CT Perfusion as an Early Biomarker of Treatment Efficacy in Advanced Ovarian Cancer: An ACRIN and GOG Study


Abstract

Purpose: ACRIN 6695 was a feasibility study investigating whether CT perfusion (CTP) biomarkers are associated with progression-free survival (PFS) at 6 months (PFS-6) in patients with advanced ovarian cancer who were treated with carboplatin and either dose-dense (weekly) or conventional (3-weekly) paclitaxel, with optional bevacizumab in the prospective phase III GOG-0262 trial.

Patients and Methods: ACRIN 6695 recruited participants with residual disease after primary cytoreductive surgery or planned interval cytoreduction following neoadjuvant therapy, to undergo CTP studies before (T0), 3 weeks (T1), and 4 weeks (T2) after chemotherapy initiation. Tumor blood flow (BF) and blood volume (BV) were derived with commercial software. Fisher exact tests assessed the associations of CTP biomarkers changes from T0 to T2 dichotomized at zero with PFS-6 and overall radiographic response rate, while Cox regression assessed the associations between CTP biomarker changes and PFS and overall survival (OS). Bonferroni correction was used to account for multiple comparisons.

Results: Seventy-six of 120 enrolled patients from 19 centers were evaluable with a median age of 61 years. BV increase was significantly associated with lower chance of PFS-6 (P = 0.028), while BF achieves borderline significance (P = 0.053). In addition, BF increase was 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). Neither BF nor BV changes were significantly associated with treatment response rate or OS.

Conclusions: Early CTP biomarkers measurement may provide early prognostic information for PFS in newly diagnosed ovarian cancer. Clin Cancer Res; 1–8. ©2017 AACR.

Introduction

Of the estimated 21,980 women diagnosed each year with epithelial ovarian cancer (EOC) in the United States, more than 70% will present with advanced (FIGO stage III or IV) disease (1). Standard primary therapy consists of cytoreductive surgery in combination with platinum and taxane-based chemotherapy (2). In 60% to 85% of patients, relapse will occur after initial treatment (3), resulting in a poor 5-year survival rate of <50% (4) and making EOC the fifth most common cause of cancer mortality in women (5). Recent strategies to improve progression-free survival (PFS) in both primary and recurrent settings have included combinations of biological agents, predominately those targeting angiogenesis, with standard-of-care chemotherapy (6–8). However, these agents have not improved overall survival (OS) in the setting of primary therapy. For example, bevacizumab is associated with higher rates of treatment-related toxicities versus chemotherapy alone, including grade ≥2 hypertension (20% vs.7%) and bowel perforation, fistula or abscess (7% vs. 0%) and increases treatment cost up to 7-fold (9). Thus, a biomarker to identify patients unlikely to benefit from a specific therapy would enable better patient selection to optimize the therapeutic ratio (10).

CT perfusion (CTP) is a dynamic contrast-enhanced computed tomography (CT) examination, in which a standard CT scanner is used to serially image the passage of a contrast bolus through a target lesion after intravenous injection. The acquired images are then processed with dedicated commercial software to calculate quantitative perfusion biomarkers that include tumor blood flow (BF), tumor blood volume (BV), and vessel permeability surface product (PS). When the treatment regimen involves inhibition of tumor-associated angiogenesis (11, 12), CT perfusion can measure treatment-induced microvascular changes. Furthermore, CTP studies can be readily incorporated

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Materials and Methods

ACRIN 6695 trial design

Cohort, study schema, and outcomes. The patient cohort would be a subset of patients enrolled into the phase III GOG-0262 trial, a prospective multicenter phase III clinical trial comparing PFS in treatment-naive patients with advanced-stage ovarian cancer who received carboplatin and either dose-dense (weekly) or conventional (3 weekly) paclitaxel, with optional concurrent bevacizumab followed by bevacizumab maintenance. Inclusion criteria for ACRIN 6695 included enrollment on GOG-0262 with histologic confirmation of epithelial ovarian peritoneal or fallopian cancer, and a suboptimal surgical cytoreduction (i.e., residual disease $>1$ cm) or a planned interval cytoreductive surgery and (ii) CTP biomarkers are associated with PFS at 6 months (PFS-6) in a cohort of GOG-0262 (clinicaltrials.gov: NCT01167712) patients.

Eligibility and enrollment. Enrolled patients were eligible for completing the three CTP studies if they had at least one target lesion as determined and confirmed by the site and central body CT radiologist, respectively, before treatment on either the initial standard-of-care RECIST CT or the baseline CTP study. Target lesions were tumors greater than 1 cm in transaxial directions and had a CT attenuation greater than or equal to 10 Hounsfield units (HU) in at least half the lesion on unenhanced CT; and an enhancement greater than or equal to 5 HU in the CTP scan. The enhancement requirement ensured that cystic lesions or hematomas (which do not enhance) were excluded as targets and ensured good signal–noise ratio in the target for reliable derivation of CT perfusion parameters. Enrolled subjects without eligible target lesions prior to treatment were excluded from further CTP studies and subsequent analysis. Because our primary objective centered on examining the association of primary and secondary outcomes with changes in tumor CT perfusion biomarker values from baseline (T0) to T2, we required successful completion and technically analyzable T0 and T2 CTP studies, of the same target lesion, for a patient to be considered evaluable for statistical analysis.

Power analysis. Assuming a 30% difference in PFS-6 between patients with a positive and negative CTP biomarker change from T0 to T2 (65% vs. 95%), and equal number of patients in each group, it was estimated that 70 evaluable participants would provide 84% power with a two-sided hypothesis and type I error of 0.05 using the Fisher exact test. Ethics approval for ACRIN 6695 was obtained centrally from the National Cancer Institute’s (NCI) central investigational review board (IRB) and the local IRBs. Other details of the ACRIN 6695 protocol are available from https://www.clinicaltrials.gov/ct2/results?term=ACRIN6695&Search=Search.

CT Perfusion Studies

The CTP studies were undertaken on routine standard-of-care CT scanners at each participating site, and consisted of sequential scans over the maximal cross-section of the target lesion in two CT scanning phases during the intravenous administration of CT contrast medium and free-breathing. The two CTP scan phases comprised 24 scans at 2.8-second scan interval, followed by 8 scans at 15-second scan interval for a total scan time of $\approx$ 3 minutes. Contrast medium was 300 to 370 mgI/mL concentration at a dose of 0.8 mL/kg body weight to a maximum of 70 mL, injected at 2 to 4 mL/second, 4–5 seconds before scanning began. CT technical parameters were: 120 kVP, 50 mA and 1 second rotation speed, and 6 to 16 CT slices, thickness $4.5–5.0$ mm (depending on the CT scanner type and model); axial ‘shuttle’ protocol as follows: baseline before chemotherapy (T0), in the last week of the first cycle of chemotherapy (T1), and in the second week of the second cycle of chemotherapy (T2; Supplementary Fig. S1). Primary outcome PFS-6 and secondary outcomes best overall radiographic response, PFS, and OS were analyzed with the CTP biomarker data. Disease progression was defined on the basis of radiographic imaging using the revised international Response Evaluation Criteria in Solid Tumors (RECIST version 1.1; ref. 13), or increased CA-125 levels based on criteria from the Gynecologic Cancer Intergroup (14).

Translational Relevance

Our study (ACRIN 6695) demonstrated that abdominopelvic CT perfusion (CTP) biomarkers can be measured successfully with sufficient uniformity across multiple sites and scanner platforms to yield positive results in a multicenter biomarker trial. CTP biomarkers measured within 4 weeks of initiating therapy may provide early prognostic information for treatment response and time to progression and could be used to refine early treatment interventions for advanced ovarian cancer in future clinical trials, particularly in removing ineffective therapeutic modalities for patients. Furthermore, because CT perfusion can be incorporated easily into routine CT imaging for the follow-up of cancer treatment, our results suggest that CTP biomarkers not only can be used in clinical trials but can also be considered for routine monitoring of cancer treatment.

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CT Perfusion as an Early Biomarker of Treatment Efficacy

In this study, absolute perfusion values and absolute blood volume values were used. Because muscle perfusion and blood volume are within the ranges of 0–10 mL/min/100 g and 0–5 mL/100 g, respectively, as an internal standard, the perfusion and blood volumes maps were accepted only when the pelvic muscle

(step and shoot) mode, which increases cranio-caudal coverage, was allowed if available.

In this study, absolute perfusion values and absolute blood volume values were used. Because muscle perfusion and blood volume are within the ranges of 0–10 mL/min/100 g and 0–5 mL/100 g, respectively, as an internal standard, the perfusion and blood volumes maps were accepted only when the pelvic muscle

appeared "blue" when these maps were displayed in the rainbow color scale as in Fig. 2. Other details of the imaging protocol can be found at: https://www.acrin.org/Portals/0/Protocols/6695/Imaging%20Materials/6695_IMPv2_03072013_FINAL.pdf

Analysis of CT perfusion scans

The CTP studies were analyzed centrally (Robarts Research Institute, London, Ontario and ACRIN). The target lesion criteria as prescribed in the study design described above were formally assessed on the baseline (T0) CTP study and determined eligibility for patients to proceed to T1 and T2 CTP studies.

Target lesion eligibility at T0 was assessed, and lesion outlines were provided by a site radiologist and corroborated by the central radiologist (C.S. Ng and S.I. Lee) from the standard-of-care RECIST scan or the CTP scan according to predefined criteria detailed above. At the other time points (T1 and T2), the outlines of the same target lesion were provided by the central radiologist being careful to match the T0 outlines as much as possible and also taking into account the possible size change of the tumor from T0 to either T1 to T2 time point. This matching was facilitated by using the average images of the respective CTP studies. These images were generated by adding together all dynamic images of the same slice together to improve the lesion contrast from surrounding anatomical features. For each CT perfusion study, following delineation, the target lesion regions of interest (ROI) in all slices were aligned using 3D rigid registration with ANALYZE software (Mayo Clinic) to correct for misregistrations from breathing motion during the scanning time of the study (~3 minutes). After registration, CT perfusion parametric maps were calculated from each study using CT perfusion software (body tumor protocol in CT Perfusion 4, GE Healthcare), which is based on the modified Johnson–Wilson model (15), and the time–density curve from the largest visualized artery as the input function. Target lesions BF, BV, and PS were calculated as the area-weighted average of the mean biomarker value in all target lesion ROIs.

![Figure 1](https://www.acrin.org/Portals/0/Protocols/6695/Imaging%20Materials/6695_IMPv2_03072013_FINAL.pdf)

Figure 1. Flow diagram of patient recruitment in ACRIN 6695. Eligible: target lesion met target lesion criteria on central review; evaluable: patient with technically analyzable CTP scans of the same target lesion from T0 to T2; suboptimal: suboptimally debulked tumor; dose-dense: weekly paclitaxel; conventional: 3-weekly paclitaxel; Bev = Bevacizumab.

![Figure 2](https://www.acrin.org/Portals/0/Protocols/6695/Imaging%20Materials/6695_IMPv2_03072013_FINAL.pdf)

Figure 2. Red arrows point to target lesion in T0, T1, and T2 CTP study of a neoadjuvant patient in the weekly paclitaxel treatment arm (patient 27). The BF and BV maps are color coded from 0 (blue) to 200 (red) mL/min/(100 g) and 0 to 50 mL/(100 g), respectively. As shown, there were a 36% and a 55% decrease in tumor BF and a 25% and a 47% decrease in tumor BV relative to T0 at T1 and T2, respectively.
Statistical analysis

Associations of primary outcome PFS-6 and secondary outcomes best overall radiographic response, PFS, and OS were CTP data were investigated. PFS-6 was the proportion of patients who had not progressed or died within 6 months of trial registration. PFS and OS were similarly calculated from the date of trial registration. Best overall radiographic response was assessed using RECIST criteria. The prognostic CTP biomarkers evaluated were changes of BF, BV, and PS relative to their baselines at T0, denoted by ΔBF, ΔBV, and ΔPS, respectively. Angiogenesis is the hallmark of a proliferating tumor which leads to increase in blood flow, blood volume, and PS; dichotomizing the perfusion parameter changes into either positive or negative, i.e., "dichotomize at zero," would be appropriate as markers for patient response. The values of ΔBF, ΔBV, and ΔPS between T0 and T1 or T2 are compared using the Wilcoxon signed rank test.

Fisher exact tests were used to test the association between dichotomized CTP biomarkers and PFS-6 and best overall radiographic response. Univariate and multivariate Cox regression models were fitted for each biomarker, either with or without other covariates to test the association between dichotomized CTP biomarkers and PFS or OS. The unadjusted or adjusted hazard ratio of each biomarker, along with its 95% confidence interval and the P value based on Wald statistic were reported. In addition, Kaplan–Meier survival curves were generated, and the median survival time with its 95% confidence interval was provided. The log-rank test was used when appropriate. All tests were two-sided, and P < 0.05 was considered statistically significant for the primary aim of PFS-6. Bonferroni correction was used to account for multiple comparisons for the secondary analyses, where P < 0.017 was considered statistically significant.

Role of the funding source

This study was funded entirely by grants from US National Cancer Institute (NCI) to American College of Radiology Imaging Network (ACRIN) and Gynecological Oncology Group (GOG). NCI supplied the drug bevacizumab used in the study and provided centralized ethics review of the ACRIN 6695 study protocol. ACRIN also provided image data storage and provided centralized ethics review of the ACRIN 6695 study protocol. ACRIN also provided image data storage and provided centralized ethics review of the ACRIN 6695 study protocol. ACRIN also provided image data storage and provided centralized ethics review of the ACRIN 6695 study protocol. ACRIN also provided image data storage and provided centralized ethics review of the ACRIN 6695 study protocol.

Results

A total of 19 centers enrolled subjects into the ACRIN 6695 trial. Of the 120 patients enrolled from August 2011 to July 2013, 76 had analyzable T0 and T2 studies and were considered evaluable (Fig. 1). Of these, 52/76 (68%) were neoadjuvant, and 24/76 (32%) were suboptimally debulked patients; 39/76 (51%) were randomized to dose-dense therapy and 37/76 (49%) to conventional therapy. Evaluable patients (91%; 69/76) received bevacizumab. The median age of patients was 61 years, range 25 to 87; 32% were suboptimally debulked patients; 39/76 (51%) were stage II (n = 2), grade 2 (7), grade 3 (55), and grade unknown (12). FIGO stage at diagnosis was stage II (n = 4), stage IIC (41), and stage IV (31). Demographic and clinical data of enrolled and evaluable patients are listed in Table 1.

Table 1. Demographic and clinical data of the enrolled and evaluable cohorts of the ACRIN 6695 study

<table>
<thead>
<tr>
<th>Age, years (mean, SD)</th>
<th>Enrolled (n = 120)</th>
<th>Evaluable (n = 76)</th>
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<tbody>
<tr>
<td>60.2 (10.5)</td>
<td>60.1 (10.5)</td>
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<tr>
<th>Race, N (%)</th>
<th>Enrolled (n = 120)</th>
<th>Evaluable (n = 76)</th>
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<tbody>
<tr>
<td>White 109 (90.8)</td>
<td>70 (92.1)</td>
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<tr>
<td>Black or African American 6 (5.0)</td>
<td>4 (5.3)</td>
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<tr>
<td>American Indian or Alaska Native 2 (1.7)</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Asian 2 (1.7)</td>
<td>0 (0.0)</td>
<td></td>
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<tr>
<td>Native Hawaiian or Pacific Islander 0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Unknown 2 (1.7)</td>
<td>1 (1.3)</td>
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<tr>
<th>Bevacizumab administration status, N (%)</th>
<th>Enrolled (n = 120)</th>
<th>Evaluable (n = 76)</th>
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<tbody>
<tr>
<td>Bevacizumab 102 (85.0)</td>
<td>69 (90.8)</td>
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<tr>
<td>No Bevacizumab 18 (15.0)</td>
<td>7 (9.2)</td>
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<tr>
<th>Stage at diagnosis (FIGO), N (%)</th>
<th>Enrolled (n = 120)</th>
<th>Evaluable (n = 76)</th>
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<tbody>
<tr>
<td>3 8 (6.7)</td>
<td>4 (5.3)</td>
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<tr>
<td>3A 1 (0.8)</td>
<td>0 (0.0)</td>
<td></td>
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<tr>
<td>3B 3 (2.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>3C 64 (53.3)</td>
<td>41 (53.9)</td>
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<tr>
<td>4 44 (36.7)</td>
<td>31 (40.8)</td>
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<tr>
<th>Histologic grade, N (%)</th>
<th>Enrolled (n = 120)</th>
<th>Evaluable (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 4 (3.3)</td>
<td>2 (2.6)</td>
<td></td>
</tr>
<tr>
<td>2 11 (9.2)</td>
<td>7 (9.2)</td>
<td></td>
</tr>
<tr>
<td>3 88 (73.3)</td>
<td>55 (72.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown 17 (14.2)</td>
<td>12 (15.8)</td>
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</table>

The overall radiographic response rate was 74% (56/76), consisting of 22 complete responders (CR) and 34 partial responders (PR). The PFS-6 rate was 96% (73/76), and the median PFS was 427 days (with 45/76 events), and median OS was 760 days (with 16/76 events).

For the cohort as a whole, BF (P < 0.0001), BV (P < 0.0001), and PS (P = 0.0035) had significant decreases from T0 to T2. The decrease of BV from T0 to T1 (P = 0.0069) was also significant (Table 2). On an individual patient basis, the T0–T2 period was associated with an increase in BF (i.e., ΔBF was positive) in 11 (14%) patients, and a decrease (i.e., ΔBF was negative) in 65 (86%) patients (Table 3). Similarly, ΔBV was positive in 8 (11%) patients and negative in 68 (89%) patients, and ΔPS was positive in 20 (26%) patients, and negative in 56 (74%) patients. Table 3 summarizes the association of change in CTP biomarkers in the periods of T0–T1 and T0–T2 with PFS-6, best overall response, PFS, and OS. Figure 2 shows the results from a neoadjuvant patient in the weekly paclitaxel treatment arm whose blood flow and volume at the two follow-up CTP studies (T1 and T2) decreased relative to baseline (T0).

Association of change of CTP biomarkers from T0 to T2 with PFS-6

There were 3 patients who progressed or died within 6 months of their trial registration. Patients whose BV increased...
had a lower chance of being progression-free at 6 months (PFS-6; 6/8, 75%), compared with patients whose BV decreased (67/68, 98.5%, \( P = 0.028 \)). Similarly, patients whose BF increased had a lower chance of PFS-6 (9/11, 81.8%), compared with patients whose BF decreased with borderline significance (64/65, 98.5%, \( P = 0.053 \)). Of the 3 patients who progressed or died within 6 months of their trial registration, 2 had increased while 1 had decreased BF and BV. No significant association was found between BF and BV. No significant association was found between OS and BF (\( P = 0.28 \)) or BV (\( P = 0.42 \)) or PS (\( P = 0.40 \)), but the study was not adequately powered to detect small differences in OS.

### Association of change of CTP biomarkers from T0 to T2 with best overall radiographic response

Fifty-six (74%) patients had either a complete or partial radiographic response. Patients whose BF increased (ABF positive) had a lower chance of being responders (5/11, 45.5%), compared with patients whose BF decreased (\( \Delta \text{BF} \) negative) (51/65, 78.5%), but this did not attain significance after applying Bonferroni correction (\( P = 0.032 \)). Similarly, patients whose BV increased had a lower chance of being responders (3/8, 37.5%), compared with patients whose BV decreased (53/68, 77.9%), again not significantly after correction for multiple comparisons in these secondary analyses (\( P = 0.026 \)). No significant association was found between \( \Delta \text{PS} \) and best overall response (\( P = 1.0 \)). Results are summarized in Table 3.

### Change of CTP biomarkers from T0 to T1

No associations in changes of CTP biomarkers from T0 to T1 were observed with any of the four outcomes.

### Discussion

In this prospectively designed pilot imaging biomarker study, we demonstrated that CTP is feasible in patients with residual lesions measuring at least 1 cm following primary cytoreductive surgery or prior to interval cytoreductive surgery. Temporal changes as early as within 4 weeks of initiating therapy in one or more CTP biomarkers of perfusion were associated with long-term outcomes of tumor treatment success, including PFS-6 and PFS; the latter association present even after adjusting for age, change in tumor volume between T0 to T2, and surgical status (neoadjuvant vs. suboptimally debulked).

The development of "early-in-treatment" biomarkers for treatment outcomes is becoming increasingly important as the portfolio of novel agents expands. This development has proceeded along several different paths including, serial tissue biopsies, repeated evaluation of circulating factors and noninvasive imaging. The latter two options provide the most acceptable form of evaluation, but validation has been difficult due to the large dynamic variability of biomarkers in body fluids in the

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**Table 3. Association of changes of CTP biomarkers (BF, BV, and PS) with clinical outcomes**

<table>
<thead>
<tr>
<th>T0-T2</th>
<th>( \Delta \text{BF} (+ \text{vs.} -) )</th>
<th>( \Delta \text{BV} (+ \text{vs.} -) )</th>
<th>( \Delta \text{PS} (+ \text{vs.} -) )</th>
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<tbody>
<tr>
<td>PFS-6</td>
<td>82% vs. 98%, ( P = 0.053 )</td>
<td>75% vs. 99%, ( P = 0.028^b )</td>
<td>90% vs. 98%, ( P = 0.17 )</td>
</tr>
<tr>
<td>Best response</td>
<td>45% vs. 78%, ( P = 0.032 )</td>
<td>58% vs. 78%, ( P = 0.026 )</td>
<td>75% vs. 73%, ( P = 1.0 )</td>
</tr>
<tr>
<td>PFS</td>
<td>HR = 2.86 (1.28, 6.42), ( P = 0.008^b )</td>
<td>HR = 1.61 (0.68, 3.82), ( P = 0.28 )</td>
<td>HR = 0.72 (0.35, 1.51), ( P = 0.39 )</td>
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<tr>
<td>OS</td>
<td>HR = 1.88 (0.59, 5.93), ( P = 0.28 )</td>
<td>HR = 1.71 (0.46, 6.29), ( P = 0.42 )</td>
<td>HR = 0.57 (0.15, 2.13), ( P = 0.40 )</td>
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<table>
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<tr>
<th>T0-T1</th>
<th>( \Delta \text{BF} (+ \text{vs.} -) )</th>
<th>( \Delta \text{BV} (+ \text{vs.} -) )</th>
<th>( \Delta \text{PS} (+ \text{vs.} -) )</th>
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<tbody>
<tr>
<td>PFS-6</td>
<td>92% vs. 98%, ( P = 0.27 )</td>
<td>96% vs. 96%, ( P = 1.0 )</td>
<td>97% vs. 96%, ( P = 1.0 )</td>
</tr>
<tr>
<td>Best response</td>
<td>65% vs. 78%, ( P = 0.28 )</td>
<td>60% vs. 80%, ( P = 0.09 )</td>
<td>66% vs. 79%, ( P = 0.28 )</td>
</tr>
<tr>
<td>PFS</td>
<td>HR = 0.88 (0.47, 1.66), ( P = 0.70 )</td>
<td>HR = 0.98 (0.46, 1.60), ( P = 0.63 )</td>
<td>HR = 0.85 (0.46, 1.60), ( P = 0.59 )</td>
</tr>
<tr>
<td>OS</td>
<td>HR = 1.12 (0.40, 3.16), ( P = 0.83 )</td>
<td>HR = 0.88 (0.30, 2.58), ( P = 0.87 )</td>
<td>HR = 1.09 (0.37, 3.18), ( P = 0.88 )</td>
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\( ^a \Delta \text{BF}, \Delta \text{BV}, \text{or} \Delta \text{PS} \) calculated as T2 value minus T0 value.

\( ^b \)Statistically significant (\( P < 0.05 \) for primary analysis; \( P < 0.017 \) for secondary analyses).

\( ^c \Delta \text{BF}, \Delta \text{BV} \) or \( \Delta \text{PS} \) calculated as T2 value minus T0 value.
former and the need for standardization of image acquisition and analysis in the latter. CTP has the advantage that it is quantitative and more amenable to standardized acquisition. However, CT perfusion has not been validated under centralized review and standardized analysis as an early imaging biomarker of treatment response in a prospective multicenter trial setting.

ACRIN 6695 is a pilot trial designed to demonstrate the feasibility of CTP as an early imaging biomarker before a formal validation trial is undertaken. It required a multislice CT (64 or more slice) scanner, capable of imaging a 2.8-cm or wider section of the abdomen/pelvis repeatedly every 1–3 seconds for a period up to 3 minutes, which is in terms of present-day CT technology is relatively standard and is widely available as a second-tier rather than premium model scanner from all commercial vendors. As such, the required CT scanner is likely to be available in most cancer treatment centers. A pilot trial is limited by nature in the number of patients and follow-up time available as well as in prior data to guide the statistical analysis of the acquired imaging biomarker data. These limitations were reflected in the design of the ACRIN 6695 trial in three important aspects: (i) the different treatment arms of GOG-0262 were treated as a single treatment and CTP was tested as an imaging biomarker of treatment response; (ii) PFS-6 was used as the primary outcome to limit the follow-up time required; and (iii) CTP-derived biomarkers were dichotomized as positive versus negative changes to access treatment response in the statistical analysis plan due to the lack of known thresholds in these imaging biomarkers. Nevertheless, results from ACRIN 6695 show that CTP did not require specialized equipment except standard clinical CT scanners, could be carried out in the multi-institutional setting with standardized acquisition and analysis protocol with good patient compliance, and demonstrated biological precision to the anticipated effects of successful (or unsuccessful) treatment under centralized review.

ACRIN 6695 focused on CTP-derived parameters—BF, BV and PS—because one rationale for anti-VEGF based therapy was normalization of the microvasculature in tumors leading to reduction in edema (PS) and interstitial fluid pressure, which could enhance chemotherapy delivery thereby enhancing its effect (16). This would also be represented by decreases in tumor blood volume, perfusion, and edema. Previous studies of perfusion imaging have suggested that effective neoangiogenesis targeting can impact these biomarkers (17). However, interobserver variability and requirements for specialized imaging equipment and protocols have limited the generalization of these early successes (18).

GOG-0262 was a phase III trial assessing the impact of dose-dense paclitaxel and carboplatin relative to standard, every 3-week paclitaxel and carboplatin on PFS. Bevacizumab use was left to the physician’s discretion and was overwhelmingly preferred based on two phase III clinical trials in patients with predominately advanced ovarian cancer. Both of these trials demonstrated a significant benefit in PFS with the use of bevacizumab combined with standard (3-weekly paclitaxel/carboplatin) chemotherapy and in maintenance (19, 20). Neither trial demonstrated a benefit in OS, raising a risk/benefit discussion for unselected patients, particularly because significant adverse effects from therapy were observed in both trials. Indeed, a recent genomic analysis of one of these trials (ICON7) suggested that patients with an immune gene upregulation actually did worse if treated with bevacizumab (21). While reproducibility of genomic characterization to predict patient outcomes a priori is still challenging, characterization of the lack of treatment effects with noninvasive imaging would be of great value in avoiding unnecessary treatment exposure of agents.

ACRIN 6695 focused on CTP-derived parameters—BF, BV and PS—because one rationale for anti-VEGF based therapy was normalization of the microvasculature in tumors leading to reduction in edema (PS) and interstitial fluid pressure, which could enhance chemotherapy delivery thereby enhancing its effect (16). This would also be represented by decreases in tumor blood volume, perfusion, and edema. Previous studies of perfusion imaging have suggested that effective neoangiogenesis targeting can impact these biomarkers (17). However, interobserver variability and requirements for specialized imaging equipment and protocols have limited the generalization of these early successes (18).

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Figure 3.
Kaplan-Meier PFS curve for patients who had increase versus decrease in BF from T0 to T2.
may also help guide more aggressive surveillance for the group of patients who are likely to recur early, so that novel therapeutics can be considered for this poor risk group, either as a maintenance strategy, or in the setting of recurrence.

**Disclosure of Potential Conflicts of Interest**

J.K. Chan reports receiving speakers bureau honoraria from AstraZeneca and Roche/Genentech, and is a consultant/advisory board member for Acerta, Clovis, OXiGENE/Mateon, and Roche/Genentech. M.A. Bookman is an employee of McKesson Specialty Health, and is a consultant/advisory board member for AbbVie, AstraZeneca, Clovis, Celgene, Endocyte, Genentech/Roche, Immunogen, and OXiGENE. T.-Y. Lee licenses the CT Perfusion software to GE Healthcare. No potential conflicts of interest were disclosed by the other authors.

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