have significant interactions with paclitaxel or carboplatin [51]. There is some preclinical evidence that atorvastatin may increase risk of peripheral neuropathy [52], however a cohort study of women treated with paclitaxel found no association with paclitaxel discontinuation for neuropathy and atorvastatin[53].

For platinum-based chemotherapy (e.g. carboplatin), the most common risks are myelosuppression, vomiting, nephrotoxicity, neurotoxicity, and ototoxicity. For taxanes (e.g. paclitaxel), the most common risks include neuropathy, hypersensitivity reaction, and bone marrow suppression.

2.3.2 KNOWN POTENTIAL BENEFITS

Preclinical evidence suggests an association between cancer outcomes and statin use, though the relationship has not been established in an RCT. Therefore, we may be able to add an already approved, well tolerated medication to chemotherapy with improved cancer outcomes.

2.3.3 ASSESSMENT OF POTENTIAL BENEFITS

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Participant: Participants will be helping to study a potentially therapeutic combination of standard of care chemotherapy and atorvastatin. Retrospective and preclinical data have indicated there may be a benefit in HGSC. They may have a personal benefit of improved survival compared to chemotherapy alone.
- To Society: Results from this study will demonstrate the safety of this combination in HGSC and effects on the TIME. Results from this study will support future phase III studies of this combination as well as ongoing research focused on cholesterol metabolism.
- Justify the importance of the knowledge gained: The combination of statin therapy and standard of care chemotherapy has shown benefits in preclinical models and for overall survival in retrospective data, however no prospective randomized trial has demonstrated this. This study will provide data on the effects of this combination in the TIME and provide safety data on the combination. This knowledge will help develop a phase III clinical trial for a well-tolerated regimen that can improve treatment outcomes. Furthermore, the translational studies will guide the development of further cholesterol and metabolic modifiers specific for the use in patients with cancer.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To determine polarization of TAMs after treatment with atorvastatin and chemotherapy	The primary efficacy endpoint is the change from baseline to the post-treatment surgical specimen in the mean CD163 H-score among CD68-positive tumor-associated macrophages. CD68 and CD163 expression will be assessed by multispectral immunohistochemistry in paired pre-treatment biopsy and post-treatment surgical samples.
Safety	
To determine safety and tolerability of combination atorvastatin and carboplatin/paclitaxel in up front treatment of patients with stage III to IV HGSC as evaluated by CTCAE v5.0 criteria	Safety will be evaluated based on the incidence, severity, seriousness, and relationship to study treatment of adverse events, as well as clinically significant laboratory abnormalities. Adverse events will

	be graded according to the Common Terminology Criteria for Adverse Events, version 5.0.
Secondary/Exploratory	
1. To evaluate further changes in the TIME secondary to treatment 2. To correlate response to treatment (as defined by PFS, OS, and CA-125 reduction)	Tumor immune and biologic markers: Additional immunohistochemical analyses will be performed on tumor tissue obtained during cytoreductive surgery. Investigator-assessed progression-free survival will be defined as the time from randomization to the first documented occurrence of objective disease progression or death from any cause, whichever occurs first. Overall survival as defined by the time of randomization to time of death from any cause. CA125 reduction as defined by GCIG criteria of at least 50% reduction in CA125 levels from pretreatment sample, confirmed and maintained at least 28 days.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single-center, open-label, randomized window-of-opportunity trial evaluating atorvastatin in combination with standard-of-care neoadjuvant chemotherapy versus standard-of-care neoadjuvant chemotherapy alone in patients with newly diagnosed stage III or IV high-grade serous carcinoma of the ovary, fallopian tube, or primary peritoneum who are not candidates for primary cytoreductive surgery. Approximately 40 participants will be randomized 1:1 using permuted block randomization to maintain approximate balance in treatment allocation throughout enrollment. No stratification factors will be used because the modest sample size and window-of-opportunity design could lead to small or sparsely populated strata, and potentially relevant biomarker

characteristics, including BRCA1/2 mutation and homologous recombination deficiency status, may not be available at the time of randomization. Participants assigned to the experimental arm will receive atorvastatin 40 mg orally once daily in addition to standard-of-care chemotherapy; those assigned to the control arm will receive standard-of-care chemotherapy alone.
Participants will be followed from randomization for up to 4 years. Safety will be assessed throughout protocol-directed treatment and for the protocol-specified period after the last dose of study treatment. Disease progression will be evaluated using standard clinical, radiographic, and biomarker assessments performed as part of routine care. Participants who discontinue study treatment or experience disease progression will continue to be followed for subsequent anticancer therapy and survival status, unless consent is withdrawn or the participant is lost to follow-up.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We propose an open label randomized control trial as this is a preliminary pilot study of the proposed intervention to evaluate macrophage polarization after treatment, therefore we do not anticipate a need for placebo control or blinding. The objective of this study is to provide further information on the TIME that will inform a larger RCT.

4.3 JUSTIFICATION FOR DOSE

Atorvastatin is FDA approved at 10-80 mg/day. 40mg is considered high intensity statin therapy and is prescribed to reduce LDL-C by $\geqslant$ 45% and is well tolerated so this dose was selected.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all the following criteria:

1. Provision to sign and date the consent form.
2. Stated willingness to comply with all study procedures and be available for the duration of the study.
3. Be a patient with ovarian cancer aged 18-89
4. Diagnosed via tissue biopsy not ascites
5. For persons of reproductive potential, use of highly effective method(s) of contraception.

6. Patients with primary Stage III/IV high-grade serous ovarian/fallopian tube/primary peritoneal cancer not amenable to upfront cytoreductive surgery.
7. ECOG performance status of 0, 1 or 2.
8. ANC 1500 cells/mL
9. Platelet count > 100,000 mL.
10. Hemoglobin 9.0 g/dL
11. Serum albumin ³ 2.5 g/dL.
12. Total bilirubin ⩽ 1.5 x ULN.
13. AST and ALT ⩽ 3.0 x ULN.
14. Serum Creatinine ⩽ 1.5x ULN

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Inability to comply with study and follow-up procedures.
2. Significant cardiovascular disease, such as New York Heart Association cardiac disease (class II or greater), myocardial infarction within the past 3 months, unstable arrhythmias, or unstable angina.
3. Known clinically significant liver disease defined as AST and ALT > 3.0 x ULN and/or total bilirubin ⩾ 1.5 x ULN, or documented history of active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease.
4. Participation in investigational clinical trial within last 30 days.
5. Medical history of untreated HIV infection. Patients with medical history of HIV infection are eligible provided they meet following criteria
    a. Are stable on antiretroviral therapy for ≥4 weeks before randomization
    b. Agree to adhere to antiretroviral therapy per WHO guidelines
    c. Have no documented multidrug resistance that would prevent effective antiretroviral therapy
    d. Have a viral load of <400 copies per mL at screening
    e. Have CD4+ T cell count at ≥ 350 cells per µL
    f. Have no history of AIDS -defining opportunistic infection ≤ 12 months before randomization.
6. Inability to provide informed consent.
7. Known CNS malignancy or CNS metastases.
8. Patients with previous malignancy within the past 2 years from cycle 1, day 1, except those with negligible risk of metastasis or death, such as adequately

controlled basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the breast.

9. History of stroke or transient ischemic attack (TIA) within 3 months prior to cycle 1 day 1(C1D1).
10. Patients with prognosis for survival less than 6 months.
11. Patients deemed otherwise clinically unfit for clinical trial per Investigator's discretion.
12. Patients with duodenal stent or other GI disorder/defect that would interfere with absorption of oral medication.
    a. Includes patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication
13. Female patients who maintain fertility potential and refuse to comply to use contraception and be followed for pregnancy by pregnancy testing.
14. Patients who are currently pregnant or lactating.
15. Prior or current statin use that would prohibit randomization into SOC arm.
16. Planned treatment with bevacizumab in the primary treatment setting.
17. Diagnosis based on ascites assessment only and not a tissue biopsy.
18. Patients deemed otherwise clinically unfit for clinical trial per investigators discretion

5.3 LIFESTYLE CONSIDERATIONS

The principal investigator and sponsor of this trial require that members of minority groups and their subpopulations be included in this clinical research. Exclusion under any circumstance must be reviewed by the principal investigator and have a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

5.4 SCREEN FAILURES

Patients who have consented to the study and have received at least 1 dose of study drug, are considered enrolled. Patients who are issued a patient number, but who do not successfully complete the screening process and are not treated will be considered screen failures. Patient numbers for patients who screen fail will not be re-issued.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential subjects will be identified and recruited from the investigators' clinical practice in gynecologic oncology. Potential subjects will present to clinic with newly diagnosed ovarian, peritoneal, and fallopian tube cancer and will not have received treatment yet.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Atorvastatin is an HMG-CoA reductase inhibitor FDA approved for treatment of hypercholesterolemia. It will be acquired from the hospital pharmacy. Patients will also receive standard of care with a platinum-based chemotherapy and a taxane administered through the infusion center. The exact standard of care doublet will be determined by the primary oncologist.

6.1.2 DOSING AND ADMINISTRATION

Both arms of patients will receive standard of care chemotherapy with a platinum and a taxane.

Patients in the trial arm will receive atorvastatin 40 mg to be taken orally daily. Atorvastatin may be taken with or without food. Patients will be advised to take the prescribed dose at approximately the same time each day. If a patient missed a scheduled dose, it is acceptable to take the missed doses within a window of 12 hours. If more than 12 hours has passed, the missed dose should not be taken and the patient should be instructed to take the next dose at the scheduled time.

Treatment with atorvastatin should be held if any of the following are observed and a dose reduction should be considered or implemented:

- Increased serum transaminases >3 times ULN
- Grade 3 or 4 hepatic failure
- Grade 3 or 4 Rhabdomyolysis
- Myopathy defined as unexplained muscle pain or weakness accompanied by a CK $\geqslant$10 times the ULN

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized site staff may dispense study treatment. At site, all study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The Principal Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The research pharmacist is responsible for handling the medication. Further guidance and information for the final disposition of unused study treatment are provided in the package insert.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Atorvastatin will be administered as 40 mg white/off-white, film-coated tablets from the hospital pharmacy.

6.2.3 PRODUCT STORAGE AND STABILITY

Store product at room temperature in compliance with package insert.

6.2.4 PREPARATION

Atorvastatin, a member of the statin class of drugs, is a selective, competitive inhibitor of HMG-CoA reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is the rate-limiting step in cholesterol biosynthesis. Atorvastatin tablets for oral use contain 40 mg of atorvastatin. These will be supplied by the hospital pharmacy.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Subjects will be randomized 1:1 block randomization. This trial will be open label so once a patient is randomized, there will be no blinding.

6.4 STUDY INTERVENTION COMPLIANCE

Patients will be assessed for medication adherence by medication diary and bringing medications to each visit to assess number of pills compared to expected number.

6.5 PROHIBITED THERAPY

Patients already receiving a statin are prohibited from participation in the study.

6.6 CONCOMITANT THERAPY

Patient's current medications, vitamins, and supplements will be recorded.

6.6.1 RESCUE MEDICINE

All concomitant medications and supportive therapy taken within 4 weeks of C1D1 and through 30 days after last study treatment must be recorded in the clinical database. The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION (STOPPING RULES)

The Sponsor-Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

Participants are free to withdraw from participation in the study at any time upon request. In addition, the investigator has the right to withdraw a patient from the study at any time. An investigator may terminate participation in the study if any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the Sponsor-Investigator determines may jeopardize the patient's safety if he or she continues in the study.
- Sponsor-Investigator determines it is in the best interest of the patient
- Patient non-compliance

Patients must discontinue study treatment if they experience any of the following:

- Increased serum transaminases >3 times ULN
- Immune-mediated necrotizing myopathy
- Grade 3 or 4 hepatic failure
- Grade 3 or 4 rhabdomyolysis
- Grade 3 or 4 myalgia

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study or study drug discontinuation should be documented on the appropriate eCRF.

7.3 LOST TO FOLLOW-UP

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

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

- Site will attempt to contact the subject and reschedule the missed visit and advise subject on importance of maintaining assigned visit schedule;

- Before a subject is deemed lost to follow-up, the investigator will make every effort to regain contact with the subject. These contact attempts must be documented in the subject's medical record or study file;
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Efficacy of statins in affecting macrophage polarization by multispectral IHC comparing initial core needle biopsy specimens to specimens at the time of interval debulking surgery. Efficacy in terms of secondary endpoints of PFS and OS will be determined by serial CA-125 measurements and CT imaging. Tumor response will be defined according to RECIST 1.1. The duration of response is defined as the time from response documentation until progression of disease. The secondary endpoint progression-free survival (PFS), will be calculated from the beginning of the treatment until the progression date, death date, or the last radiological assessment without progressive disease (PD). PFS will be estimated using Kaplan-Meier method.

8.2 SAFETY AND OTHER ASSESSMENTS

Physical examination with cardiac, pulmonary, and abdominal exam will be performed at every visit except the safety follow-up visit. Additionally, CBC and CMP will be performed at each visit. Adverse events/toxicity screening will occur at visits for cycles 1-3 and 4-6 and post-therapy follow-up but not at interval surgery.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse event or **serious suspected adverse reaction**. An AE or suspected adverse reaction is considered "serious" if, in the view of the Sponsor-Investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/ birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 DEFINITION OF ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

Adverse events of special interest (AESIs) are a subset of adverse events of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Sponsor-Investigator and IRB leadership is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Sponsor-Investigator to other parties (e.g., Regulatory Authorities) may also be warranted.

AESIs for this study are as follows: Hepatotoxicity, rhabdomyolysis

8.3.4 CLASSIFICATION OF AN ADVERSE EVENT

8.3.4.1 SEVERITY OF EVENT

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. The following table will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE (v5.0).

Grade	Severity

1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated
5	Death related to adverse event

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event.

8.3.4.2 RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be Related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/ or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.4.3 EXPECTEDNESS

Expectedness will only be documented for SAEs. The principal investigator will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's

condition deteriorates at any time during the study, it will be recorded as an AE. UAPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days after the last day of study treatment or until initiation of new treatment, whichever comes first. SAEs will be followed until resolution or stabilization. At each study visit, the investigator will inquire about the occurrence of AE/ SAEs since the last visit.

8.3.6 ADVERSE EVENT REPORTING

The investigator must record non-serious adverse events and report to DSMC and IRB according to timetable for reporting specified in section 10.1.5.

8.3.7 SERIOUS ADVERSE EVENT REPORTING

The investigator must record all serious adverse events and report to DSMC and IRB according to timetable for reporting specified in section 10.1.5. Per institutional policy, all serious adverse events occurring at UCCC/UCHealth will be entered into OnCore according to timetable for reporting specified in section 10.1.5.

The sponsor-investigator must notify FDA and all participating PIs in an IND safety report of potential serious risks as soon as possible, but in no case later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting. (21 CFR 312.32(c)(1)).

The sponsor-investigator must notify FDA of any unexpected fatal or life-threatening adverse reactions as soon as possible, but in no case later than 7 calendar days after the sponsor-investigator's initial receipt of the information. (21 CFR 312.32(c)(2)).

All SAEs will be followed until satisfactory resolution or until the site PI deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the sponsor-investigator and should be provided as soon as possible.

All SAEs will be reported using the FDA 3500A Mandatory MedWatch report form unless funding sponsor or drug manufacturer requires use of proprietary form. SAE form can be found at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

To submit an SAE, email as follows within 24 hours becoming aware of the event:

To: Nicole.Marjon@cuanshutz.edu
cpdm.iit@cuanschutz.edu

Subject: COMIRB #26-0543 SAE Report Form

Attach: SAE form completed and signed by the Investigator

Follow-up of unresolved serious adverse events

Any SAEs that are unresolved at the time of the initial report submission should be followed up by the investigator for as long as medically indicated, and an updated SAE report submitted at the time new information regarding the event becomes available.

8.3.8 ADVERSE EVENT OF SPECIAL INTEREST REPORTING

All Adverse Events of Special Interest will be reported using the FDA 3500A Mandatory MedWatch report. Reporting form can be found at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

To submit an AESI or special situation, email as follows within 24 hours of becoming aware of the event.

To: Nicole.Marjon@cuanshutz.edu
cpdm.iit@cuanschutz.edu
DSMC@cuanschutz.edu (EXTERNAL SITES ONLY)

Subject: COMIRB #26-0543 SAE Report Form

Attach: MedWatch 3500A Form completed and signed by the Investigator

Per institutional policy, all adverse events of special interest occurring at UCCC/UCHealth will be reported to the DSMC according to timetable for reporting specified in section 10.1.5.

8.3.9 REPORTING OF PREGNANCY

Pregnancy and lactation are exclusion criteria. Women of childbearing potential, defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (ie, who has had menses any time in the preceding 12 consecutive months) must agree to use highly effective contraceptive methods (as defined in Section 6.9.6) while on study drug

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Pregnancies and lactations will be reported on a MedWatch Form and submitted within 24 hours from first becoming aware. Please follow the instructions for Serious Adverse Event Reporting specified in section 8.3.6.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

This study will use the COMIRB definition of UAP. An unanticipated problem is any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized.

8.4.2 REPORTING OF UNANTICIPATED PROBLEMS

This study will follow COMIRB's guidance for UAP reporting and the DSMC's requirements (discussed below). AEs, noncompliance and protocol violations will be recorded and reported as required either promptly or at the time of the study's continuing review.

It is the responsibility of the PI to report incidents or events that meet the criteria for UAPs reporting to their IRB using the IRB's standard UAP form. The PI is also responsible for reporting the UAP to the UCCC DSMC.

The UAP report will include the following protocol-identifying information: protocol title and number, PI's name, and the IRB project number, in addition to:

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UAP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UAP.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  The primary efficacy endpoint is the change from baseline to the post-treatment surgical specimen in the mean CD163 H-score among CD68-positive tumor-associated macrophages. CD68 and CD163 expression will be assessed by multispectral immunohistochemistry in paired pre-treatment biopsy and post-treatment surgical samples. Images will be analyzed using Akoya inForm software, and the mean H-score will be calculated across at least five

prespecified regions of interest or the entire evaluable tumor section when feasible. Primary human tonsil tissue will serve as a positive control.

Primary Hypothesis

Let μA and μC denote the mean change from baseline to post-treatment in the CD163 H-score among CD68-positive tumor-associated macrophages in the atorvastatin plus standard-of-care arm and the standard-of-care-alone arm, respectively.

The primary hypotheses are:

$$H_0: \mu A - \mu C \geq 0$$
$$H_1: \mu A - \mu C < 0$$

- Safety Endpoint(s)

  Safety and tolerability: Safety will be evaluated based on the incidence, severity, seriousness, and relationship to study treatment of adverse events, as well as clinically significant laboratory abnormalities. Adverse events will be graded according to the Common Terminology Criteria for Adverse Events, version 5.0.

- Secondary/Exploratory Endpoints
  - Tumor immune and biologic markers: Additional immunohistochemical analyses will be performed on tumor tissue obtained during cytoreductive surgery. Prespecified markers will include cleaved caspase-3 as a measure of apoptosis, Ki-67 as a measure of cellular proliferation, IL-6 expression, γH2AX as a marker of DNA damage, ABCA1 and ABCG01 as a measure of cholesterol metabolism, T-cell infiltration, and natural killer cell infiltration.
  - Progression-free survival: Investigator-assessed progression-free survival will be defined as the time from randomization to the first documented occurrence of objective disease progression or death from any cause, whichever occurs first. Disease progression will be determined by radiographic assessment according to RECIST version 1.1 or by CA-125 progression according to Gynecologic Cancer InterGroup criteria. Participants without documented disease progression or death at the time of analysis will be censored at the date of their last adequate disease assessment demonstrating no progression.
  - Overall survival: Overall survival will be defined as the time from randomization to death from any cause. Participants who are alive at the time of analysis will be censored at the date of last follow-up.
  - CA-125 response: CA-125 response will be defined according to Gynecologic Cancer InterGroup criteria as a reduction of at least 50%

from the pretreatment CA-125 concentration, confirmed by a subsequent measurement and maintained for at least 28 days.

- Justification for Endpoints:

  Despite retrospective analysis of the combination of statins and chemotherapy in EOC demonstrating a 43% reduction in cancer-related mortality [55] to date no prospective studies have examined the effects of statin use on the HGSC tumor microenvironment or the patients' tumor response to standard-of-care (SOC), which is a combination of platinum/taxane-based chemotherapies and cytoreductive surgery. Given the prevalence of hypercholesterolemia, using data from the University of Colorado Gynecologic Tumor and Fluid Bank (GTFB, IRB #07-935) we identified 9 patients who were receiving statin during the course of their treatment and compared them to 9 age-matched HGSC patients who did not receive statin. Given the small sample size, we did not achieve statistical significance; however, we noted a 27-month increase in median overall survival in patients treated with rosuvastatin (median survival: 90.6 vs. 62.9 months). Data in a mouse model of EOC demonstrates repolarization of tumor promoting macrophages, which is potential mechanism for how statins affect survival. Therefore, we have elected to perform a window of opportunity trial evaluating the effects of statin therapy on tumor associated macrophages. We have powered the study based on the mouse modeling performed in our lab. Secondary endpoints will be PFS and OS as well as other translational exploratory endpoints. These data will support the development of a Phase III trial evaluating the efficacy of statin therapy on PFS and OS as well a further translational studies to better understand the cholesterol pathway in HGSC and develop novel therapeutics.

9.2 SAMPLE SIZE DETERMINATION

No published human data are currently available to estimate the effect of adding a statin to standard-of-care chemotherapy on the change in CD163 expression among CD68-positive tumor-associated macrophages. Therefore, the sample size calculation was informed by the preclinical mouse experiment presented in Figure 2, which directly evaluated the biologic effect underlying the primary clinical hypothesis.

In the mouse experiment, the standardized mean difference between the cisplatin and cisplatin plus rosuvastatin groups was estimated as Cohen's d = 1.77. Because treatment effects observed under controlled preclinical conditions may be attenuated in a heterogeneous human population, the clinical trial was not powered using the full

observed preclinical effect. Instead, a substantially smaller and more conservative standardized effect size of 0.91, approximately one-half of the observed mouse effect, was assumed.

Assuming equal allocation, a two-sided significance level of 0.05, and a two-sample comparison, 20 evaluable participants per arm will provide approximately 80% power to detect a standardized mean difference of 0.91 in the primary endpoint, defined as the change from baseline to the post-treatment surgical specimen in the mean CD163 H-score among CD68-positive tumor-associated macrophages.

The primary analysis will use a linear mixed-effects model with fixed effects for treatment arm, time point, and the treatment-by-time interaction, and a participant-specific random intercept to account for within-participant correlation. The treatment effect will be assessed using the treatment-by-time interaction, with the estimated between-arm difference in change from baseline reported with a 95% confidence interval. Because the sample size calculation was based on an unadjusted two-sample comparison and did not account for the efficiency gained from incorporating baseline and post-treatment measurements within the mixed-effects model, the power calculation is considered conservative.

To account for missing or non-evaluable paired tissue specimens, withdrawal, and other sources of attrition, 50 participants will be enrolled and randomized in a 1:1 ratio, with 25 participants assigned to each treatment arm. This sample size is expected to yield at least 40 evaluable participants, with 20 per arm.

9.3 POPULATION FOR ANALYSES

Intent-to-Treat Population: The intention-to-treat population will include all randomized participants. Participants will be analyzed according to the treatment arm to which they were randomized, regardless of treatment received, treatment adherence, protocol deviations, or availability of post-baseline assessments. The intention-to-treat population will be used for the primary efficacy analysis.

Per-Protocol Population: The per-protocol population will include participants in the intention-to-treat population who receive the assigned study treatment, have no major protocol deviations considered likely to affect evaluation of the primary endpoint, and have sufficient primary endpoint data for analysis. Participants will be analyzed according to randomized treatment assignment. The per-protocol analysis will serve as a sensitivity analysis.

Safety Population: The safety population will include all participants who receive at least one dose of any study treatment. Participants will be analyzed according to the treatment actually received.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For each treatment arm, continuous variables will be summarized using the number of evaluable observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages. Longitudinal patterns and changes from baseline will be summarized by treatment arm and time point and displayed graphically, as appropriate. Exploratory descriptive summaries may also be stratified by receipt of PARP inhibitor maintenance therapy. These subgroup analyses will be considered exploratory, and no formal inferential conclusions will be drawn unless otherwise prespecified.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint will be analyzed in the intention-to-treat population using a linear mixed-effects model including fixed effects for treatment arm, time point, and the treatment-by-time interaction, with a participant-specific random intercept to account for within-participant correlation. The treatment effect will be assessed using the treatment-by-time interaction and reported as the between-arm difference in mean change from baseline to post-treatment, with a two-sided 95% confidence interval and p-value. A two-sided significance level of 0.05 will be used. Model residuals will be examined to assess normality and homoscedasticity. If substantial violations are identified, an appropriate transformation will be considered.
The model will use all available baseline and post-treatment CD163 H-score measurements without single-value imputation. Under likelihood-based estimation, missing outcome data will be accommodated under a missing-at-random assumption. The extent and reasons for missing data will be summarized by treatment arm, and sensitivity analyses will be performed to assess the robustness of the findings to alternative missing-data assumptions. A per-protocol analysis will also be conducted as a sensitivity analysis.

9.4.3 ANALYSIS OF THE SECONDARY/EXPLORATORY ENDPOINT(S)

All secondary/exploratory analyses will be conducted primarily using the intention-to-treat (ITT) population. The per-protocol population will be used for sensitivity analyses, as appropriate. Because these analyses are exploratory, two-sided p-values and 95%

confidence intervals will be reported without adjustment for multiplicity, unless otherwise specified.

Tumor immune and biologic markers: Cleaved caspase-3, Ki-67, IL-6 expression, T-cell infiltration, and natural killer cell infiltration will be summarized by treatment arm using descriptive statistics appropriate to the distribution of each marker. Between-arm comparisons will be performed using analysis of covariance models when corresponding baseline measurements are available, with the post-treatment marker value as the dependent variable, treatment arm as the primary independent variable, and the baseline marker value as a covariate. When no baseline measurement is available, between-arm comparisons of post-treatment marker values will be performed using a two-sample t-test or Wilcoxon rank-sum test, as appropriate. Treatment effects will be reported with corresponding two-sided 95% confidence intervals.

Progression-free survival: Progression-free survival will be summarized using the Kaplan-Meier method by treatment arm. Median progression-free survival and progression-free survival probabilities at clinically relevant time points, including 3 years when estimable, will be reported with corresponding two-sided 95% confidence intervals. Treatment arms will be compared using a two-sided log-rank test. A Cox proportional hazards regression model will also be used to estimate the hazard ratio and corresponding 95% confidence interval for the atorvastatin plus standard-of-care arm relative to the standard-of-care-alone arm. An adjusted Cox model will include receipt of PARP inhibitor maintenance therapy as a covariate. The proportional hazards assumption will be assessed using graphical and model-based methods. If the median progression-free survival is not reached or the 3-year survival probability is not estimable because of limited follow-up, the available Kaplan-Meier estimates will be reported.

Overall survival: Overall survival will be analyzed using methods analogous to those described for progression-free survival. Kaplan-Meier curves, median overall survival, and overall survival probabilities at clinically relevant time points, including 3 years when estimable, will be reported with corresponding two-sided 95% confidence intervals. Treatment arms will be compared using a two-sided log-rank test, and Cox proportional hazards regression will be used to estimate unadjusted and PARP inhibitor-adjusted hazard ratios with corresponding 95% confidence intervals.

CA-125 response: The proportion of participants achieving a CA-125 response according to Gynecologic Cancer InterGroup criteria will be summarized by treatment arm with corresponding two-sided 95% confidence intervals. Treatment arms will be compared using Fisher's exact test or the chi-square test, as appropriate. The treatment effect will be reported as the difference in response proportions and may also be summarized using an odds ratio with corresponding two-sided 95% confidence intervals. Participants without sufficient post-baseline CA-125 measurements to determine response will be classified according to the prespecified missing-data rules for the mITT analysis, with alternative assumptions evaluated in sensitivity analyses when appropriate.

All statistical analyses will be performed using R and appropriate validated R packages. Unless otherwise specified, statistical tests will be two-sided and evaluated at a nominal significance level of 0.05.

9.4.4 SAFETY ANALYSES

Safety analyses will be conducted in the Safety Population, defined as all participants who receive at least one dose of study treatment, analyzed according to treatment received. Treatment-emergent adverse events will be coded using MedDRA and graded according to CTCAE version 5.0.

Adverse events will be summarized by treatment arm by system organ class, preferred term, maximum severity, seriousness, relationship to study treatment, and action taken. Grade 3 or higher adverse events, serious adverse events, treatment-related adverse events, adverse events leading to dose modification or discontinuation, deaths, and clinically significant laboratory abnormalities will be summarized separately.

Safety analyses will be descriptive, with counts and percentages reported by treatment arm.

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9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics, including age, race, ethnicity, disease stage at diagnosis, body mass index, baseline LDL and HDL cholesterol levels, and BRCA status, will be summarized descriptively by treatment arm. Continuous variables will be summarized using the number of evaluable observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages. No formal statistical comparisons of baseline characteristics between treatment arms will be performed. Exploratory descriptive summaries stratified by receipt of PARP inhibitor maintenance therapy may also be provided.

9.4.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be presented in subject-level listings, as appropriate. Listings may include demographic and baseline characteristics, treatment exposure,

concomitant medications, efficacy assessments, protocol deviations, and participant disposition.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/ administering study product.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that

the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading participants. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Lead PI and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

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

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB, DSMC, and/or FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

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

The study monitor, other authorized representatives of the sponsor-investigator, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator,

including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Colorado Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center.

10.1.4 BANKING AND FUTURE USE OF STORED SPECIMENS AND/OR DATA

- **Intended Use:** Samples and data collected under this protocol may be used to study high grade serous carcinoma of the ovary, fallopian tube, or peritoneum in the future.
- **Storage:** Access to stored samples will be limited. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

The following information obtained from the subject's medical record may be recorded and may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if required
- Demographic data

These samples could be used for research into the causes of HGSC its complications and to improve treatment. University of Colorado Pathology Shared Resource will also be

provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, and individual participant can choose to withdraw consent to have biological specimens stored for future research. If future use is denied or withdrawn by the participant, best efforts will be made to stop any additional studies and to destroy the specimens. However, withdrawal of consent with regard to bio-sample storage will not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Pathology Shared Resource.

Specimens will be stored indefinitely or until they are used up. However, once the study is completed, specimens must be transferred to a COMIRB approved tissue bank/data repository protocol designed specifically for secondary research.

10.1.5 SAFETY OVERSIGHT

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-

threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

10.1.6 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

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

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

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

Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI. Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, for high-risk studies, as determined by OCRST risk assessment, with an Investigator held IND or IDE. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of an investigational marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations or institutional policies. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the PI when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. These practices are consistent with ICH E6(R3), sections:

- Compliance with Protocol (Section 2.5)
- Quality Assurance & Quality Control (Section 3.11)
- Noncompliance (Section 3.12)

It is the responsibility of the study team to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to COMIRB, Protocol deviations must be sent to the local IRB per institutional guidelines. The site PI/ study staff is responsible for knowing and adhering to their IRB requirements.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will ensure that the public has access to the published results of this research.

As required, either for publication (the ICMJE or other publication policy), or according to U.S. regulations (Section 801 of the Food and Drug Administration Amendments Act of 2007) this clinical trial will be registered in a public trials registry including ClinicalTrials.gov, which is sponsored by the National Library of Medicine, and the NCI CTRP Registry for cancer clinical trials.

10.1.11 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

11 REFERENCES

1. Siegel, R.L., et al., *Cancer statistics, 2025.* CA: a cancer journal for clinicians, 2025. **75**(1): p. 10–45.
2. Bowtell, D.D., et al., *Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer.* Nature Reviews. Cancer, 2015. **15**(11): p. 668–679.
3. Guppy, A.E., P.D. Nathan, and G.J.S. Rustin, *Epithelial ovarian cancer: a review of current management.* Clinical Oncology (Royal College of Radiologists (Great Britain)), 2005. **17**(6): p. 399–411.
4. Ozols, R.F., *Systemic therapy for ovarian cancer: current status and new treatments.* Seminars in Oncology, 2006. **33**(2 Suppl 6): p. S3–11.
5. Arora, T., et al., *Epithelial Ovarian Cancer*, in *StatPearls*. 2025, StatPearls Publishing: Treasure Island (FL).
6. Bicaku, E., et al., *In vitro analysis of ovarian cancer response to cisplatin, carboplatin, and paclitaxel identifies common pathways that are also associated with overall patient survival.* Br J Cancer, 2012. **106**(12): p. 1967–75.
7. Patch, A.-M., et al., *Whole–genome characterization of chemoresistant ovarian cancer.* Nature, 2015. **521**(7553): p. 489–494.
8. Wang, Y., et al., *Chemoresistance Evolution in Ovarian Cancer Delineated by Single-Cell RNA Sequencing.* International Journal of Molecular Sciences, 2025. **26**(14): p. 6760.
9. Shield, K., et al., *Multicellular spheroids in ovarian cancer metastases: Biology and pathology.* Gynecol Oncol, 2009. **113**(1): p. 143–8.
10. Sehouli, J., et al., *Intra-abdominal tumor dissemination pattern and surgical outcome in 214 patients with primary ovarian cancer.* J Surg Oncol, 2009. **99**(7): p. 424–7.

11. Penet, M.F., et al., *Ascites Volumes and the Ovarian Cancer Microenvironment.* Front Oncol, 2018. **8**: p. 595.
12. Rana, S.V., S.G. Babu, and R. Kocchar, *Usefulness of ascitic fluid cholesterol as a marker for malignant ascites.* Med Sci Monit, 2005. **11**(3): p. Cr136–42.
13. Jiang, W., W.L. Jin, and A.M. Xu, *Cholesterol metabolism in tumor microenvironment: cancer hallmarks and therapeutic opportunities.* Int J Biol Sci, 2024. **20**(6): p. 2044–2071.
14. Chen, Y.Y., et al., *Copy number amplification of ENSA promotes the progression of triple-negative breast cancer via cholesterol biosynthesis.* Nat Commun, 2022. **13**(1): p. 791.
15. Han, B., et al., *A chemokine regulatory loop induces cholesterol synthesis in lung-colonizing triple-negative breast cancer cells to fuel metastatic growth.* Mol Ther, 2022. **30**(2): p. 672–687.
16. Kim, S., et al., *Activation of LXRa/ß by cholesterol in malignant ascites promotes chemoresistance in ovarian cancer.* BMC Cancer, 2018. **18**(1): p. 1232.
17. Shangguan, X., et al., *Squalene Epoxidase Metabolic Dependency Is a Targetable Vulnerability in Castration-Resistant Prostate Cancer.* Cancer Res, 2022. **82**(17): p. 3032–3044.
18. Wang, Y., et al., *N(1)-methyladenosine methylation in tRNA drives liver tumourigenesis by regulating cholesterol metabolism.* Nat Commun, 2021. **12**(1): p. 6314.
19. Goossens, P., et al., *Membrane Cholesterol Efflux Drives Tumor-Associated Macrophage Reprogramming and Tumor Progression.* Cell Metab, 2019. **29**(6): p. 1376–1389 e4.
20. Jové, M., et al., *Human omental and subcutaneous adipose tissue exhibit specific lipidomic signatures.* Faseb j, 2014. **28**(3): p. 1071–81.
21. Khan, S.M., et al., *In vitro metastatic colonization of human ovarian cancer cells to the omentum.* Clin Exp Metastasis, 2010. **27**(3): p. 185–96.
22. Nieman, K.M., et al., *Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth.* Nat Med, 2011. **17**(11): p. 1498–503.
23. Habis, M., et al., *Statin therapy is associated with improved survival in patients with non-serous-papillary epithelial ovarian cancer: a retrospective cohort analysis.* PLoS One, 2014. **9**(8): p. e104521.
24. Elmore, R.G., et al., *Impact of statin therapy on survival in epithelial ovarian cancer.* Gynecologic Oncology, 2008. **111**(1): p. 102–105.
25. Jiang, W., et al., *Statins: a repurposed drug to fight cancer.* J Exp Clin Cancer Res, 2021. **40**(1): p. 241.
26. Jordan, K.R., et al., *The Capacity of the Ovarian Cancer Tumor Microenvironment to Integrate Inflammation Signaling Conveys a Shorter Disease-free Interval.* Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 2020. **26**(23): p. 6362–6373.
27. Lane, D., et al., *Inflammation-regulating factors in ascites as predictive biomarkers of drug resistance and progression-free survival in serous epithelial ovarian cancers.* BMC Cancer, 2015. **15**: p. 492.
28. Dalal, V., et al., *Biomarker potential of IL-6 and VEGF-A in ascitic fluid of epithelial ovarian cancer patients.* Clinica Chimica Acta; International Journal of Clinical Chemistry, 2018. **482**: p. 27–32.
29. Chang, H., et al., *Construction of a Macrophage Infiltration Regulatory Network and Related Prognostic Model of High-Grade Serous Ovarian Cancer.* J Oncol, 2021. **2021**(1): p. 1331031.
30. Tan, Q., et al., *Integrated analysis of tumor-associated macrophage infiltration and prognosis in ovarian cancer.* Aging (Albany NY), 2021. **13**(19): p. 23210–23232.
31. Toh, B., et al., *Myeloid cells: Prime drivers of tumor progression.* Oncoimmunology, 2012. **1**(8): p. 1360–1367.
32. Gordon, S., *Phagocytosis: An Immunobiologic Process.* Immunity, 2016. **44**(3): p. 463–475.
33. Mosser, D.M. and J.P. Edwards, *Exploring the full spectrum of macrophage activation.* Nature Reviews. Immunology, 2008. **8**(12): p. 958–969.
34. Liu, Y., et al., *Metabolic reprogramming in macrophage responses.* Biomark Res, 2021. **9**(1): p. 1.
35. Jha, A.K., et al., *Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization.* Immunity, 2015. **42**(3): p. 419–30.
36. Lane, D., et al., *Prognostic significance of IL-6 and IL-8 ascites levels in ovarian cancer patients.* BMC Cancer, 2011. **11**: p. 210.
37. Cohen, S., et al., *Platinum-resistance in ovarian cancer cells is mediated by IL-6 secretion via the increased expression of its target cIAP-2.* J Mol Med (Berl), 2013. **91**(3): p. 357–68.

38. Browning, L., et al., *IL-6 and ovarian cancer: inflammatory cytokines in promotion of metastasis.* Cancer Manag Res, 2018. **10**: p. 6685–6693.
39. Duluc, D., et al., *Tumor-associated leukemia inhibitory factor and IL-6 skew monocyte differentiation into tumor-associated macrophage-like cells.* Blood, 2007. **110**(13): p. 4319–30.
40. Watson, Z.L., et al., *Histone methyltransferases EHMT1 and EHMT2 (GLP/G9A) maintain PARP inhibitor resistance in high-grade serous ovarian carcinoma.* Clin Epigenetics, 2019. **11**(1): p. 165.
41. Han, Z. and J.H. Wyche, *Lovastatin induces apoptosis in a metastatic ovarian tumour cell line.* Cell Death and Differentiation, 1996. **3**(2): p. 223–228.
42. Liu, H., et al., *Statins induce apoptosis in ovarian cancer cells through activation of JNK and enhancement of Bim expression.* Cancer Chemother Pharmacol, 2009. **63**(6): p. 997–1005.
43. Gobel, A., et al., *Anti-tumor effects of mevalonate pathway inhibition in ovarian cancer.* BMC Cancer, 2020. **20**(1): p. 703.
44. Stine, J.E., et al., *The HMG-CoA reductase inhibitor, simvastatin, exhibits anti-metastatic and anti-tumorigenic effects in ovarian cancer.* Oncotarget, 2016. **7**(1): p. 946–60.
45. Moscoso, A., N. Mohammad Mirzaei, and L. Shahriyari, *Analysis of ovarian cancer immune cell profile identifies immunosuppressive states associated with adverse clinical attributes and survival times.* PLoS One, 2026. **21**(4): p. e0346746.
46. Autio, K.A., et al., *Immunomodulatory Activity of a Colony-stimulating Factor-1 Receptor Inhibitor in Patients with Advanced Refractory Breast or Prostate Cancer: A Phase I Study.* Clin Cancer Res, 2020. **26**(21): p. 5609–5620.
47. Goldstein, L.J., et al., *A window-of-opportunity trial of the CXCR1/2 inhibitor reparixin in operable HER-2-negative breast cancer.* Breast Cancer Res, 2020. **22**(1): p. 4.
48. Al Dujaily, E., et al., *Reduced Protumorigenic Tumor-Associated Macrophages With Statin Use in Premalignant Human Lung Adenocarcinoma.* JNCI Cancer Spectr, 2020. **4**(2): p. pkz101.
49. Newman, C.B., et al., *Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association.* Arterioscler Thromb Vasc Biol, 2019. **39**(2): p. e38–e81.
50. Jang, H.J., et al., *The Effect of Statin Added to Systemic Anticancer Therapy: A Meta-Analysis of Randomized, Controlled Trials.* J Clin Med, 2018. **7**(10): p. 325.
51. Chou, E., et al., *Statin Use in Patients With Cancer: Drug Interaction and Statin Usage.* JACC Adv, 2025. **4**(11 Pt 1): p. 102259.
52. Aizawa, F., et al., *Statins ameliorate oxaliplatin- and paclitaxel-induced peripheral neuropathy via glutathione S-transferase.* Neurochem Int, 2024. **180**: p. 105863.
53. Simonsen, E., et al., *The Molecular and Clinical Impact of Atorvastatin Exposure on Paclitaxel Neurotoxicity in Sensory Neurons and Cancer Patients.* Basic & Clinical Pharmacology & Toxicology, 2025. **136**(5): p. e70022.
54. Wheeler, L.J., et al., *CBX2 identified as driver of anoikis escape and dissemination in high grade serous ovarian cancer.* Oncogenesis, 2018. **7**(11): p. 92.
55. Visvanathan, K., et al., *Abstract 5782: Lipophilic Statins show promise for treatment of epithelial ovarian cancer.* Cancer Research, 2020. **80**(16_Supplement): p. 5782.