ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAE161

Perfusion CT to Predict Progression-free Survival and Response Rate in Bevacizumab and Paclitaxel Treatment of Platinum-Resistant Persistent or Recurrent Epithelial Ovarian, Fallopian Tube, or Peritoneal Carcinoma

STUDY CHAIR:	Susanna Lee, M.D., Ph.D.
STUDY CO-CHAIR:	Avinash Kambadakone, MBBS, M.D., DNB, FRCR, FSAR, FSCBT-MR
MODALITY CO-CHAIR(S):	Russell Schilder M.D. Robert Mannel M.D. Andrew Smith, M.D., Ph.D., FSAR, FSCBT-MR
STUDY STATISTICIAN:	Bradley S. Snyder, M.S.
GYNECOLOGY COMMITTEE CHAIR:	Susanna Lee, M.D., Ph.D.

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STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology
SWOG / SWOG

ACTIVATION DATE

February 4, 2018
Addendum #1

NCTN GROUP STUDY CHAMPIONS

NRG: Russell Schilder, M.D.
Robert Mannel, M.D.

Agents	IND#	NSC#	Supply
Bevacizumab	IND Exempt Study	NSC# 704865	Commercial

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STUDY CHAIR

Susanna Lee, M.D., Ph.D.
Massachusetts General Hospital
Department of Radiology
55 Fruit St., White 270
Boston, MA 02114
Phone: (617) 643-2009
Fax: (617) 726-4891
Email: slee0@mgh.harvard.edu

STUDY CHAIR LIAISON (SCL)

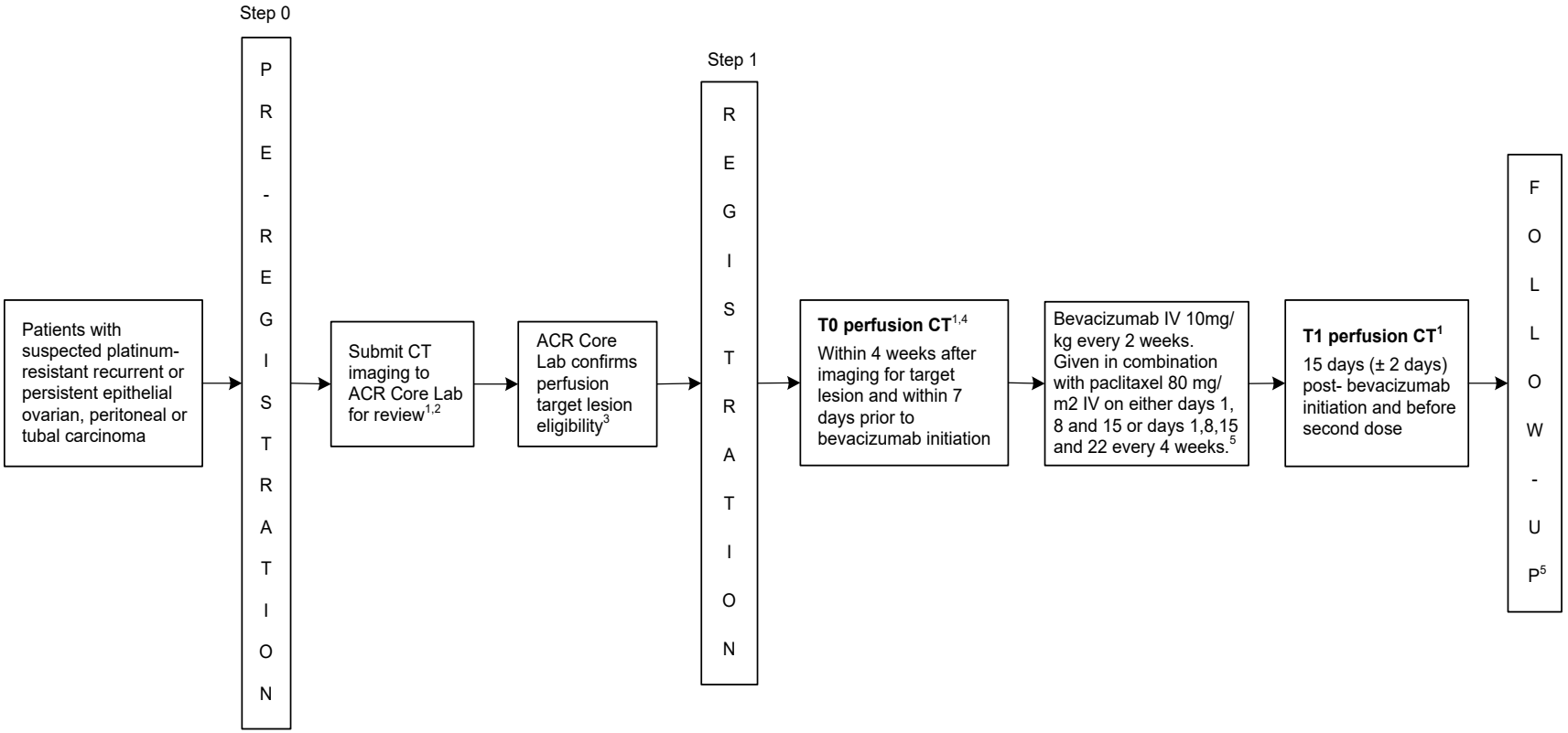
EAE161 Study Team
Phone: 215-717-0833
Email: EAE161@acr.org

CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

Rev. Add1

Schema



1. Conventional chest abdomen and pelvis CT images demonstrating recurrent tumor must be submitted to the ACR Core Lab within 21 days from acquisition. T0 and T1 perfusion CT scan must be submitted within 48 hours to ACR Core Lab from acquisition.
2. Trial Radiologist (via the ACR Core Lab) identifies target lesion amenable to perfusion CT imaging. (See imaging manual for perfusion CT target lesion description.)
3. ACR Core Lab will inform site within 5 business days if patient is eligible.
4. CA-125 to be collected +/-2 days of T0 and T1 perfusion CT.
5. Patient continues chemotherapy and is followed for survival up to 18 months after last patient is enrolled.

1. Introduction

1.1 Abstract

Bevacizumab in combination with cytotoxic chemotherapy has been shown to prolong PFS in epithelial ovarian cancer patients, both in the primary and recurrent setting. Perfusion CT changes have been associated with anti-angiogenesis therapy response independent of tumor type and treatment setting. We hypothesize that in patients with platinum-resistant, recurrent ovarian cancer, changes in tumor vascularity parameters, as measured by perfusion CT from baseline (T0) to 15 days (+/- 2 days) post initiation (T1) of bevacizumab therapy, are associated with progression-free survival (PFS) and rates of objective tumor response assessed by standard anatomic response evaluation criteria (RECIST 1.1).

1.2 Background and Rationale for a Phase II Study

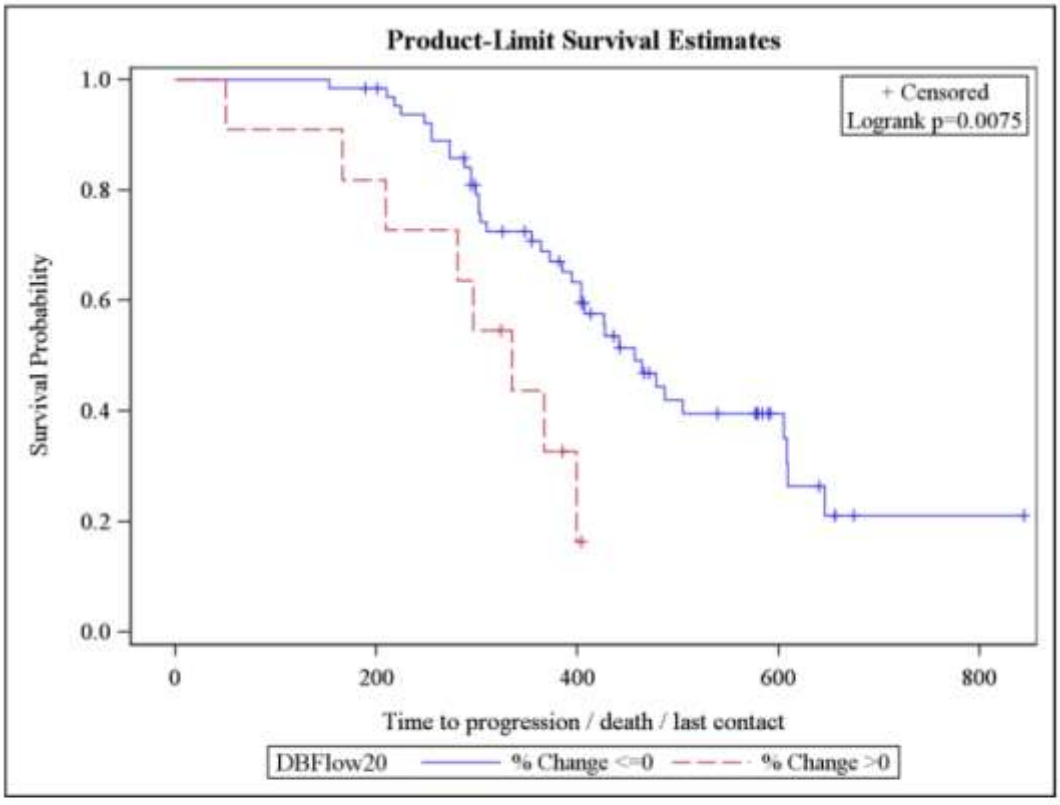
In 2014, the FDA approved bevacizumab (Avastin®, made by Genentech, Inc.) in combination with paclitaxel, pegylated liposomal doxorubicin (PLD), or topotecan for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Three Phase III trials (OCEANS, AURELIA and GOG-0213) showed that antiangiogenic therapy using bevacizumab, which targets vascular endothelial growth factor (VEGF)-A, in combination with cytotoxic chemotherapy has efficacy in treating recurrent disease. OCEANS tested gemcitabine and carboplatin with or without the addition of bevacizumab given concurrently and then as maintenance in patients considered to have platinum-sensitive disease. Progression-free survival (PFS) in patients who received bevacizumab plus chemotherapy was 12.4 months, compared to 8.4 months for patients who received chemotherapy alone ($P<0.001$) [1]. AURELIA studied platinum-resistant recurrent disease and observed a statistically significant increase in PFS from 3.4 months in the single-agent chemotherapy-alone arm (weekly paclitaxel, PLD, topotecan or investigator's choice) to 6.7 months in the chemotherapy plus bevacizumab arm ($P<0.001$) [2] and increased the proportion of patients (12.7% greater in bevacizumab arm, $p = .002$) achieving a 15% improvement in patient-reported abdominal or gastrointestinal symptoms during chemotherapy [3]. On subgroup analysis by conventional chemotherapy, the response rate by RECIST was higher with bevacizumab-containing therapy versus chemotherapy alone in the paclitaxel cohort (53.3% v 30.2%, respectively) and the topotecan cohort (17.0% v 0.0%), with a less pronounced effect in the PLD cohort (13.7% v 7.8%). Median PFS with bevacizumab and paclitaxel was the longest at 10.4 months [35]. These findings established addition of bevacizumab as standard of care for the recurrent ovarian cancer population.

Improvements in efficacy attained by adding bevacizumab are offset by some disadvantages. Addition of the agent increases chemotherapy costs up to 7-fold. Added cost and morbidity are incurred by higher rates of treatment-related toxicities in the bevacizumab plus chemotherapy vs. chemotherapy alone arm. These include grade > 2 hypertension (20% vs. 7%) and bowel perforation, fistula, or abscess (7% vs. 0%). Moreover, emerging molecular analysis indicates a subgroup of patients in whom survival outcomes is adversely affected by bevacizumab [4]. Thus, a biomarker that can successfully distinguish the patient

subgroup that is unlikely to benefit from bevacizumab could serve as a tool to identify the cohort most likely to benefit from future trials of targeted agents for ovarian cancer therapy. Further, a validated biomarker could enable precision-medicine tailoring of the therapy regimen in recurrent ovarian cancer patients to maximize its potential benefits while minimizing morbidity and cost [5,6].

ACRIN 6695/GOG-0262, carried out by this study team, demonstrated that perfusion CT could serve as a quantitative early biomarker in ovarian cancer therapy in a multicenter trial setting [7,8]. In brief, from August 2011 to July 2013, 120 patients were screened, yielding 76 evaluable patients from 19 centers, and completed perfusion CT scans on scanners from four different vendors before and after start of therapy. Ninety-one percent of the analyzable cohort received bevacizumab. Blood volume (BV) increase was significantly associated with lower chance of PFS-6 (p=0.028), while blood flow (BF) achieved borderline significance (p=0.053). BF and BV increases were both significantly associated with lower treatment response rate (p=0.032 and 0.026, respectively). However, on Cox regression analysis, BF increase was the parameter most strongly associated with shorter PFS (HR 2.9, 95% CI 1.3-6.4, p=0.008), and remained significant after adjusting for age, change in tumor volume and surgery status (p=0.007).

Figure 1. ACRIN 6695/GOG-0262 Kaplan-Meier PFS curve comparing subjects with increase versus decrease in BF.



Of note, changes in perfusion CT parameters during the first cycle of cytotoxic chemotherapy prior to initiation of bevacizumab demonstrated no association with PFS.

ACRIN 6695/GOG-0262 was the first trial to demonstrate the feasibility of quantitative perfusion CT assessment across multiple sites, vendors, and scanner platforms. Image intervals, CT noise, spatial uniformity, and temporal stability was identified and monitored as important factors affecting the precision of the derived perfusion parameters. No technical failures in scanning were observed at any individual site after the first or second exam, indicating a relatively low barrier for implementation. All scans were within acceptable radiation dose range. This study established a practical quality assurance protocol for site scanner qualification, image acquisition, dose monitoring and a real-time feedback communication between the trial radiologists and site investigators to ensure reproducibility and safety of perfusion CT. Ninety-five percent of the subjects on this trial were treated with bevacizumab. Current clinical practice standard uses bevacizumab in combination with conventional cytotoxic chemotherapy in patients with platinum-resistant recurrent tumor. Consequently, there is a need to verify that the utility of perfusion CT as a biomarker demonstrated with bevacizumab therapy in ACRIN 6695/GOG-0262 holds true in a clinical setting where anti-angiogenesis therapy is considered standard of care. Moreover, beyond the phase I proof of principle setting, the generalizability of perfusion CT prediction to multiple readers and post-processing vendor platforms must be demonstrated.

1.3 Rationale for Perfusion CT

1.3.1 Imaging Science

Perfusion CT is a dynamic contrast-enhanced CT exam, in which the scanner is used to follow the passage of contrast bolus through the target lesion after injection. The acquired images are then processed to calculate quantitative parameters that include tumor blood flow (BF), blood volume (BV), and permeability surface product (PS). Bevacizumab targets VEGF-A overexpressed in tumor-associated angiogenesis to reduce proliferation of neovessels, which are more permeable than normal vessels [9]. This leads to normalization of the tumor vasculature, manifested as a decrease in microvessel blood flow (or perfusion) and permeability. As seen in ACRIN 6695/GOG-0262, where perfusion CT outputs were performed in ovarian cancer patients undergoing conventional chemotherapy, with a subset in combination with bevacizumab, the test appears to specifically image microvascular changes resulting from VEGF inhibition and does not seem to serve as a predictive biomarker in the setting of conventional chemotherapeutics [7,8]. Finally, the exam can be readily integrated with morphologic RECIST 1.1 CT protocols in the same exam [10].

Currently, a number of software packages based on different kinetic models of tumor perfusion are used for post-processing of the CT images, resulting in a lack of standardization. Studies using these models have yielded different values and perfusion maps in similar or even the same cohorts. All of these studies have been performed in brain imaging of acute stroke patients at a single time point [11,12]. In contrast, development of perfusion CT as an oncologic biomarker has relied on measuring the magnitude or direction of change of a specific variable (e.g., BF, BV) between two time points during therapy. This theoretically increases the likelihood that any associations seen in

perfusion CT output with treatment outcome will be software-independent. Hence, one of the secondary aims of this trial is to study whether a biomarker relying on measuring perfusion CT changes over a therapy course is robust when different post-processing platforms are used. Testing the direction of change of BF (the variable with the strongest association with PFS in ACRIN 6695/GOG-0262) rather than its absolute value will increase the likelihood that any association we demonstrate will be generalizable to multiple perfusion CT platforms.

MRI is the other imaging modality in which perfusion imaging has been studied. Major advantages compared to CT are lack of ionizing radiation and a greater dynamic range of signal. Exam performance is similar where a target volume of tissue is imaged during transit of a bolus of intravenous contrast. Several phase I, single-center trials have demonstrated that perfusion MR output can serve as a biomarker in VEGF inhibition, such as hepatocellular carcinoma treated with sunitinib [13] and renal cell carcinoma treated with sorafenib [14]. However, unlike with CT density, the MR T1 signal does not directly measure the tissue concentration of the administered contrast. The resulting necessity for scanner calibration and modeling to correct for the variability introduced by multiple factors, including scanning hardware, acquisition protocol, underlying tissue T1 signal, and the molecular composition of the contrast agent, represent intellectual challenges that still need to be solved before this technology can be successfully tested in a multicenter trial.

Vascular tumor burden (VTB) is a recently developed quantitative CT imaging biomarker that is based on routine CT images [30, 31]. VTB is a size metric that quantifies the amount of vascularized tumor (cm^2) with free form regions of interest drawn around the peripheral margin of target lesions on the axial CT images where the target lesions are the largest. Technically, VTB is the area of tumor within the region of interest that measures between 40 and 300 Hounsfield Units (HU) for contrast-enhanced CT and between 20 and 300 HU for non-enhanced CT images. The tumor segmentation and these thresholds are designed to exclude air, lung, fat, necrotic tumor, non-enhancing tumor, cortical bone, dense tumor calcification, hyperattenuating contrast within large blood vessels, and metal clips. As VTB is a size metric that is measured in continuous units, VTB from various target lesions can be summed to derive a total VTB for each time point, and a percent change in total VTB can be calculated, similar to percent change in tumor length used in RECIST 1.1. VTB is highly reproducible and provides a direct measure of tumor devascularization, allowing for early detection of tumor response in a population of patients with heterogeneous therapeutic efficacy.

1.3.2 Feasibility

Perfusion CT is performed on multidetector CT (MDCT) scanners, which are widely available as the current standard for clinical exams. The scanning protocol is available as a standard software option on most scanners. This will enable enrollment of a diverse population at a variety of sites ranging from urban to rural, and academic to

community centers. Perfusion CT post-processing software is commercially available from multiple vendors and is in use at many sites for perfusion CT scanning of the brain in stroke patients and for tumor perfusion assessment in oncology patients. However, for the purposes of this trial, as with ACRIN 6695/GOG-0262, perfusion CT images acquired at the site will be collected by the core lab, and all post-processing will be performed centrally by the trial team.

Perfusion scans in this study have been timed to coincide with therapy-related patient visits to minimize patient inconvenience and cost. In ACRIN 6695/GOG-262, the post-bevacizumab perfusion scan occurred on days 8-10 post first dose of bevacizumab (T2 scan in ACRIN6695 trial). Changes in tumor vascularity detected with perfusion CT seem to occur within the first 5-7 days after first dose anti-angiogenesis therapy, and are thought to remain unchanged for the first several weeks of the therapeutic response [32, 33]. Thus, the timing of the post-bevacizumab scan to day 13-17 on this trial is unlikely to significantly alter the range of perfusion CT output from that observed on ACRIN 6695/GOG-262.

1.4 Significance of the Study

1.4.1 Potential Value of Perfusion CT as a Non-Invasive Biomarker

Currently, biomarkers to assess treatment response of ovarian carcinoma include morphologic assessment with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and cell surface glycoprotein antigen CA125. Unfortunately, these biomarkers are less than accurate in predicting a patient's outcome, especially in those treated with newer molecular targeted agents [15]. Further, tissue biopsy for monitoring treatment response remains impractical, in part due to invasiveness. Additionally, the inherent heterogeneity of ovarian cancer at the tissue level results in significant inaccuracy from biopsy sampling. Hence, the identification of a non-invasive early biomarker to predict response to treatment in ovarian carcinoma would prove a powerful tool. Perfusion CT may serve as such a biomarker for evaluation of angiogenesis. As changes in tumor perfusion parameters have been noted to precede morphologic changes by weeks to months, perfusion CT represents a test that could accurately assess changes in tumor angiogenesis, predict long-term efficacy, and identify candidates unlikely to incur benefit from bevacizumab early during the course of initial therapy [16].

Anti-angiogenic agents such as bevacizumab produce disease stabilization (cytostatic) in addition to tumor regression (cytotoxic). Consequently, conventional imaging strategies that rely on changes in tumor size, such as World Health Organization (WHO) and/or RECIST morphological criteria, are suboptimal for evaluating the efficacy of these agents [17,18]. While primary endpoints of PFS and overall survival (OS) remain the most valid and least ambiguous endpoints for clinical efficacy, the cytostatic effect of these new agents requires significantly more time and expense before their efficacy, or lack thereof, becomes evident using these parameters. Finally, response to these agents can be limited. Changes in the tumor

microenvironment (e.g., hypoxia) that result from vascular pruning and other consequences of VEGF inhibition can promote angiogenesis escape and tumor progression [8, 19]. Conventional assessment tools, including RECIST 1.1 or CA125, are inadequate to identify these patients in whom response to bevacizumab therapy will be short-lived. Because multiple trials have demonstrated that only a subset of patients respond, and the overall clinical benefit is limited, biomarker development resources has been directed toward finding a marker to predict the likelihood of anti-angiogenesis treatment failure [20].

In summary, the identification of an alternative, early, non-invasive imaging biomarker that can be integrated into the current RECIST 1.1 assessments, and which is proven to accurately predict long-term efficacy of anti-angiogenesis therapy, is of paramount importance. Such a biomarker has the potential to guide drug choice and dosing, evaluate pharmacodynamic response, and anticipate angiogenesis resistance and escape. This study, if successful, would provide necessary information toward validation of perfusion CT as an integral biomarker for future therapy trials. For ovarian cancer patients, such a biomarker would facilitate and expedite the development of drugs for the subgroup of patients who are at the highest risk for poor outcome.

1.4.2 Impact on Future Cancer Clinical Practice and Trials

Perfusion CT has demonstrated a spectrum of potential biomarker applications in oncology, providing prognostic information and predicting therapeutic effects of various treatment regimens that target the tumor microvasculature. Preliminary data from metastatic colon cancer studies have suggested an association between progressive disease and a poor response to chemotherapy with perfusion parameters [21]. In head and neck cancers, perfusion CT has been able to identify tumors that are likely to have a favorable outcome following radiotherapy [22]. For anti-angiogenesis therapy of metastatic renal carcinoma with sorafenib and sunitinib [23] and primary hepatocellular carcinoma with bevacizumab [24], responders to therapy demonstrate significantly higher percentage decreases in tumor vascular parameters than non-responders. These observations indicate that perfusion CT measures the changes in the tumor microenvironment (e.g., hypoxia) that results from vascular pruning and other consequences of VEGF inhibition.

Agents targeted for VEGF inhibition are widely used in advanced or recurrent colorectal, renal cell, and ovarian cancers. Patients who fail to respond to these conventional anti-angiogenesis agents are those with the poorest prognosis, and are the most likely to benefit from future drug development. With this in mind, extensive biomarker programs have been built into numerous clinical studies with bevacizumab [20]. In future trials, perfusion CT could be used identify patients who demonstrate resistance to anti-angiogenesis therapy, in whom novel agents should be tested. In this context, perfusion CT would serve as an integral biomarker in future phase II and III drug development trials. In clinical practice, once successfully validated as a biomarker in future trials, perfusion CT has the potential to provide

early identification of those patients unlikely to benefit from the current standard anti-VEGF therapy, who could then be triaged to other agents more likely to succeed.

1.4.3 Impact on ECOG-ACRIN Scientific Objectives

This trial fulfills multiple scientific objectives laid out by ECOG-ACRIN. Development and validation of advanced imaging methods to determine risk, identify treatment targets, monitor response to treatment, and establish markers for use in clinical trials and clinical care represent a major ECOG-ACRIN scientific objective. This trial furthers the development of an advanced imaging technique, perfusion CT, as a validated biomarker in VEGF-targeted therapy for early monitoring of response in clinical care and for use as an integral biomarker in future therapy trials. Collaboration across the NCTN in the development and implementation of high-impact clinical trials is another important ECOG-ACRIN objective. This trial has been designed to align with the research goals of NRG investigators who have identified the need for an integral biomarker in future trials of therapeutic agents in platinum- and bevacizumab-resistant ovarian cancer patients.

2. Objectives

2.1 Primary Aim:

2.1.1 To evaluate whether those patients with an increase in perfusion CT tumor blood flow (BF) from T0 to T1 demonstrate poorer progression-free survival (PFS) compared to those patients with a decrease in BF from T0 to T1, among platinum-resistant, recurrent ovarian cancer patients treated with bevacizumab in combination with paclitaxel.

2.2 Secondary Aims

2.2.1 To evaluate whether change in perfusion CT tumor BF from T0 to T1, as a continuous variable, is associated with PFS.

2.2.2 To evaluate whether changes in perfusion CT tumor blood volume (BV) or permeability surface product area (PS) from T0 to T1 are associated with PFS.

2.2.3 To evaluate whether changes in perfusion CT tumor BF, BV, or PS from T0 to T1 are associated with response rate according to the standard anatomic response evaluation criteria (RECIST 1.1).

2.2.4 To identify which combination of perfusion CT parameters, including tumor BF, BV, and PS, can serve to optimally distinguish patients in terms of PFS outcome.

2.2.5 To evaluate whether the association between change in perfusion CT parameters and treatment outcome (PFS or tumor response) is stable when analyzed with various commercially available post-processing software.

2.3 Exploratory Aims

2.3.1 In the subset of patients with multiple, eligible perfusion target lesions within the CT imaging volume, we will describe the variability of perfusion CT changes across different lesions within the same patient, and evaluate the impact of multiple target lesions on the association between change in perfusion CT parameters and PFS. [8]

2.3.2 To evaluate the reliability of perfusion CT parameters by analyzing the same perfusion imaging dataset using different readers and different post-processing software.

2.3.3 To evaluate whether change in global vascular tumor burden (VTB) from T0 to T1 is associated with PFS, and with changes in BF, BV, or PS.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

3.1.1 Registration to Step 0

_____ 3.1.1.1 Patient must be female ≥ 18 years of age.

_____ 3.1.1.2 Patient must have epithelial ovarian, fallopian tube, or primary peritoneal cancer. This includes high-grade serous ovarian cancer, endometroid, clear cell, mixed epithelial, undifferentiated carcinoma, transitional cell carcinoma histologies.

3.1.1.2.1 Patients with carcinosarcoma, non-epithelial, low grade tumors, or tumors with low malignant potential are excluded.

_____ 3.1.1.3 Patient must have suspected platinum-resistant disease (disease progression ≤ 6 months of platinum therapy).

_____ 3.1.1.4 Patient must be expected to undergo therapy with bevacizumab in combination with paclitaxel at recommended standard of care doses if suspected recurrence is confirmed with imaging. Patient must be able and willing to provide written informed consent.

_____ 3.1.1.5 Patient must have a life expectancy of ≥ 3 months.

_____ 3.1.1.6 Patient must have adequate bone marrow, coagulation, renal, and hepatic function; eGFR calculation ≥ 60 mL/min/1.73 m2 (within 28 days of screening CT submission)

_____3.1.1.7 Patient must demonstrate an ECOG performance status of 0-2.

Rev. Add1 _____3.1.1.8 Patient must not have undergone therapy with any VEGF monoclonal antibodies in the last twelve weeks. Patient must not have received any small molecule anti-VEGF drug within the previous 4 weeks.

_____3.1.1.9 Patient must not have undergone major surgery or radiotherapy to the pelvis or abdomen within previous 4 weeks.

_____ 3.1.1.10 Patients must not have known contraindications to bevacizumab, including but not limited to abdominal fistula, GI perforation, intra-abdominal abscess, thrombotic or hemorrhagic disorders, uncontrolled hypertension or active clinically significant cardiovascular disease, non-healing wound, ulcer, or bone fracture within previous 4 weeks.

_____ 3.1.1.11 Patient must not have untreated or symptomatic CNS metastasis.

_____3.1.1.12 Patient must not have another active (within past 3 years) or concurrent malignancy. Resected basal cell skin cancer is allowed within past 3 years.

_____ 3.1.1.13 Patient must not have contraindication to iodinated contrast.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3.1.2 Registration to Step 1

NOTE: The ACR Imaging Core Lab will evaluate the potential target lesion once all required images are received and inform the site within **five business days if patient is eligible** and may be registered to Step 1 and scheduled for perfusion CT imaging. The local site will receive notification of eligibility via RAVE.

_____ 3.1.2.1 Patient must be evaluable using RECIST 1.1 criteria.

_____ 3.1.2.2 Patient must have perfusion CT target lesion (e.g., ≥ 1 cm in both the long and short axis, at least one half of the tumor appears enhancing and solid on a contrast-enhanced scan or has an attenuation of ≥ 10 HU on the unenhanced CT scan) on a contrast-enhanced conventional CT.

_____ 3.1.2.3 Conventional chest abdomen and pelvis CT images demonstrating recurrent tumor must be submitted within 21 days from acquisition to the ACR Core Lab

_____ 3.1.2.4 Eligibility of a perfusion CT target lesion must be confirmed by the ACR Core Lab prior to study enrollment and the T0 perfusion CT scan.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Registration Procedures

Rev. Add1

4.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR Help Desk by email at <RCRHelpDesk@nih.gov>.

4.2 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

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4.3 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients.

Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.4 Downloading Site Registration Documents

Site registration forms may be downloaded from the EAE161 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol #EAE161
- Click on LPO Documents, select the Site Registration Documents link and download and complete the forms provided

4.5 Requirements for EAE161 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

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4.6 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

4.7 Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:

   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

4.8 Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

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4.9 Patient Enrollment

Patient enrollment will be performed in two steps. Patients with clinically suspected recurrent platinum-resistant, epithelial ovarian, fallopian tube or peritoneal carcinoma intended for treatment with bevacizumab and paclitaxel will consent to a review of a standard of care chest, abdomen and pelvis CT for screening (Registration Step 0; for the full list of eligibility requirements at Step 0, see Section 3.1.1). If the standard of care imaging demonstrates evidence of recurrent tumor amenable to follow up with RECIST 1.1 as assessed by the site radiologist, the images will be submitted to the ACR Core Lab to evaluate if there is a lesion amenable to perfusion CT. If a perfusion CT target lesion is present as assessed by the trial radiologist, the site will be informed via RAVE within 5 business days that the patient is eligible for the trial and the patient will be consented to enroll in the study (Registration Step 1). Patient eligibility for Registration Step 1 is determined centrally. The patient will then be scheduled for the T0 perfusion CT scan.

T0 perfusion CT scan should be performed 0-28 days from the standard of care baseline/eligibility chest, abdomen and pelvis CT. **Patients must not start standard of care therapy (bevacizumab) prior to the T0 CT Perfusion scan.** Bevacizumab and paclitaxel should be initiated 0-7 days from the T0 perfusion CT.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.10 Step 0 Registration Content Requirements

NOTE: Patients must not start protocol procedures prior to Step 0 registration.

4.10.1 The following information will be collected at the time of preregistration (Step 0).

4.10.1.1 Protocol Number

4.10.1.2 Investigator Identification

4.10.1.2.1 Institution and affiliate name

4.10.1.2.2 Investigator's name

4.10.1.3 Patient Identification

4.10.1.3.1 Patient's initials (first and last)

4.10.1.3.2 Patient's Hospital ID and/or Social Security number

4.10.1.3.3 Patient demographics

- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.10.2 Eligibility Verification

Patient must be consented to and be considered a viable candidate for registration to Step 0 of ECOG-ACRIN EAE161.

Patients must meet all of the eligibility requirements listed in Section 3.1.1.

4.11 Step 1 Registration Content Requirements

Once the ACR Core Lab confirms the patient's eligibility with a review of the standard of care chest, abdomen and pelvis CT, the patient will be permitted to proceed with enrollment.

4.11.1 The following information will be collected at the time of registration (Step 1).

4.11.1.1 Protocol Number

4.11.1.2 Investigator Identification

4.11.1.2.1 Institution and affiliate name

4.11.1.2.2 Investigator's name

4.11.1.3 Patient Identification

4.11.1.3.1 Patient's initials (first and last)

4.11.1.3.2 Patient's Hospital ID and/or Social Security number

4.11.1.3.3 Patient demographics
- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.11.2 Eligibility Verification

Patient must be consented to and have received ACR Imaging Core Lab confirmation of eligibility for registration to Step 1 of ECOG-ACRIN EAE161.

4.12 Patients must meet all of the eligibility requirements listed in Section 3, including ACR Imaging Core Lab Confirmation of a target lesion for perfusion CT.

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4.12.1 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site.To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.13 Additional Requirements

4.13.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.13.2 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. See Section 4.13.1 for instructions on accessing Medidata Rave.

4.13.3 Digital Image Submission Using TRIAD

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM images and other objects. TRIAD anonymizes and validates the images as they are transferred.

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TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account and be registered as an AP, NPIVR or IVR. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- To submit images, the site physics user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role. RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

4.14 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If the T0 perfusion CT is not performed, the T1 perfusion CT should not be performed, and no further clinical data beyond baseline data will be collected for the study.

Baseline and follow-up data will be collected on all patients who receive the T0 perfusion CT, even if they do not receive the T1 perfusion CT and/or do not

receive bevacizumab therapy. Data must be submitted through Medidata Rave according to the schedule in the EAE161 Forms Completion Guidelines.

5. Treatment Plan

5.1 Perfusion CT with Iodinated Contrast

Perfusion CT will be performed at participating institutions that are ACR certified and qualified for dynamic perfusion CT imaging. The participating institutions must have the appropriate multidetector CT scanner technology for the required scanning protocols. For an institution to be eligible, the multidetector CT scanner technology should have 64 or higher detector rows and should be capable of imaging a ≥ 2.8 cm section of the abdomen and pelvis repeatedly every 1-3 seconds for a period up to 2 minutes. ACR Core qualification of the perfusion CT scanner is required for T0 and T1 perfusion CT imaging. This qualification is independent and separate from the ACR or ICACTL accreditation requirement.

For the perfusion CT, the **local site** radiologist will assess the potential target lesion on the standard of care chest abdomen and pelvis CT scan using the following criteria:

a) ≥ 1 cm in both the long and short axis;
b) At least one-half of the tumor appears enhancing and solid on a contrast-enhanced scan or an attenuation of ≥ 10 HU on an unenhanced CT scan.

The potential target lesion **will be confirmed** by the **ACR Imaging Core Lab** to ascertain whether:

a) The size of the tumor is ≥ 1 cm in both the long and short axis;
b) At least one-half of the tumor appears enhancing and solid on a contrast-enhanced scan or an attenuation of ≥ 10 HU on an unenhanced CT scan.

This will determine eligibility for perfusion CT.

Image Submission and Review Timeline

- Screening Chest, Abdomen and Pelvis CT must be submitted to the ACR Core Lab via TRIAD within 21 days following acquisition.
- The ACR Imaging Core Lab will evaluate the potential target lesion once all required images are received and inform the site within **five business days if patient is eligible** and may be registered to Step 1 and scheduled for perfusion CT imaging.
- T0 perfusion CT must be submitted within 48 hours following acquisition.
- T1 perfusion CT must be submitted within 48 hours following acquisition.

5.2 Perfusion CT Scan Timeline and Analysis

5.2.1 T0 Perfusion CT should be performed within 4 weeks after standard of care imaging to assess for a perfusion CT target lesion and within 7 days prior to bevacizumab initiation.

5.2.1.1 The baseline T0 perfusion CT scan must be performed before initiation of bevacizumab treatment.

5.2.2 T1 Perfusion CT should be performed within 15 days (+/- 2 days) post-bevacizumab initiation and before second dose of bevacizumab.

5.3 Perfusion CT Scanning Procedures

5.3.1 Additional information regarding the perfusion CT scan parameters can be found in the EAE161 Imaging Manual. The Imaging Manual is located on the CTSU EAE161 page located under the LPO tab in the Case Reports Forms section. The manual outlines scanner qualification, imaging submission, tumor eligibility etc in relation to this trial.

5.3.2 T0 Perfusion CT Scan Protocol

5.3.2.1 Localization scan: Refer to Imaging Manual for details.

5.3.2.2 Iodinated Intravenous Contrast and Perfusion CT Imaging: A single dose of low or isoosmolar iodinated contrast ≤ 150 cc will be administered in two separate boluses. The first bolus will be done for the CT imaging that looks at targeted tumor perfusion of a ≥ 4cm section of the abdomen/pelvis (covering the maximal cross-section of or the whole potential target lesion). The second bolus will be administered after a delay of ten minutes for CT scanning of the chest, abdomen and pelvis to determine global tumor perfusion. The details are as follows:

Target Tumor perfusion CT: Dynamic perfusion CT imaging of the ≥ 4cm section of the abdomen/pelvis will be performed with 0.7 to 0.8 ml per kg of body weight low osmolar iodinated contrast (50-70 ml) at a concentration of 300 – 370 mgI/ml. The contrast will be injected at a rate of 2 to 5 ml/sec. A scanning delay of ≤ 5-15 seconds between scanning and injection is allowed.

Global tumor perfusion CT: CT imaging of the chest, abdomen and pelvis will be performed with 0.7 to 1.0 ml per kg of body weight low osmolar iodinated contrast (80-100ml) at a concentration of 300 – 370 mgI/ml. The contrast will be injected at a rate of 2 to 5 ml/sec. CT imaging of the chest, abdomen and pelvis will be performed in a single acquisition beginning at the apex of the chest and continuing through the pubic symphysis. Scanning will be initiated 60 seconds after the initiation of the intravenous contrast bolus. ***The volume of second bolus of contrast will be determined by volume of contrast injected for the targeted perfusion CT to ensure that the total volume does not exceed 150ml.***

5.3.3 T1 Perfusion CT Scan Protocol

5.3.3.1 Prior to T1 scan: Site to assess kidney sufficiency per local institution standard.

5.3.3.2 Localization scan: Refer to Imaging Manual for details.

5.3.3.3 Iodinated Intravenous Contrast and Perfusion CT Imaging: A single dose of low or isoosmolar iodinated contrast ≤ 150 cc will be administered in two separate boluses. The first

bolus will be done for the CT imaging that looks at targeted tumor perfusion of a ≥ 4cm section of the abdomen/pelvis (covering the maximal cross-section of or the whole potential target lesion). The second bolus will be administered after a delay of ten minutes for CT scanning of the chest, abdomen and pelvis to determine global tumor perfusion.

The details are as follows:

Target Tumor perfusion CT: Dynamic perfusion CT imaging of the ≥ 4cm section of the abdomen/pelvis will be performed with 0.7 to 0.8 ml per kg of body weight low osmolar iodinated contrast (50-70 ml) at a concentration of 300 – 370 mgI/ml. The contrast will be injected at a rate of 2 to 5 ml/sec. A scanning delay of ≤ 5-15 seconds between scanning and injection is allowed.

Global tumor perfusion CT: CT imaging of the chest, abdomen and pelvis will be performed with 0.7 to 1.0 ml per kg of body weight low osmolar iodinated contrast (80-100ml) at a concentration of 300 – 370 mgI/ml. The contrast will be injected at a rate of 2 to 5 ml/sec. CT imaging of the chest, abdomen and pelvis will be performed in a single acquisition beginning at the apex of the chest and continuing through the pubic symphysis. Scanning will be initiated 60 seconds after the initiation of the intravenous contrast bolus. ***The volume of second bolus of contrast will be determined by volume of contrast injected for the targeted perfusion CT to ensure that the total volume does not exceed 150ml.***

5.3.3.4 Perfusion CT scan analysis: Perfusion CT images submitted to the ACR core lab will then be transferred to the Tumor Imaging Metrics Core (TIMC) laboratory at Massachusetts General Hospital for post-processing and analysis by the trial radiologist. Post-processing of the dynamic CT data for analysis of perfusion characteristics will be performed on a dedicated CT workstation. Semi-quantitative assessment of targeted tumor perfusion involves generation of perfusion maps followed by manual outlining of the tumor ROI by the trial radiologist (Imaging Manual). The acquired perfusion CT images of the outlined tumor will depict the rates of wash-in and wash-out of contrast from the tumor, which will be compared with those of the aorta (or its major branches) to calculate the tumor vascular parameters: tumor blood flow (BF), blood volume (BV) and permeability surface area product (PS). In order to study reproducibility, the same perfusion data set will be analyzed using the perfusion CT by two different radiologists. The perfusion CT data sets will be analyzed on different perfusion CT software platforms selected to be neutral to scanner vendor to establish the ability of

perfusion CT to depict changes in tumor vascularity independent of analytical post processing software used. GE Healthcare software will be used for the first processing and MIStar software will be used for the second processing. Global tumor perfusion assessment will be performed using eMASS software at Dr. Andrew Smith's Advanced Imaging Lab at the University of Alabama at Birmingham (UAB). Refer to protocol Section 7.4.

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5.4 Standard of Care Systemic Therapy

Patients will initiate standard of care systemic therapy with bevacizumab and paclitaxel chemotherapy 0-7 days from T0 perfusion CT.

Paclitaxel and Bevacizumab

- Paclitaxel 80mg/m^2 can be delivered intravenously:
  a. Days 1, 8, 15 and 22 of a 28-day cycle OR
  b. Days 1, 8, 15 of a 28-day cycle
- Bevacizumab 10mg/kg, to be delivered intravenously every two weeks

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5.5 Adverse Event Reporting Requirements

All toxicity grades described in this protocol and all reportable adverse events on this protocol will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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5.5.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents/procedures.

5.5.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an imaging agent/procedure in humans, whether or not considered imaging agent/procedure related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to imaging agent/procedure.
Unlikely	The AE is *doubtfully related* to imaging agent/procedure.
Possible	The AE *may be related* to imaging agent/procedure.
Probable	The AE is *likely related* to imaging agent/procedure.
Definite	The AE is *clearly related* to imaging agent/procedure.

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the imaging agent/procedure. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.

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5.5.3 Mechanisms for Adverse Event Reporting

Routine reporting: Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to section 4 of the protocol for more information on how to access the Medidata Rave system and the EAE161 forms packet for instructions on where and when adverse events are to be reported routinely.

Expedited reporting: In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provide information and instructions regarding expedited adverse event reporting.

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5.5.4 Expedited Adverse Event Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

For this study, a CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov so that ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner. In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to:

- the AE Team at ECOG-ACRIN (857-504-2900)
- the FDA (1-800-FDA-1088)

An electronic report MUST be submitted via CTEP-AERS immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to FDA (800-332-0178) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.5.5 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of imaging agent/procedure vs. ≥ 30 days after the last administration of imaging agent/procedure)
- the relationship to the study treatment (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol EAE161 and outline the specific expedited adverse event reporting requirements for study EAE161.

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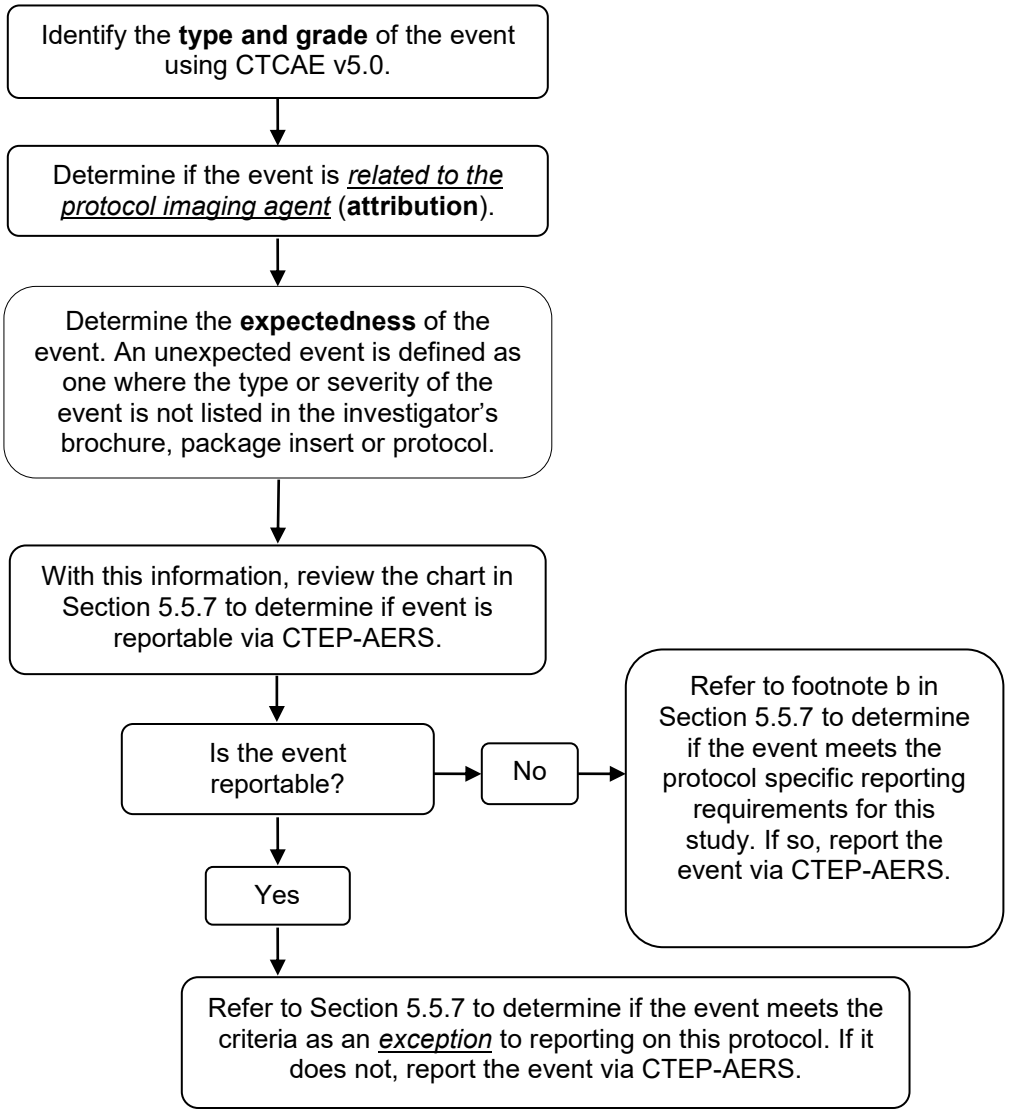
5.5.6 Steps to determine if an adverse event is to be reported in an expedited manner



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5.5.7 Expedited Reporting Requirements for protocol EAE161

Expedited reporting requirements for adverse events occurring within 24 hours of the CT Perfusion and last dose of the iodonated contrast agent)

Attribution[c]	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a A death occurring while on study or within 24 hours of the CT Perfusion and last dose of the iodinated contrast agent requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: Any death that occurs > 24 hours after the CT Perfusion and last dose of the iodinated contrast agent and is attributed possibly, probably, or definitely to the CT Perfusion and iodinated contrast agent treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

c For this protocol, attribution is assessed as the relationship between the adverse event and the MRI/gadolimium-based contrast agent.

- Other recipients of adverse event reports and supplemental data

  Adverse events determined to be required expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

- Second Primary Cancer Reporting Requirements

  All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

  - **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.6 <u>Off-study Criteria</u>

The following are situations that would result in the patient being removed from the study:

- Patient withdraws consent.
- Patient experiences unacceptable toxicity from perfusion CT imaging.
- Patient does not receive T0 CT Perfusion Scan

All data up until the date the patient was removed from the study are still required to be submitted.

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5.7 Duration of Follow-up

Patients will undergo medical history, physical examination, and CA-125 every nine weeks (+/-7 days) until death, withdrawal of consent, or up until 18 months of the last accrued patient. In addition, patients will undergo imaging assessment of the abdomen and pelvis +/- chest (chest only for patients with evidence of measurable disease on baseline chest imaging) every nine weeks (+/- 7 days) for the first year and every 12 weeks (+/- 7 days) thereafter until withdrawal of consent, death, or until 18 months after the last patient accrual. Follow-up data should be submitted quarterly for patients on study < 2 years and every 6 months thereafter. Data can be obtained via clinical visits, imaging visits, phone calls, etc. If multiple medical history, physical examination, CA-125 and imaging occur during the follow-up period, site should report the last test/visit occurring during the follow-up period on the follow-up form.

Treatment response per RECIST 1.1, drug administration dates and treatment doses will be recorded for each patient. If bevacizumab is discontinued, date and reason should be recorded.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every nine weeks (+/- 7 days) in the first year and every twelve weeks (+/- 7 days) after the first year.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [10]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm

with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum

of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before registration.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be

measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, the PET portion of the CT imaging will not be included in the follow-up assessment.

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response in recurrent ovarian cancer have been published [27]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [28].

Cytology, Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g.,

residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

NOTE: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression, See Section 6.1.5.2.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks (+/- 2 days) (in general, not less than six to eight weeks).

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

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

Non-CR/Non-PD

Persistence of one or more non-target lesion(s).

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression

status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or

b) there is new pathological confirmation that it is disease (regardless of size).

new effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 9 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

6.1.4.5 Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 9 weeks (+/-7 days) (in general, not less than six to eight weeks).

7. Study Parameters

7.1 Study Parameters

7.1.1 Scanner qualification for perfusion CT. Refer to the Imaging Manual on the CTSU EAE161 page for full scanner qualification parameters. The Imaging Manual is located under the LPO tab in the Case Reports Forms section on the EAE161 page.

7.1.1.1 A multidetector CT (64 slice or greater) scanner capable of imaging a 2.8 cm or wider section of the abdomen/pelvis repeatedly every 1-3 seconds for up to 2 minutes is required.

7.1.1.2 ACR Core Lab qualification of the perfusion CT scanner is required prior to enrollment of study participants. This qualification is independent and separate from the clinical imaging ACR or ICACTL accreditation requirement.

7.1.1.3 Sites are required to submit two (2) phantom series: one water section and one high contrast spatial resolution section. This will require the use of the quality control phantom supplied by the CT scanner vendor. The water and high contrast spatial resolution sections of the phantom are to be scanned according to the perfusion CT protocol.

7.1.1.4 The first imaging dataset of the first enrolled patient submitted within 48 hours of acquisition will serve as the final qualification scan.

7.1.2 Screening (up to -28 days from Registration to Step 0)

- A signed consent form will be obtained prior to screening.
- Patient undergoes SOC Chest, Abdomen, Pelvis CT. Patient images will be submitted to ACR Imaging Core Lab for confirmation of target lesion for perfusion CT within 21 days of acquisition.
- Review of CT imaging will be completed by ACR Imaging Core Lab and the site will be informed whether or not the patient is eligible for the perfusion CT component of the trial, as well as the eligible target lesion if eligible, within 5 business days of the SOC chest, abdomen and pelvis CT image submission through Medidate Rave. Patients determined to be eligible can then proceed with Step 1 Registration.

  NOTE: Patient needs to sign imaging consent prior to Registering to Step 1.
- If an eligible target lesion is present, the ACR Core lab will provide an image annotating the lesion to the site through Medidata Rave. This image should be provided to the site radiologist for use in perfusion CT scanning.
- The screening assessment will include collection of demographics, tumor histology, date of last platinum-based

chemotherapy, eGFR, calculation, CA-125 +/- 28 days (if available) from Step 0 Registration, and name/date of any prior VEGF therapy.

7.1.3 Visit 1 (+0 to 28 days from the SOC Chest, Abdomen, Pelvis; Prior to treatment)

- Medical history, demographics, height, weight, and physical exam will be obtained. This information does not need to be repeated if available in clinical records and dated within 28 days from Step 0 registration.
- Patient will undergo T0 perfusion CT.
  - CA-125 to be collected (+/-) 2 days of T0 perfusion CT.
- An adverse event evaluation will be performed by phone at 24 hours.

7.1.4 Visit 2 (+0 to 7 days from the T0 perfusion CT)

- Treating physician will initiate bevacizumab plus paclitaxel treatment.

7.1.5 Visit 3 (+15 days +/- 2 days from the initiation of bevacizumab)

- Prior to T1 scan: Site to assess renal function per local standard.
- Patient will undergo T1 perfusion CT. T1 perfusion CT should be performed after the first dose of bevacizumab but before the second dose.
  - CA-125 to be collected (+/-) 2 days of T1 perfusion CT.
- An adverse event evaluation will be performed by phone at 24 hours.

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7.1.6 Follow-up occurs until withdrawal of consent, death, or until 18 months after the last patient accrual. Data to be submitted quarterly if patient is on study < 2 years, and every six months thereafter. If any of the visits/tests below happen more than once during the follow-up period, sites should report the last event occurring in the follow-up period on the follow-up form.

- Medical history, physical exam and CA-125 every 9 weeks (+-7 days)
- For the first year patient undergoes SOC Abdomen, Pelvis CT +/- Chest (chest only done if patient has evidence of measurable disease on baseline chest imaging) every 9 weeks (+/- 7 days). After year one, imaging will be completed every 12 weeks.
- Objective response based on standard anatomic response evaluation criteria (RECIST 1.1) reported very 9 weeks (+/- 7 days) then, after year one, every 12 weeks.
- Quarterly report of interval therapy since last point of follow up.

7.1.7 Date of progression

- Report date.
- Report basis for assessing progression: CA-125, imaging results, physical exam, etc.

- Report interval therapy since last point of follow up.

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7.1.8 Date of death (if applicable during follow-up)

- Report date.
- Report interval therapy since last point of follow up

Rev. Add1

7.2 Schedule of Procedures

	Screening: Up to 28 Days from Step 0 Registration	Visit 1 (T0 Scan): +0 to 28 Days from SOC Chest Abdomen & Pelvis CT; prior to start of treatment	Visit 2: +0 to 7 Days After Visit 1	Visit 3 (T1 Scan): +15 +/- 2 Days After Visit 2[4]	Follow-up[8]
Consent to Screening	X				
SOC Chest, Abdomen & Pelvis CT	X				X[1]
Consent to Study		X			
Medical History and Physical examination		X			X[6]
Assessment of Renal Function[2]	X				
CA-125[3]	X	X		X	X[6]
T0 Perfusion CT		X			
Initiation of Bevacizumab Therapy + Paclitaxel			X		
T1 Perfusion CT[4]				X	
Assess renal function per site standard of care				X	
Adverse Event Collection/Reporting[5]		X		X	
Report of therapy, progression/death[7]					X

Rev. Add1

1. Follow-up imaging can just be CT of Abdomen and Pelvis, chest only needs imaging if patient had evidence of measurable disease on baseline chest imaging. Patients will be imaged every 9 weeks (+/- 7 days) the first year and thereafter every 12 weeks (+/- 7 days). Follow-up will occur every 3 months if patient is < 2 years from study entry, and every 6 months thereafter. Study follow-up will continue until 18 months after the last accrued patient. Report interval therapy since last point of follow-up.
2. Assess Creatinine and eGFR calculation within 28 days of Step 0; must be > 60 mL/min/1.73 m2.
3. CA-125 to be submitted, ***if collected***, within 28 days prior to Step 0 Registration; CA-125 to be collected (+/-) 2 days of T0 and T1 perfusion CT.
4. T1 Perfusion CT should be performed after the first dose of bevacizumab but before the second dose of bevacizumab.
5. Adverse event collection will be performed by phone 24 hours following acquisition of perfusion CT.

Rev. Add1

6. Medical history, physical examination and CA-125 should be completed every 9 weeks (+/- 7 days) until death or until study follow-up completed (18 months after the last patient accrued).
7. Report date of progression/death; report basis of assessing progression (CA125, imaging results, physical exam, etc); report interval therapy since last point of follow up.

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8. For tests/exams happening more than one time during a follow-up period, sites should report the last reported test/exam that occurred on the follow-up form. Follow-up form to be completed quarterly for the first two years and every six months thereafter.

7.3 Continuing Quality Assurance of Perfusion CT Scans

Sites performing perfusion CT scans are required to submit images to the ACR Core Lab via TRIAD within 48 hours of acquisition of the T0 and T1 perfusion CT scans. Submissions to the ACR Imaging Core Lab must include a completed Image Transmittal Worksheet (ITW) and site-completed report of the dose length product (DLP) from each perfusion CT exam. These forms will include an ACR identification number and technical information for the perfusion CT scans.

7.3.1 Scanning Protocol

The perfusion CT scan protocols from each site will be reviewed by the trial radiologist prior to scanning of the first patient to ensure that perfusion CT protocol of each site is congruent with the study protocol. Subsequently, timing of the scans (T0 and T1), kVp, mA, slice thickness and time interval used for the perfusion CT scans as noted in the DICOM header will be checked against the protocol (see Imaging Manual). Discrepancies will be noted and communicated to the site within one week to ensure that concerns will be corrected in the next scan.

7.3.2 Radiation Dose

From the information recorded in the ITW (T0 and T1 forms), the effective dose and skin dose of perfusion CT scans will be calculated and compared with those listed in Imaging Manual. If discrepancies larger than 30% from pre-specified dose limits are present, investigation as to the cause of the discrepancies will be initiated by the medical physicist immediately. These calculations will occur within 14 days of the perfusion CT image submission.

7.3.3 Image Noise

If the standard deviation of CT numbers inside a region in the paraspinal muscle recorded on the ITW and the technical assessment forms (T0, and T1 forms) is outside of the range of 17-48, investigation will be initiated by the medical physicist.

7.3.4 Image Quality

The Imaging Co-PI will train the ACR Imaging Core Lab staff in the technical evaluation of the perfusion CT data. The initial technical analysis will be performed under the ACR Core lab and trial team radiologist supervision.

All perfusion CT exams will be analyzed within 14 days of image submission for correct scanning procedure, selection of target lesion and adherence to radiation dose limits by a Core Lab technologist under the supervision of the ACR Medical Physicist and Radiologist. All problems and difficulties associated with the analysis of perfusion CT will be identified and resolved.

7.4 Central Reader Study

7.4.1 Primary Aim

For the primary aim, all perfusion CT analyses will be performed centrally by a single experienced reader (referred to as the primary reader), blinded to both the time point of the scan (T0 or T1) and patient data. T0 and T1 scans will be read as a pair together and BF change will be ***available*** to sites within 14 days of when BOTH scans have been submitted to the Core Lab

Perfusion maps will be created using a single post-processing platform, Body Tumor CT Perfusion Software version 4D (GE Healthcare, also used in ACRIN 6695). The region of interest on the target lesion will be drawn by the primary reader according to a pre-defined protocol. From this, BF and BV values will be calculated. Direction of change in these values from T0 and T1 will be noted.

7.4.2 Secondary and Exploratory Aims

For secondary aim 2.2.5, evaluating whether the association between change in perfusion CT parameters and patient outcome is stable when analyzed with different commercially-available software, image analysis will be performed by the primary reader in batch at or before the completion of cohort follow-up, where a second set of perfusion maps will be created using a different post-processing platform by a non-GE vendor, MIStar CT Perfusion Body Tumor Module (Apollo Medical Imaging Technology). Again, reads will be performed blinded to both the time point of the scan (T0 or T1) and patient data. The region of interest on the target lesion will be drawn according to a pre-defined protocol. From this, BF and BV values will be calculated. Direction of change in these values from T0 and T1 will be noted.

For exploratory aim 2.3.2, evaluating the reliability of perfusion CT parameters using different readers and different post-processing software, analysis will be performed by a second, independent reader in batch at or before the completion of cohort follow-up, where regions of interest will be drawn on the same target lesion according to the same pre-defined protocol as performed by the primary reader. This will be carried out on the two sets of perfusion maps from the two different vendors (GE Healthcare and MIStar). From this, BF and BV values will be calculated. Direction of change in these values from T0 and T1 will be noted.

For exploratory aim 2.3.1, evaluating the impact of multiple target lesions on the association between change in perfusion CT parameters and PFS, analysis will be performed by the primary reader in batch at or before the completion of cohort follow-up. Analysis will be performed only on the subset of the cohort that demonstrate >1 eligible target lesion within the perfusion CT image volume. Regions of interest will be drawn according to a pre-defined protocol on all eligible target lesions. From this, BF and BV values will be calculated for all target lesions. Direction of change in these values from T0 and T1 will be noted.

For exploratory aim 2.3.3, the analysis of vascular tumor burden (VTB) will be performed centrally by a single experienced reader blinded to clinical outcomes data. VTB analysis will be performed at the Advanced Imaging Lab at the University of Alabama at Birmingham (UAB) using eMASS software, an advanced image processing software platform used to quantify global tumor perfusion as assessed by measuring VTB. Analysis will be selected per RECIST 1.1 guidelines. Free-form regions of interest will be drawn around the periphery of the target lesions. The software automatically extracts the VTB from the ROIs and calculates the total VTB (sum of VTB from individual target lesions) and percent change in total VTB. This data and the DICOM header information are then exported into a database. The software also generates a summary image, and individual key images are automatically archived for quality control purposes.

8. Statistical Considerations

8.1 Endpoints

8.1.1 Primary aim (8.2.1): The endpoint for the primary aim is progression-free survival (PFS). PFS will be calculated as the time to progression or death from the T1 scan (day 15 +/- 2 days post bevacizumab initiation). Patients without documented progression or death will be censored as of the last follow-up date.

8.1.2 Secondary aim #1 (8.2.2.1): The endpoint for secondary aim #1 is progression-free survival (PFS). PFS will be defined as per the primary aim.

8.1.3 Secondary aim #2 (8.2.2.2): The endpoint for secondary aim #2 is progression-free survival (PFS). PFS will be defined as per the primary aim.

8.1.4 Secondary aim #3 (8.2.2.3): The endpoint for secondary aim #3 is objective response rate, based on standard anatomic response evaluation criteria (RECIST 1.1).

8.1.5 Secondary aim #4 (8.2.2.4): The endpoint for secondary aim #4 is progression-free survival (PFS). PFS will be defined as per the primary aim.

8.1.6 Secondary aim #5 (8.2.2.5): The endpoint for secondary aim #5 is progression-free survival (PFS). PFS will be defined as per the primary aim.

8.1.7 Exploratory aim #1 (8.2.3.1): The endpoint for exploratory aim #1 is progression-free survival (PFS). PFS will be defined as per the primary aim.

8.1.8 Exploratory aim #2 (8.2.3.2): The endpoint for exploratory aim #2 is the reliability of CT perfusion measures, as assessed by the intraclass correlation coefficient (ICC).

8.1.9 Exploratory aim #3 (8.2.3.3): The endpoint for exploratory aim #3 is progress-free survival (PFS). PFS will be defined as per the primary aim.

8.2 Aims

8.2.1 Primary Aim

To evaluate whether those patients with an increase in perfusion CT tumor blood flow (BF) from T0 to T1 demonstrate poorer progression-free survival (PFS) compared to those patients with a decrease in BF from T0 to T1, among platinum-resistant, recurrent ovarian cancer patients treated with bevacizumab in combination with paclitaxel.

The PFS of patients with increased (≥ 0) tumor BF from T0 to T1 will be compared with that of patients with decreased (< 0) tumor BF from T0 to T1. Kaplan-Meier survival curves will be generated, and a one-sided log-rank test will be used to compare PFS between the two groups.

The primary aim will be analyzed from the central readings performed by the primary reader using the GE Healthcare Body Tumor CT perfusion platform (refer to Section 7.4).

8.2.2 Secondary Aims

1. *To evaluate whether change in perfusion CT tumor BF from T0 to T1, as a continuous variable, is associated with PFS.*

   To examine the association between continuous change in tumor BF (T0 to T1) and PFS, Cox proportional hazards regression will be used. Both a univariable and a multivariable model will fit, with the multivariable model adjusting for potential confounders, including patient age and baseline cancer stage/histology. Hazard ratios and associated 95% CIs will be reported.

   Finally, if the primary endpoint is not successful in declaring a statistically significant difference in PFS between those patients with increase (≥ 0) versus decrease (< 0) in tumor BF (T0 to T1), then an optimal threshold for change in tumor BF will be identified using recursive partitioning in a conditional inference framework (25). A 95% confidence interval will be derived using the bootstrap technique.

   Secondary aim #1 will be analyzed from the central readings performed by the primary reader using the GE Healthcare Body Tumor CT perfusion platform (refer to Section 7.4).

2. *To evaluate whether changes in perfusion CT tumor blood volume (BV) or permeability surface product area (PS) from T0 to T1 are associated with PFS.*

   The PFS of patients with increased (≥ 0) tumor BV from T0 to T1 will be compared with that of patients with decreased (< 0) tumor BV from T0 to T1. Kaplan-Meier survival curves will be generated and a one-sided log-rank test will be used to compare PFS between the two groups. In addition, Cox proportional hazard models will be fit, similar to secondary aim #1.

   The analysis for PS will be conducted in a similar manner.

   Secondary aim #2 will be analyzed from the central readings performed by the primary reader using the GE Healthcare Body Tumor CT perfusion platform (refer to Section 7.4).

3. *To evaluate whether changes in perfusion CT tumor BF, BV, or PS from T0 to T1 are associated with response rate according to the standard anatomic response evaluation criteria (RECIST 1.1).*

   Fisher's exact test, or chi-squared test as appropriate, will be used to test the association between change in BF, BV, or PS from T0 to T1 and tumor response, where tumor response is defined using RECIST 1.1, and each CT perfusion parameter is dichotomized using a change threshold of increase (≥ 0) versus decrease (< 0).

   Secondary aim #3 will be analyzed from the central readings performed by the primary reader using the GE Healthcare Body Tumor CT perfusion platform (refer to Section 7.4).

4. *To identify which combination of perfusion CT parameters, including tumor BF, BV, and PS, can serve to optimally distinguish patients in terms of PFS outcome.*

   To identify which combination of perfusion CT parameters can serve to optimally distinguish patients in terms of PFS outcome, a multivariable Cox proportional hazards regression model will be developed, including change in each of tumor BF, BV, and PS (T0 to T1) as potential predictors. A penalized regression technique will be considered, such as elastic net or ridge regression with tuning parameter selected by 10-fold cross-validation, in order to prevent over-fitting and to improve prediction performance.

   The estimated performance of the resulting model will be assessed through the C-statistic, using nested cross-validation. [34])

   In addition to the above multivariable Cox regression model, potential binary cut-offs for the combination of parameters will be explored using recursive binary partitioning in a conditional inference framework to develop a tree-structured survival model (25).

   Secondary aim #4 will be analyzed from the central readings performed by the primary reader using the GE Healthcare Body Tumor CT perfusion platform (refer to Section 7.4).

5. *To evaluate whether the association between change in perfusion CT parameters and treatment outcome (PFS or tumor response) is stable when analyzed with various commercially-available post-processing software.*

   Two software platforms, Body Tumor CT Perfusion Software version 4D (GE Healthcare, also used in ACRIN 6695) and MIStar CT Perfusion Body Tumor Module (Apollo Medical Imaging Technology), will be evaluated using the identical set of cases and CT images, with the same perfusion CT parameters computed at T0 and T1. For the PFS outcome, we will first determine if the primary endpoint comparison yields the same conclusion across the software platforms. Next, we will fit Cox regression models and report hazard ratios across platform for each CT perfusion parameter, as outlined in secondary aims #1 and #2.

   For the response outcome, we will report the result of Fisher's exact test, or chi-square test as appropriate, across the software platforms, as outlined in secondary aim #3.

   Secondary aim #5 will be analyzed from the central readings performed by the primary reader (refer to section 7.4), where the MIStar readings will be done at or before the completion of cohort follow-up.

8.2.3 Exploratory Aims

1. *In the subset of patients with multiple, eligible perfusion target lesions within the CT imaging volume, we will describe the variability of perfusion CT changes across different lesions within the same patient, and evaluate the impact of multiple target*

lesions on the association between change in perfusion CT parameters and PFS.

The number of subjects in the study cohort with multiple, eligible perfusion target lesions will be reported, as well as distributional summary statistics of the number of lesions per patient, lesion size, and change in perfusion CT parameters for those subjects with multiple perfusion target lesions.

We will also explore reassessing the primary endpoint and secondary endpoints #1 and #2, where, for subjects with multiple, eligible perfusion target lesions, in place of the using change in CT perfusion parameters (T0 to T1) corresponding to the single, original target lesion, we will use a summary statistic (mean, median, max) across the multiple lesions within a patient.

Secondary aim #4 will be analyzed from the central readings performed by the primary reader using the GE Healthcare Body Tumor CT perfusion platform (refer to Section 7.4).

2. *To evaluate the reliability of perfusion CT parameters by analyzing the same perfusion imaging dataset using different readers and different post-processing software.*

   Refer to Section 7.4. For all enrolled patients, we will estimate the reliability of CT perfusion parameters by having both the T0 and T1 scans read by a second, independent reader, in addition to the primary reader, across two different software platforms, Body Tumor CT Perfusion Software version 4D (GE Healthcare, also used in ACRIN 6695) and MIStar CT Perfusion Body Tumor Module (Apollo Medical Imaging Technology). The reliability intraclass correlation coefficient (ICC) and corresponding 95% confidence interval will be derived from an appropriately constructed random effects ANOVA model (26). Separate estimates of reliability will be derived and reported for each software platform by time point.

   In addition, method comparison and quantification of agreement of the software platforms will be conducted using the Bland-Altman approach (26). This will be done both separately by reader, and (assuming good reliability) using the average across the two readers.

3. *To evaluate whether change in global vascular tumor burden from T0 to T1 is associated with PFS, and with changes in BF, BV, or PS.*

   To examine the association between vascular tumor burden (VTB) and PFS, Cox proportional hazards regression will be used. VTB will be acquired for all enrolled patients (refer to section 7.4). Both a univariable and a multivariable model will be fit for continuous change in VTB (T0 to T1), with the multivariable model adjusting for potential confounders, including patient age and baseline cancer stage/histology.

   In addition to evaluating association with PFS on a continuous scale, we will seek to identify a threshold for decrease in VTB to

categorize responders versus non-responders. In previous work for renal cell carcinoma, a threshold of a 30% decrease in VTB was used to define responders [30]. We will examine this same pre-specified threshold for platinum-resistant, recurrent ovarian cancer patients treated with bevacizumab in combination with paclitaxel using a one-sided log rank test. Finally, as the optimal threshold for VTB for recurrent ovarian cancer patients may differ from that of renal cell carcinoma patients, an optimal threshold for change in VTB will be identified using recursive partitioning in a conditional inference framework (25). A 95% confidence interval will be derived using the bootstrap technique.

The spearman correlation coefficient between VTB and each perfusion CT parameter (BF, BV, and PS), along with corresponding 95% confidence interval, will also be reported.

8.3 Sample Size Considerations

The rate of increase versus decrease in CT perfusion tumor blood flow (BF) in ACRIN 6695/GOG-0262 (baseline to T2, or day 8-10 post bevacizumab initiation) was 14% vs. 86%, and the PFS-6 rate in the trial was 96%, with increase in BF being associated with worse patient outcomes. However, unlike ACRIN 6695/GOG-0262, the population for the proposed study will be patients with recurrent disease. Given this population, we expect a lower PFS-6 rate and, correspondingly, a larger proportion of patients with increase in BF at time point T1 (day 15 +/- 2 days post bevacizumab initiation). We will examine the effect on sample size using breakdowns of 50%/50% up to 80%/20% for BF increase versus decrease.

In addition, in ACRIN 6695/GOG-0262 a difference of 4.1 months in median PFS was observed among patients with increase in BF versus decrease in BF. Further, the AURELIA trial, studying a similar cohort of recurrent disease patients, demonstrated a median PFS of 10.4 months (95% CI 7.9 to 11.9 months) in the bevacizumab + paclitaxel arm [2, 35]). As the proposed trial will consist of bevacizumab plus paclitaxel for all patients, we would expect roughly similar PFS in our cohort overall, but with the expectation that the subgroup of patients exhibiting an increase in BF will exhibit a lower median PFS compared to those with a decrease in BF. We will thus split the difference in median PFS around the median of 10 months demonstrated in AURELIA, and will examine the effect on sample size using a difference in median PFS among the two groups ranging from 4 to 4.5 months.

We assume accrual over a 24-month period, with 18 months of patient follow up. However, we note that a 6-month ramp-up period will likely be needed for site qualification before steady state accrual is achieved. Using a one-sided log-rank test with an alpha level of 0.1 and power of 80%, and allowing for an inflation factor of 15% to account for cases with non-analyzable scans and/or cases lost-to-follow up, results in the following sample sizes shown in the table below. Calculations were performed using PASS15 [29,36].

Percent of cohort with increase in tumor BF vs. decrease	Median PFS for patients with increase in tumor BF	Median PFS for patients with decrease in tumor BF	Difference in median PFS	Overall required number of events	Overall required sample size	Final sample size allowing for 15% inflation
50% / 50%	7.75 mos	12.25 mos	4.5 mos	88	102	118
50% / 50%	7.88 mos	12.13 mos	4.25 mos	98	114	132
50% / 50%	8 mos	12 mos	4 mos	111	129	149
60% / 40%	7.75 mos	12.25 mos	4.5 mos	95	108	125
60% / 40%	7.88 mos	12.13 mos	4.25 mos	107	122	141
60% / 40%	8 mos	12 mos	4 mos	120	137	158
70% / 30%	7.75 mos	12.25 mos	4.5 mos	112	126	145
70% / 30%	7.88 mos	12.13 mos	4.25 mos	126	142	164
70% / 30%	8 mos	12 mos	4 mos	141	160	184
75% / 25%	7.75 mos	12.25 mos	4.5 mos	128	143	165
75% / 25%	7.88 mos	12.13 mos	4.25 mos	142	160	184
75% / 25%	8 mos	12 mos	4 mos	160	180	207
80% / 20%	7.63 mos	12.38 mos	4.75 mos	137	152	175
80% / 20%	7.75 mos	12.25 mos	4.5 mos	152	169	195
80% / 20%	7.88 mos	12.13 mos	4.25 mos	169	189	218
80% / 20%	8 mos	12 mos	4 mos	190	213	245

A sample size of 184 subjects (160 analyzable) would provide 80% power at alpha=0.1 to detect a difference in PFS among patients with increase versus decrease in tumor blood flow (BF) by perfusion CT (T0 to T1), where up to 70% of patients exhibit an increase in tumor BF, and the difference in median PFS is 4 months or greater. If the percentage of patients exhibiting an increase in tumor BF is 75%, then the study will be powered to detect a difference in median PFS of 4.25 months or greater; if the percentage of patients exhibiting an increase in tumor BF is 80%, then the study will be powered to detect a difference in median PFS of 4.75 months or greater. Appropriately powered scenarios correspond to the shaded portion of the above table.

Regarding exploratory aim #2 (refer to Section 8.2.3.2 above), assessing the reliability of CT perfusion parameters, all enrolled, analyzable patients will be read centrally by two independent readers, blinded to both clinical and patient outcome data (refer to Section 7.4). A total of 160 analyzable subjects, as derived for the primary aim, using a two-way random effects model to estimate the intraclass correlation coefficient (ICC), would yield a two-sided 95% confidence interval for the ICC with a width no larger than 0.26 when the estimated ICC is as low as 0.4. If the ICC is 0.7 or above, then the width of the two-sided 95% confidence interval would be no larger than 0.16. Calculations were performed using PASS15 [29, 37].

Patients who are eligible for the EAE161 trial have been diagnosed with ovarian, peritoneal or fallopian tube cancer, and have platinum resistant, recurrent disease. We estimate that approximately 60% of patients who are screened in Step 0 will successfully have a target lesion identified for CT perfusion, and thus be eligible for enrollment onto Step 1. Therefore, we expect the need to enroll and screen 300 patients in Step 0 of the study in order to accrue the required 184 eligible patients in Step 1 of the study necessary for statistical analysis.

8.4 Gender and Ethnicity

Based on previous data from ACRIN 6695/GOG-0262 the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	11	0	11
Not Hispanic or Latino	173	0	173
Ethnic Category: Total of all subjects	**184**		**184**

Racial Category			
American Indian or Alaskan Native	4	0	4
Asian	4	0	4
Black or African American	14	0	14
Native Hawaiian or other Pacific Islander	0	0	0
White	162	0	162
Racial Category: Total of all subjects	**184**	**0**	**184**

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

8.5 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group-meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

NOTE: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

9. Electronic Data Capture

Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site

(http://ctep.cancer.gov/reporting/cdus.html).

10. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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Perfusion CT to Predict Progression-free Survival and Response Rate in Bevacizumab Treatment of Platinum-Resistant Persistent or Recurrent Epithelial Ovarian, Fallopian Tube, or Peritoneal Carcinoma

Appendix I

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Perfusion CT to Predict Progression-free Survival and Response Rate in Bevacizumab Treatment of Platinum-Resistant Persistent or Recurrent Epithelial Ovarian, Fallopian Tube, or Peritoneal Carcinoma

Appendix II

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.