Metabolic response as assessed by $^{18}$F-fluorodeoxyglucose positron emission tomography-computed tomography does not predict outcome in patients with intermediate- or high-risk rhabdomyosarcoma: A report from the Children's Oncology Group Soft Tissue Sarcoma Committee

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ABSTRACT

Background: Strategies to optimize management in rhabdomyosarcoma (RMS) include risk stratification to assign therapy aiming to minimize treatment morbidity yet improve outcomes. This analysis evaluated the relationship between complete metabolic response (CMR) as assessed by $^{18}$F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET) imaging and event-free survival (EFS) in intermediate-risk (IR) and high-risk (HR) RMS patients.

Methods: FDG-PET imaging characteristics, including assessment of CMR and maximum standard uptake values (SUVmax) of the primary tumor, were evaluated by central review. Institutional reports of SUVmax were used when SUVmax values could not be determined by central review. One hundred and thirty IR and 105 HR patients had FDG-PET scans submitted for central review or had SUVmax data available from institutional report at any time point. A Cox proportional hazards regression model was used to evaluate the relationship between these parameters and EFS.

Results: SUVmax at study entry did not correlate with EFS for IR ($p = 0.32$) or HR ($p = 0.86$) patients. Compared to patients who did not achieve a CMR, EFS was not superior for IR patients who achieved CMR at weeks 4 ($p = 0.66$) or 15 ($p = 0.46$), nor for HR patients who achieved CMR at week 6 ($p = 0.75$) or 19 ($p = 0.28$). Change in SUVmax at week 4 ($p = 0.21$) or 15 ($p = 0.91$) for IR patients or at week 6 ($p = 0.75$) or 19 ($p = 0.61$) for HR patients did not correlate with EFS.

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INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma (STS) in children and adolescents with approximately 350 cases documented in the United States each year. Clinical features present at diagnosis can stratify patients into low-, intermediate-, and high-risk groups to predict outcome and modulate treatment intensity. Patients with low-risk and intermediate-risk (IR) RMS have a relatively favorable long-term event-free survival (EFS) of approximately 90% and 60%, respectively, whereas patients with high-risk (HR) disease have poor outcomes with a 5-year EFS of approximately 30%. Recent studies to improve outcomes in RMS have explored novel ways of stratifying risk to identify patients that may require more intensive or novel therapies.

Response to induction chemotherapy is a well-established predictor of survival in many pediatric cancers, including acute lymphoblastic leukemia, Hodgkin lymphoma, osteosarcoma, and Ewing sarcoma. Both radiographic and histologic response have been used to adapt treatment intensity in an overall effort to minimize toxicity for lower risk patients and escalate therapy for higher risk patients. Radiographic response to treatment (as measured by change in tumor size), however, has not proven to be a reliable predictor of outcome in RMS, limiting the ability to identify patients who could benefit from more intensive or novel therapy.

Metabolic activity as assessed by $^{18}$F-FDG-PET/CT (FDG-PET) has recently been shown to improve accuracy of staging in pediatric RMS. Preliminary data from a single institution suggested that a complete metabolic response (CMR) as assessed by FDG-PET following radiation therapy for local control may predict local relapse-free survival (LRFS) in pediatric patients with Group III RMS. A follow-up analysis by the same group confirmed these findings in a larger cohort of RMS patients showing that metabolic response by FDG-PET predicted EFS, overall survival, and local tumor control. The predictive value of FDG-PET response, however, has not been evaluated in a prospective multi-institutional RMS clinical trial.

In this analysis, we present the FDG-PET imaging data from two large, prospective Children’s Oncology Group Studies—ARST0531 and ARST08P1—of pediatric patients with intermediate- and high-risk rhabdomyosarcoma, respectively. The study examined several FDG-PET variables on imaging submitted from patients enrolled on each study to determine if FDG-PET imaging could be correlated with event-free survival (EFS) in rhabdomyosarcoma. None of the variables tested were found to correlate with EFS in rhabdomyosarcoma suggesting the imaging modality does not have a role in predicting outcome in intermediate- or high-risk rhabdomyosarcoma.
Group (COG) studies for newly diagnosed IR RMS and HR RMS: ARST0531 (Randomized Study of Vincristine, Dactinomycin, and Cyclophosphamide (VAC) versus VAC Alternating with Vincristine and Irinotecan (VI) for Patients with Intermediate-Risk Rhabdomyosarcoma) and ARST08P1 (A Pilot Study to Evaluate Novel Agents (Temozolomide and Cixutumumab) in Combination with Intensive Multi-Agent Interval Compressed Therapy for Patients with High-Risk Rhabdomyosarcoma). The purpose of this analysis was to determine whether complete metabolic response as assessed by FDG-PET imaging correlates with EFS in these two subpopulations of RMS patients.

2 | PATIENTS AND METHODS

2.1 | Patient population

Details of the design, eligibility criteria, treatment, and outcome for ARST0531 (NCT00354835) and ARST08P1 (NCT01055314) have been previously published.5,7 ARST0531 enrolled newly diagnosed patients with IR RMS defined as patients with non-metastatic (Group I-III) alveolar RMS arising at any site (Stage 1–3) and incompletely excised (Group III) embryonal RMS arising in an unfavorable site (Stage 2–3). Patients received 42 weeks of either VAC alone or alternating cycles of VAC with VI. Only patients with measurable disease at study entry (Clinical Group III) were included in this analysis. Radiation therapy (50.4 Gy in 1.8 Gy fractions for Clinical Group III patients) was given at week 4 of therapy. Patients enrolled on both treatment arms were combined for the purpose of this FDG-PET analysis, as there was no statistical difference in EFS between the two treatment arms.5 FDG-PET imaging was optional for all patients and was recommended prior to chemotherapy, at week 4, and at week 15. ARST08P1 enrolled newly diagnosed patients with HR RMS defined as patients with metastatic (Stage 4/Group IV) alveolar or embryonal RMS. Patients were treated with a multi-agent chemotherapy backbone which included two cycles of VI (Weeks 1–6), followed by six cycles of alternating interval compressed vincristine, doxorubicin, and cyclophosphamide (VDC) and ifosfamide and etoposide (IE) (weeks 7–19). Two VI cycles were repeated at weeks 20–25 and weeks 47–51. Interval-compressed VDC/IE cycles were administered again at weeks 28 through 34 followed by four cycles of VAC administered every 3 weeks during weeks 35–46. Patients were enrolled in sequential pilot cohorts to receive the described chemotherapy backbone in conjunction with cixutumumab or temozolomide with the primary aim to evaluate the feasibility of the combination.7 Radiation therapy was administered at week 20 to the primary tumor as well as to sites of metastatic disease at the discretion of the treating institution. FDG-PET imaging was performed prior to chemotherapy, at week 6, and week 19 (prior to radiation therapy) if clinically indicated and available at the treating institution.

2.2 | Measurement of response and definition of endpoints

We evaluated both FDG-PET tumor response and baseline maximum standard uptake values. Two nuclear imaging physicians (MTP and BLS) centrally reviewed FDG-PET response. Response was classified according to European Organization for Research and Treatment of Cancer criteria.24 CMR was defined as complete resolution of abnormal FDG uptake within the tumor region defined on baseline scan. SUVmax values were assessed by central review or institutional report if central review was not available. SUVmax was determined by manually drawing a region of interest over the area of FDG activity corresponding to the tumor in question. Quality assurance of the treating institution included documentation of: blood glucose level before injection, injected 18F-FDG dose, time of injection, time that image acquisition began, patient weight and height for determination of SUV, and assurance that the DICOM header was intact. Both transverse CT files and transverse 18F-FDG-PET attenuation corrected files were required.

2.3 | Statistical analysis methods

EFS was defined as the time from study enrollment to disease progression, disease recurrence, occurrence of a second malignant neoplasm, or death from any cause. EFS for patients who did not experience disease progression or death was censored at the subject's last contact date. Follow-up is current as of 31 December 2018. The Kaplan–Meier method was utilized to estimate the EFS.25 EFS was compared between groups using the log-rank test.26 A Cox proportional hazards regression model was used to evaluate SUVmax and ratio of SUVmax.27 Software SAS 9.4®, was used for the analysis.

3 | RESULTS

3.1 | Patient demographics and disease characteristics

Demographic data for the evaluated patient cohort are shown in Table 1 for ARST0531 and ARST08P1. Figure 1 shows the disposition of patients enrolled on ARST0531 and ARST08P1 and the distribution of available FDG-PET imaging data. Of the 387 eligible patients with Clinical Group III disease enrolled on ARST0531, 130 patients had FDG-PET...
scans submitted for central review or had SUVmax data available from institutional report at any time point. Twenty-six IR patients had week 4 and 51 patients had week 15 FDG-PET imaging available for response evaluation. FDG-PET SUVmax at the primary tumor site was reported by the treating institution and evaluated by central imaging review if available. On the IR study, SUVmax data were analyzed for 111 patients prior to chemotherapy, 39 patients at week 4, and 84 patients at week 15. Of the 167 eligible and evaluable patients enrolled on ARST08P1, 105 patients had FDG-PET scans submitted for central review or had SUVmax data available from institutional report at any time point. Seventy HR patients had week 6, and 69 patients had week 19 FDG-PET imaging available for response evaluation. FDG-PET SUVmax of the primary tumors was reported by the treating institution and evaluated by central review if available. On the HR study, SUVmax data were analyzed for 95 patients prior to chemotherapy, 69 patients at week 6, and 55 patients at week 19.

### 3.2 Relationship between complete metabolic response and EFS

Of the 26 IR RMS patients who had FDG-PET imaging available for review at week 4 following one cycle of chemotherapy, a CMR was achieved in three (11.5%). No significant improvement in 3-year EFS was seen in patients who achieved a CMR compared to those who did not at week 4 (3-year EFS 67% vs 52%, \( p = 0.66 \)). Of the 51 patients who had FDG-PET imaging available for review at week 15 following five cycles of chemotherapy and local radiotherapy, CMR

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### TABLE 1 (Continued)

| Clinical characteristic | Number of 0531 patients (%) | Number of 08P1 patients (%) |
|-------------------------|----------------------------|-----------------------------|
| **Gender**              |                            |                             |
| Male                    | 67 (51.5%)                 | 53 (50.5%)                  |
| Female                  | 63 (48.5%)                 | 52 (49.5%)                  |
| **Age, years**          |                            |                             |
| 0–0.99                  | 3 (2.3%)                   | 1 (1.0%)                    |
| 1–9.99                  | 67 (51.5%)                 | 22 (21.0%)                  |
| ≥10                     | 60 (46.2%)                 | 82 (78.1%)                  |
| **Race**                |                            |                             |
| White                   | 99 (76.2%)                 | 78 (74.3%)                  |
| Black                   | 15 (11.5%)                 | 11 (10.5%)                  |
| Asian                   | 4 (3.1%)                   | 3 (2.9%)                    |
| Other/unknown           | 12 (9.2%)                  | 13 (12.4%)                  |
| **Ethnicity**           |                            |                             |
| Hispanic or Latino      | 17 (13.1%)                 | 23 (21.9%)                  |
| Not Hispanic or Latino  | 108 (83.1%)                | 78 (74.3%)                  |
| Unknown                 | 5 (3.9%)                   | 4 (3.8%)                    |
| **RMS histology**       |                            |                             |
| Embryonal               | 67 (51.5%)                 | 23 (21.9%)                  |
| Alveolar                | 57 (43.9%)                 | 75 (71.4%)                  |
| NOS/unknown             | 6 (4.6%)                   | 7 (6.7%)                    |
| **Maximum tumor size, cm** |                      |                             |
| <5                      | 55 (42.6%)                 | 21 (20.0%)                  |
| 5–9.99                  | 65 (50.4%)                 | 49 (46.7%)                  |
| ≥10                     | 9 (7.0%)                   | 35 (33.3%)                  |
| **Regional lymph node status** |                      |                             |
| N0                      | 100 (76.9%)                | 48 (45.7%)                  |
| N1                      | 30 (23.1%)                 | 56 (53.3%)                  |
| Not evaluated/unknown   | N/A                        | 1 (1.0%)                    |
| **Primary site**        |                            |                             |
| Orbit                   | 1 (0.8%)                   | 0 (0%)                      |
| Head or neck            | 4 (3.1%)                   | 5 (4.8%)                    |
| Parameningeal           | 76 (58.5%)                 | 13 (12.4%)                  |
| GU, bladder/prostate    | 12 (9.2%)                  | 5 (4.8%)                    |
| GU, non-bladder/prostate| 0 (0%)                     | 9 (8.6%)                    |
| Extremity               | 20 (15.4%)                 | 30 (28.6%)                  |
| Retroperitoneal/perineal| 15 (11.5%)                 | 25 (23.8%)                  |
| Trunk                   | 2 (1.5%)                   | 9 (8.6%)                    |
| Other or Missing Data   | 0 (0%)                     | 9 (8.6%)                    |
| **Fusion status**       |                            |                             |
| FOXO1−                  | 76 (58.5%)                 | 26 (24.8%)                  |
| FOXO1+                  | 44 (33.9%)                 | 38 (36.2%)                  |

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Abbreviations: GU, Genitourinary; N0, Regional nodes not clinically involved; N1, Regional nodes clinically involved by neoplasm; NOS, Not otherwise specified; RMS, rhabdomyosarcoma; VAC, Vincristine/antimycin/cyclophosphamide; VAC/VI, Vincristine/antimycin/cyclophosphamide alternating with vincristine/irinotecan.

aData missing for one patient.

bERMS/Spindle cell/BRMS were treated as FOXO1−.
was achieved in 32 (62.7%). No significant improvement in 3-year EFS was seen in patients who achieved a CMR compared to those who did not at week 15 (3-year EFS: 56% vs 68%, \( p = 0.46 \); Table 2; Figure 2).

Of the 70 HR RMS patients who had FDG-PET imaging available for review at week 6, a CMR was achieved in 24 (34.3%). No significant improvement in 3-year EFS was seen in patients who achieved a CMR compared to those who did not at week 6 (3-year EFS 16% vs 21%, \( p = 0.75 \)). Of the 69 patients who had FDG-PET imaging available for review at week 19, CMR was achieved in 50 (72.5%). No significant improvement in 3-year EFS was seen in patients who achieved a CMR compared to those who did not at week 19 (3-year EFS 13% vs 31%, \( p = 0.28 \); Table 2; Figures 2 and 3).

### 3.3 Relationship between SUVmax and EFS

The median (range) SUVmax of the primary tumor at diagnosis of IR and HR patients was 6.0 (range, 1.3–24.5) and 7.9 (range, 1.6–26.8), respectively. Increased SUVmax at study entry did not correlate with EFS in IR RMS patients (Hazard ratio: 0.97, \( p = 0.32 \)) or HR RMS (Hazard ratio: 1.00, \( p = 0.86 \); Table 3).

To determine if change in SUVmax during therapy was associated with EFS, a ratio of SUVmax during therapy to SUVmax at study entry (SUVmax0) was calculated. For IR RMS there was no difference in EFS based on change in SUVmax at week 4 or week 15. (Hazard ratio SUVmax4/ SUVmax0: 2.72, \( p = 0.21 \); Hazard ratio SUVmax15/ SUVmax0: 0.95, \( p = 0.91 \)). Similarly, for HR RMS, there

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**TABLE 2** Relationship between the presence/absence of complete metabolic response (CMR) and EFS in IR RMS (ARST0531) and HR RMS (ARST08P1) at different timepoints as assessed by central imaging review

| PET imaging criterion | N | 3 year event-free survival (95% CI) | \( p \)-value |
|-----------------------|---|-------------------------------------|-------------|
| **ARST0531**          |   |                                     |             |
| Response at week 4    |   |                                     |             |
| CMR                   | 3 | 67% (13.3–100%)                     | 0.66        |
| <CMR                  | 23| 52% (31.8–72.6%)                    |             |
| Response at week 15   |   |                                     |             |
| CMR                   | 32| 56% (39.1–73.4%)                    | 0.46        |
| <CMR                  | 19| 68% (46.7–90.2%)                    |             |
| **ARST08P1**          |   |                                     |             |
| Response at week 6    |   |                                     |             |
| CMR                   | 24| 16% (0–32.7%)                       | 0.75        |
| <CMR                  | 46| 21% (6.0–35.7%)                     |             |
| Response at week 19   |   |                                     |             |
| CMR                   | 50| 13% (2.4–24.0%)                     | 0.28        |
| <CMR                  | 19| 31% (1.8–59.9%)                     |             |
was no difference in EFS based on change in SUVmax at week 6 or week 19. (Hazard ratio SUVmax6/SUVmax0: 1.23, \( p = 0.75 \); Hazard ratio SUVmax19/SUVmax0: 0.66, \( p = 0.61 \); Table 3).

**4 | DISCUSSION**

This is the first prospective cooperative group study evaluating whether FDG-PET imaging predicts outcome in RMS patients. We evaluated SUVmax at diagnosis, change in SUVmax with therapy, and CMR during treatment (both early CMR following 4 and 6 weeks of chemotherapy in IR RMS and HR RMS, respectively, and late CMR following 15 and 19 weeks of chemotherapy in IR RMS and HR RMS, respectively); none of these parameters predicted EFS in either IR or HR RMS. We conclude that, at the timepoints we used, FDG-PET is not a useful tool to predict outcome for either IR or HR RMS.

Metabolic assessment of tumors using FDG-PET evaluation remains a relatively novel modality for assessing response and how best to incorporate this imaging modality into treatment paradigms is an active area of research. Multiple studies have documented FDG-PET response to be a predictor of outcome in several malignancies including Hodgkin lymphoma, renal cell carcinoma, non-small cell lung cancer, Ewing sarcoma, and osteosarcoma. A potential prognostic relevance for metabolic response as assessed by FDG-PET in pediatric RMS is supported by the adult STS literature. Adult patients with high-grade STS who attain an early metabolic response as defined by a greater than 26% drop in SUVmax after one cycle of chemotherapy have
a significantly improved overall survival (OS). Late metabolic response following chemotherapy significantly correlates with OS in univariate but not multivariate analysis. Moreover, several studies in the STS patient population have shown SUVmax at diagnosis to be a significant predictor of outcome, although these have been limited by small sample size and the inclusion of several differing histologic subtypes and tumor primary sites.

Since RMS is uncommon in adults, it has rarely been represented in STS studies conducted evaluating the utility of FDG-PET. The value of FDG-PET imaging for patients with RMS, thus, remains an open question. In osteosarcoma, the most common primary malignant sarcoma of bone in both the pediatric and adult population, FDG-PET has been shown to be a potential predictor of histologic response following neoadjuvant chemotherapy, a well-documented surrogate for outcome in this disease. While our results do not support the use of FDG-PET to predict outcome in IR or HR RMS, several studies have documented the value of FDG-PET imaging for disease staging. For example, FDG-PET has been found to have increased sensitivity and specificity compared to conventional imaging including 99mTechnetium methylene diphosphonate bone scintigraphy in the identification of distant RMS metastases, particularly bone and distant nodal metastases. A retrospective evaluation of FDG-PET showed improved sensitivity and specificity in identifying nodal metastases in RMS when compared with conventional imaging. This finding was confirmed in a recent prospective study. This study, however, documented a low concordance rate between FDG-PET and pathology after tissue biopsy with nodal tissue sampling and thus, tissue sampling should remain the gold standard when defining

TABLE 3 Relationship between FDG PET maximum standard uptake value (SUVmax) at study entry and ratio of later SUVmax values relative to baseline on EFS as assessed by the Cox proportional hazards model

| Study       | Sample size | Hazard ratio | 95% CI, for HR | p-value |
|-------------|-------------|--------------|----------------|---------|
| ARST0531    |             |              |                |         |
| SUVmax0     | 111         | 0.97         | (0.911, 1.031) | 0.32    |
| SUVmax4/SUVmax0 | 32     | 2.72         | (0.569, 13.047)| 0.21    |
| SUVmax15/SUVmax0 | 68      | 0.95         | (0.409, 2.226) | 0.91    |
| ARST08P1    |             |              |                |         |
| SUVmax0     | 95          | 1.00         | (0.945, 1.048) | 0.86    |
| SUVmax6/SUVmax0 | 64      | 1.23         | (0.344, 4.420) | 0.75    |
| SUVmax19/SUVmax0 | 50     | 0.66         | (0.128, 3.363) | 0.61    |
sites requiring local control with radiotherapy. At present, the data clearly support a role for FDG-PET imaging in the initial staging evaluation of RMS.

Our data contrast with prior single institution reports that supported a role for using CMR to predict EFS in patients with Group III RMS following 15 weeks of chemotherapy and radiation therapy for local control. The reasons for this discrepancy remain unclear. The prior studies were performed at a single institution where the timing of the FDG-PET imaging and techniques used could be well controlled, as opposed to our cooperative group study which relied on imaging performed at multiple institutions. Furthermore, the ARST0531 study requested FDG-PET imaging at Week 4 immediately prior to radiotherapy and at Week 15, approximately 6 weeks after completion of radiotherapy. Both of these timepoints are significantly earlier than the above single institution studies that delivered radiation therapy at week 15.

This study has several limitations, most notably the small sample size of the patient population available for this analysis—particularly the small number of paired baseline and follow-up studies at each timepoint. FDG-PET imaging was not a requirement for enrollment on either study, and there may have been bias introduced by selective submission of imaging studies, although we could detect no significant differences in the clinical features of the population with and without FDG-PET imaging available for review (data not shown). Several limitations similarly exist regarding the collection of the FDG-PET data. While the guidelines for FDG-PET imaging were specific in both protocols, precise standardization of imaging equipment was not practical due to the large number of institutions involved. Furthermore, while several FDG-PET imaging variables and their relationship to outcome were evaluated, more advanced parameters such as metabolic tumor volume and total lesion glycolysis that were beyond the scope of this analysis were not evaluated although could be considered for future analyses. Finally, FDG-PET imaging was performed at diagnosis, week 4 and week 15 of therapy in ARST0531, and at diagnosis, week 6, and week 19 in ARST08P1. It remains possible that FDG-PET response later in therapy, immediately following local control, or at the conclusion of all planned treatment could potentially be prognostic.

In conclusion, our analysis does not support using FDG-PET as a predictor for outcome in the IR or HR RMS population. Further prospective studies are needed to determine whether this imaging modality has a role in predicting response to therapy or outcome in other RMS subpopulations, and whether FDG-PET imaging at a later timepoint would be more predictive of outcome. Additional research is needed to identify other methods to measure therapy response that can reliably predict outcome in RMS.

**ETHICAL APPROVAL STATEMENT**
The planning, conduct, and reporting of this research are in accordance with the Helsinki Declaration as revised in 2013 (www.wma.net/policies-post/wma-declaration-of-helsinkietorical-principles-for-medical-research-involving-humansubjects/). The research was approved by institutional review board as per ICJME guidelines.

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**CONFLICT OF INTEREST**
The authors have no conflict of interest.

**AUTHOR CONTRIBUTIONS**
Each author has made substantial contributions to the conception and design, acquisition of data, and analysis and interpretation of data of this project. Each has been involved in drafting the manuscript or revising it critically for important intellectual content. All have reviewed the final manuscript and agreed upon the manuscript content.

**DATA AVAILABILITY STATEMENT**
Children’s Oncology Group Data Sharing Statement: The Children’s Oncology Group Data Sharing policy describes the release and use of COG individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) Guidelines. Only data expressly released from the oversight of the relevant COG Data and Safety Monitoring Committee (DSMC) are available to be shared. Data sharing will ordinarily be considered only after the primary study manuscript is accepted for publication. For phase 3 studies, individual-level de-identified datasets that would be sufficient to reproduce results provided in a publication containing the primary study analysis can be requested from the NCTN/NCORP Data Archive at https://ncn-data-archive.nci.nih.gov/. Data are available to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. For non-phase 3 studies, data are available following the primary publication. An individual-level de-identified dataset containing the variables analyzed in the primary results paper can be expected to be available upon request. Requests for access to COG protocol research data should be sent to: datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use. For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests. In addition to above, release of data collected in a clinical trial conducted under a binding
collaborative agreement between COG or the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical/biotechnology company must comply with the data sharing terms of the binding collaborative/contractual agreement and must receive the proper approvals.

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