

NRG-GY007

NCI Version Date: February 28, 2020

SUMMARY OF CHANGES

For Protocol Amendment #8 to: NRG-GY007

NCI Protocol #: NRG-GY007

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Summary of Changes

#	Section	Comments
1.	Title Pages	<ul style="list-style-type: none">• NCI Version Date is now February 28, 2020.• The Study Chair is now Charles Landen, M.D.• Wenxin Zheng's address was updated.• Hee Sun Kim-Suh is no longer the study Research Nurse, and this position will not be replaced at this time.
2.	6.6	In the last sentence, "using D2R and T forms" was changed to "via Rave."
3.	ICDs	The only change made to the Phase I and II ICDs was the NCI Version Date.

NRG-GY007
(ClinicalTrials.gov NCT #02713386)

**A PHASE I/II STUDY OF RUXOLITINIB WITH FRONT-LINE NEOADJUVANT AND
POST-SURGICAL THERAPY IN PATIENTS WITH ADVANCED EPITHELIAL
OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CANCER**

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI).

Lead Organization: NRG / NRG Oncology
This study is limited to NRG Oncology participation

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Protocol Agents

<u>Agent</u>	<u>Supply</u>	<u>NSC #</u>	<u>IND #</u>	<u>IND Sponsor</u>
Ruxolitinib	Incyte	752295	129988	NRG Oncology
Carboplatin	Commercial	241240	N/A	N/A
Paclitaxel	Commercial	673089	N/A	N/A

Participating Sites

- U.S.
- Canada
- Approved International Member Sites

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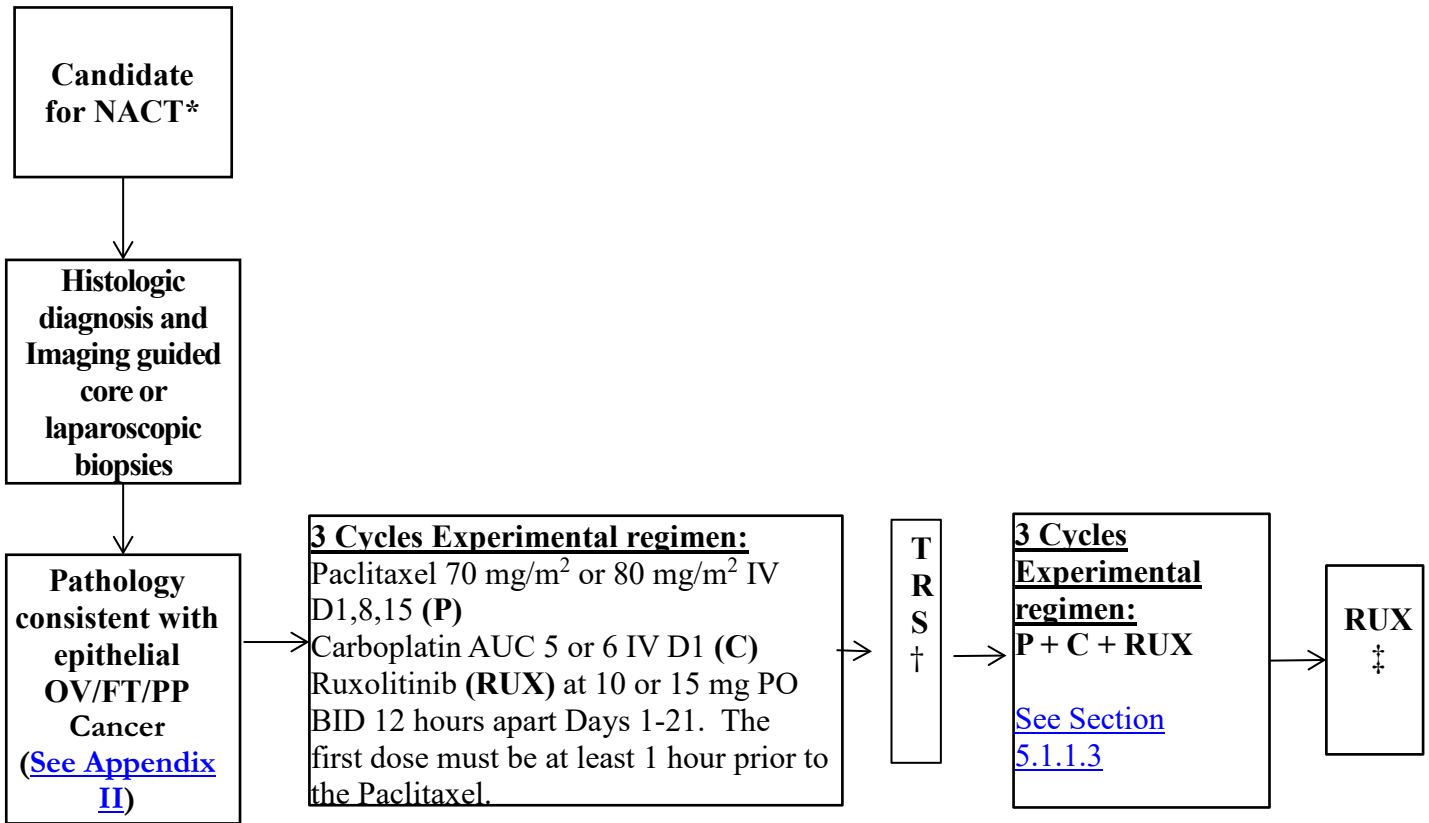
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**NRG-GY007
SCHEMA**

Phase I Component (01/09/2017) (04/06/2018)

NOTE: The Phase I Component is Complete



A Cycle is 21 days in length

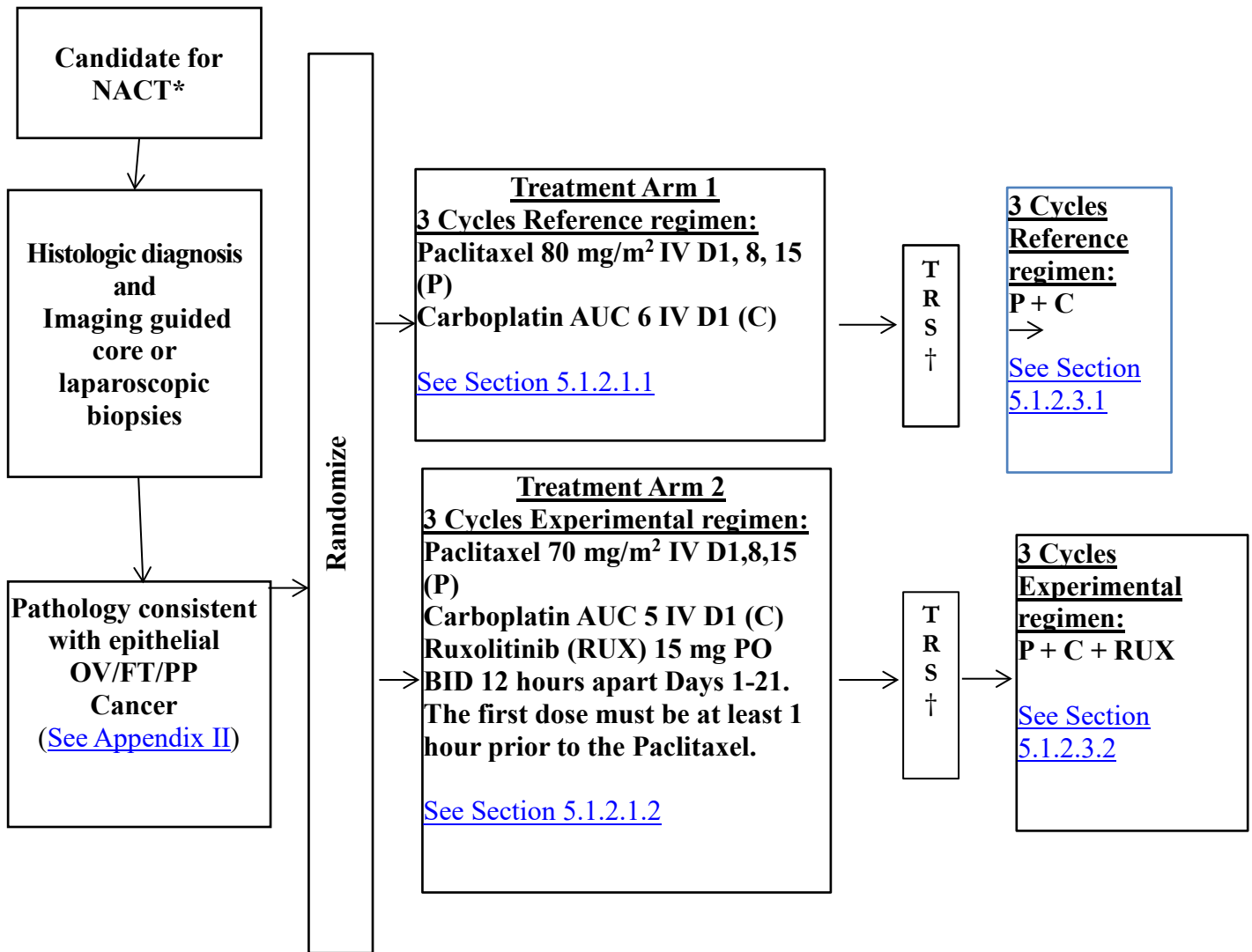
*NACT = Neoadjuvant chemotherapy

† TRS = Tumor Reductive Surgery (See [Section 5.1.1.2](#) and [Appendix VIII](#))

‡ Maintenance ruxolitinib will be evaluated only in participants who complete all 6 cycles of chemotherapy with RUX, until disease progression, unacceptable toxicity, or voluntary withdrawal. (See [Section 5.1.1.4](#))

Primary Endpoint: Safety/tolerability of RUX combined with chemotherapy: N = 12 to 42 patients (10/10/2016)

Phase II Component (01/09/2017) (04/06/2018) (07/30/2018)



A Cycle is 21 days in length

*NACT = Neoadjuvant chemotherapy

† TRS = Tumor Reductive Surgery

Primary Endpoint: Progression-Free Survival

N = Maximum 87 patients enrolled to experimental regimen, 43 enrolled to reference regimen (10/10/2016)

† Interval tumor reductive surgery; or core biopsies in case of progression, failure to respond to first 3 cycles or tumor reductive surgery medically contraindicated (See Section 5.1.2.2)

1. OBJECTIVES

1.1 Primary Objective

1.1.1 Phase I – Determine whether treatment with ruxolitinib in combination with conventional neoadjuvant and post-surgical chemotherapy is safe and tolerable in the primary therapy for epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

1.1.2 Phase II – Demonstrate whether treatment with ruxolitinib in combination with conventional neoadjuvant and post-surgical chemotherapy results in a prolonged progression-free survival when compared to chemotherapy alone, in primary therapy for epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

1.2 Secondary Objectives

1.2.1 Phase I:

- Determine frequency of patients who do not receive surgery within 6 weeks of completing cycle 3 therapy for reasons other than non-response, disease progression, or medical contraindications. **(03/20/2017)**
- Determine if continuation of ruxolitinib as maintenance therapy in participants who complete 6 cycles of standard chemotherapy in combination with ruxolitinib and have not experienced unacceptable toxicity or disease progression is safe and tolerable.

1.2.2 Phase II:

- Determine the impact of ruxolitinib in combination with chemotherapy on progression-free survival as a function of proposed exploratory biomarkers - ALDH+CD133+ (possibly also CD24+CK19+) co-staining by AQUA immunofluorescence (IF); ratio of tumor expression of CD8:FOXP3 by immunohistochemistry (IHC); and tumor CD3, CD4, TAI-1, HLA class I and II, CD68 expression by IHC in archived tumor tissue, BRCA status, and serum C-reactive protein (CRP) and IL-6 levels in pre-treatment serum. (04/05/2019)

Note: Testing of banked biospecimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and improved in accordance with Clinical Trials Network (NCTN) policies.

- Investigate the prognostic significance of exploratory biomarkers (see above) in terms of both progression-free survival and overall survival in women receiving conventional chemotherapy alone.
- Determine whether treatment with ruxolitinib in combination with conventional chemotherapy is associated with total gross resection rate at time of interval cytoreductive surgery.

- Determine whether treatment with ruxolitinib in combination with conventional chemotherapy is associated with complete pathologic response defined at interval cytoreductive surgery.
- Demonstrate whether treatment with ruxolitinib in combination with conventional chemotherapy results in an improvement in overall survival in primary management of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

2. BACKGROUND

2.1 Rationale for selected approach and trial design

The constellation of diseases commonly referred to as “ovarian cancer,” includes epithelial ovarian, primary peritoneal and fallopian tube carcinomas, and is diagnosed in approximately 22,000 women in the United States annually. More sobering is the projection that annually approximately 14,000 will die of disease.¹ Based on this high relative mortality to incidence rate, ovarian cancer ranks as the third most lethal malignancy affecting women. Its lethality has been attributed largely to advanced stage at diagnosis (and absence of effective screening for potentially early stage disease). In addition, after standard management of newly diagnosed advanced disease including surgical cytoreduction and platinum/taxane chemotherapy, the vast majority of patients will recur and die of disease. The benefits of “standard” front-line therapy are limited by both intrinsic and acquired drug resistance and the lack of specificity for mechanisms of disease progression. Thus, there is a need for the development of new agents with activity against ovarian cancer, primarily those specifically targeting such mechanisms.

Although in clinical practice, based on selection factors, these patients are at higher risk for disease progression over time compared with patients selected for primary debulking surgery, whether or not there are fundamental differences in tumor biology that would affect the application of novel approaches remains to be determined. In the absence of data to the contrary, it remains reasonable to consider the population receiving neoadjuvant chemotherapy with interval tumor reductive surgery to be representative of all women with stage III and IV epithelial ovarian cancer. Furthermore, patients treated with neoadjuvant chemotherapy and interval tumor reductive surgery represent the ideal population for the study of targeted agents. In this circumstance, tumor tissue is obtained as part of standard care prior to and at a standard interval after treatment exposure, thereby allowing a pharmacodynamic evaluation of tumor based correlative laboratory parameters for their ability to predict therapeutic efficacy and assessment of surgically defined intermediate surrogate endpoints. In addition, with progression free survival as the goal standard primary outcome measure for efficacy, the event rate for this population allows relatively rapid screening of novel agents.

Biologic agents directed against specific therapeutic targets are postulated to be more likely to be effective in patients with overexpression or activation of the intended target. Such is the promise of personalized medicine. However, the ability to demonstrate this principle conclusively within a clinical trial has been difficult. Neoadjuvant

chemotherapy with interval tumor reductive surgery has become a progressively pervasive approach to primary treatment in the U.S. and abroad. This trend has been bolstered by two randomized phase III trials comparing neoadjuvant chemotherapy followed by interval tumor reductive surgery to primary debulking surgery followed by post-operative chemotherapy.^{2,3} These trials demonstrated no survival advantage for primary debulking surgery; however, primary debulking surgery was associated with slightly greater perioperative major morbidity and mortality. The incorporation of neoadjuvant chemotherapy with interval surgery into clinical practice is likely to increase over time, given the randomized trial results and lack of well-defined selection criteria for primary debulking surgery. The proposed study reflects emerging clinical practice, and we anticipate rapid accrual of patients who meet all eligibility criteria, without excessive comorbidities or poor performance status that might compromise the outcome measures.

Interleukin-6 (IL-6)-Janus Kinase (JAK)-STAT3 signaling axis. There is increasing evidence that the Interleukin-6 (IL-6)-Janus Kinase (JAK)-STAT3 signaling axis is fundamental to disease progression in ovarian cancer and JAK mediated activation of STAT3 in ovarian cancer and that members of this pathway may serve as rational therapeutic targets. STAT3 is constitutively active in the majority of epithelial ovarian cancers.⁴ JAK mediated activation of STAT3 in ovarian cancer cells was reported as a therapeutic target of ovarian cancer cells over 10 years ago. Burke and colleagues demonstrated that the JAK2 inhibitor AG490 restricted cancer cell growth via the induction of apoptosis.⁴ There are likely multiple mechanisms by which JAK1/2 signaling can act as a driver of tumor progression. Recently, Gritsina et al. noted, “persistent activation of signal transducer and activator of transcription (STAT3) is frequently detected in ovarian carcinoma. STAT3 is activated by Janus family kinases (JAK) via cytokine receptors, growth factor receptor and non-growth factor receptor tyrosine kinases. Activation of STAT3 mediates tumor cell proliferation, survival, motility, invasion, and angiogenesis, and recent work demonstrates that STAT3 activation suppresses anti-tumor immune responses and supports tumor-promoting inflammation.”⁵

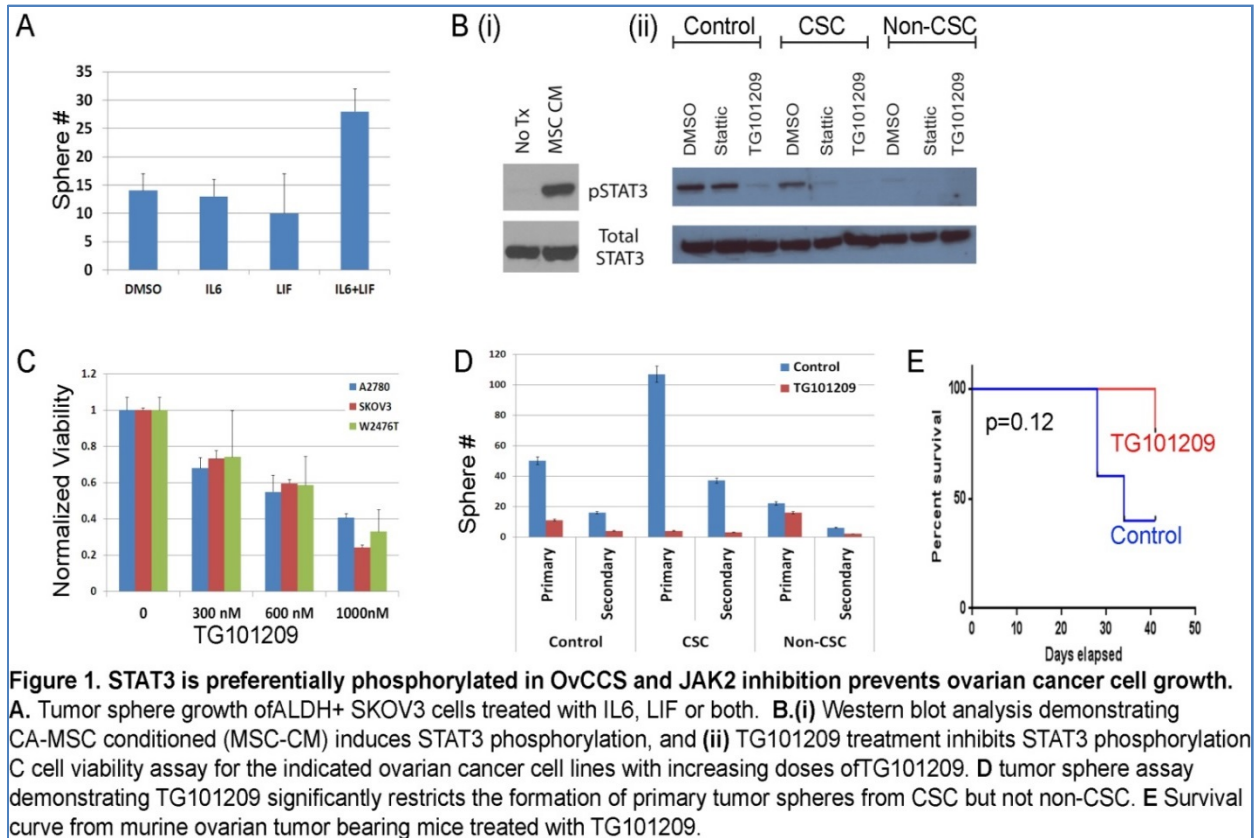
JAKs are known to upregulate inflammation in the tumor microenvironment, and the degree of chronic inflammation/desmoplasia has been associated with poor prognosis and may play a critical role in tumor progression and chemotherapeutic drug resistance for epithelial ovarian cancer. It has been shown that JAKs can mediate pro-inflammatory cytokine signaling through activation of STAT transcription factors.⁶ Systemic inflammation and tumor desmoplasia are known features of advanced solid tumors, and the degree of chronic inflammation and tumor desmoplasia have been considered poor prognostic factors.^{7,8} Furthermore, inflammatory signaling has been shown to mediate several metabolic features of advanced malignancy such as cachexia.⁹ Elevated serum levels of C-reactive protein (CRP), a well-established peripheral marker of systemic inflammation, have been associated with poor prognosis for a variety of solid tumors.¹⁰⁻²³ In a clinical trial of patients with metastatic pancreatic cancer, the median survival for those with baseline CRP level greater than 10 mg/L (median value) was 3.8 months, compared with 9.7 months for those with levels less than or equal 10 mg/L (hazard ratio 2.3, 95% confidence interval 1.6 – 3.1).¹² Chronic inflammation may also play a critical

role in tumor progression and chemotherapeutic drug resistance for epithelial ovarian cancer.²⁴⁻²⁶ The NFκB pathway has been found to be a major source of pro-inflammatory cytokines. Furthermore, a major characteristic of CD44+ ovarian cancer stem cells is constitutive activation of the NFκB pathway, and inhibition of this pathway has been shown to induce cell death in ovarian cancer stem cells.²⁷ Consistent with the literature for pancreatic cancer, the degree of systemic inflammation appears to be a negative prognostic factor in patients with advanced ovarian cancer. Hefler et al. showed in a multi-institution study of 623 women with epithelial ovarian cancer that serum CRP was associated with platinum resistance and poor overall, independent of other established prognostic factors.²⁰ Similarly, Sharma et al. showed that the Glasgow Prognostic Score,²⁸ an index of systemic inflammatory response based on serum CRP level > 10 mg/L and hypoalbuminemia (albumin < 3.5 g/dL) independently predicted poor overall survival in a multivariate analysis.²⁹ IL-6, a pro-inflammatory cytokine synthesized and secreted in both tumor cells and stroma in the tumor microenvironment, is a) a key upstream promoter JAK/STAT3 signaling,³⁰ b) typically present at high levels in the serum and ascites of women with advanced epithelial ovarian cancer,³¹ and c) a negative prognostic factor.³¹

Emerging data suggest that the IL-6/JAK/STAT3 pathway is important in the regulation of growth and differentiation of tumor cells with stem cell properties. Though the definition of tumor cells with stem cell properties has been debated, several studies have identified aldehyde dehydrogenase (ALDH) enzymatic activity as a marker for cancer stem cells (CSCs). In a study of breast cancer, ALDH(+) cells were present in a majority of tumors and capable of directly generating tumors in vivo.³² Independent studies in colon cancer suggested that ALDH identifies colon CSCs; as few as 25 ALDH(+) cells could generate tumors whereas ALDH(-) cells could not.^{33,34 33,3433,34} Based on the evidence for ALDH as a stem cell marker in solid tumors, we showed that ALDH(+) cells isolated from both ovarian cancer cell lines and primary debulking specimens were chemo-resistant and preferentially grew tumors, compared with ALDH(-) cells, validating ALDH as a marker of ovarian CSCs.³⁵ Using ALDH in combination with CD133 (another marker identified in association with CSCs in many solid tumors), we observed even greater growth in the ALDH(+)CD133(+) cells compared with ALDH(+)CD133(-) cells from primary ovarian cancer samples, suggesting a further enrichment of ovarian CSCs in the ALDH(+)CD133(+) population. Finally, the presence of ALDH(+)CD133(+) cells in debulked primary tumor specimens correlated with reduced disease-free and overall survival in ovarian cancer patients. Taken together, our findings defined ALDH and CD133 as a functionally significant set of markers to identify ovarian CSCs.

STAT3 is preferentially phosphorylated in CSCs from breast and colon cancers.^{36,37}
^{36,3736,37} IL-6 has been shown to be a primary activator of STAT3 in breast CSCs leading to increased tumor growth and resistance to therapy.³⁸ Importantly, JAK2 or STAT3 inhibition decreased CSC number and blocked the growth of tumor xenografts.^{36,39}
^{36,3936,39}

We also previously reported the presence of large numbers of carcinoma associated



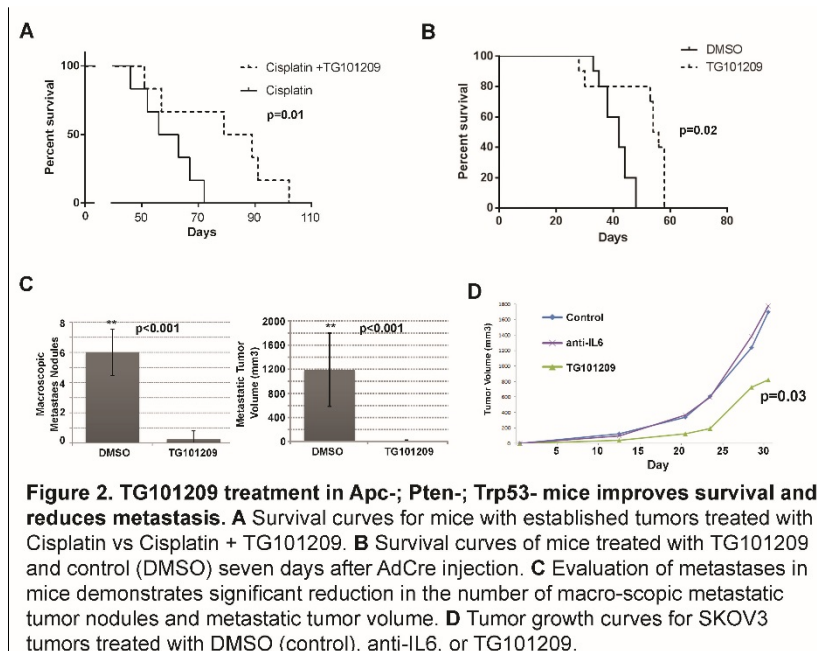
mesenchymal stem cells (CA-MSCs) in ovarian cancer.⁴⁰ CA-MSCs significantly promoted ovarian cancer growth via their actions on ovarian CSCs—increasing ‘stemness’. Importantly, we have found that compared to mesenchymal stem cells, CA-MSCs secrete large amounts of IL-6 and the hematopoietic stem cell regulatory factor leukemia inhibitory factor (LIF). As shown in Figure 1, we investigated whether IL-6 and LIF could impact ovarian CSCs. We found that while neither protein alone had significant impact, the combination of both IL-6 and LIF dramatically promoted the growth of ALDH+ CSCs (Figure 1A). Both IL-6 and LIF signal via the GP130/JAK2 receptor complex to activate STAT3 signaling. We therefore evaluated the impact of CA-MSC on tumor cell STAT3 activation. Consistent with increased IL-6 and LIF expression, we observed that CA-MSC conditioned media significantly increases STAT3 phosphorylation (Figure 1Bi). We next tested the impact of a STAT3 inhibitor (Stattic) and a JAK2 inhibitor (TG101209) on ovarian carcinoma CSC STAT3 phosphorylation. Similar to that observed for breast and colon cancers,^{36,37} we noted preferential phosphorylation of STAT3 in ovarian CSCs versus non-CSCs (sorted based upon ALDH, CD133, or CD24 depending on the cell line) (Figure 1Bii). Interestingly, in unsorted cells we observed that JAK2 inhibition was more effective at inhibiting STAT3 phosphorylation than was the STAT3 inhibitor (Figure 1Bii). We next performed cytotoxicity assays with the JAK2 inhibitor. In both human and murine cell lines we observed significant toxicity, with an average IC₅₀ of ~750nM (Figure 1C). We also tested the JAK2 inhibitor in a tumor sphere assay with cell lines and cells derived from primary tumors. As expected, isolated ovarian carcinoma CSCs demonstrated far greater

tumor sphere forming capacity than unsorted controls and non-CSCs (Figure 1D). While JAK2 inhibition had minimal impact on primary tumor sphere growth for non-CSCs, treatment resulted in a 28-fold reduction in primary tumor sphere formation from ovarian carcinoma CSCs. In addition, secondary sphere formation was similarly blocked.

Using a p53^{-/-},PTEN^{-/-},APC^{-/-} murine orthotopic model of epithelial ovarian cancer (Wu, 2007), we have performed survival studies to evaluate the impact of JAK2 inhibition on ovarian cancer growth.

Tumors were initiated via intrabursal injection of CRE recombinase expressing adenovirus (AdCre) and monitored until tumors reached ~500 mm³. Tumors were paired based on size and then randomized to cisplatin vs. cisplatin plus TG101209 for 21 days. Combinatory treatment of cisplatin plus TG101209 improved survival of mice compared with mice treated with cisplatin only (Fig 2A).

We next treated ‘early stage’ ovarian cancers with TG101209. AdCre was injected into the ovarian bursa to initiate tumors and then treatment with TG101209 or vehicle was initiated one week after injection and maintained for 21 days. Mice were monitored until they became ill or primary tumor volumes reached humane endpoints for euthanasia per institutional guidelines (~1000 mm³). TG101209-treated mice demonstrated significantly increased survival (Fig. 2B). In addition, at the time of sacrifice control mice were ill appearing, with evidence of ascites and bowel obstructions. In contrast, TG101209 treated mice were well at the time of euthanasia but were sacrificed because of primary tumor volumes met euthanasia criteria. At necropsy, vehicle treated mice had widespread metastatic disease with metastatic nodules in the intestine, liver, peritoneum, adipose and bladder (Fig. 2C). In contrast, only 1 of 14 mice treated with TG101209 had demonstrable metastases (Fig 2C).



Consistent with our work, Abubaker and colleagues reported that JAK2 inhibition, with a different small molecular JAK2 inhibitor, resulted in loss of stem-like cells and suppression of tumor growth in combination with paclitaxel.⁴¹

The above data suggest that JAK2 targeting might be therapeutically beneficial in advanced epithelial ovarian and related malignancies, by selectively eliminating the CSC fraction of tumors *in vivo* and thereby reducing metastasis.

Recent data suggest that IL-6/JAK/STAT3 signaling may impede intrinsic cell mediated anti-tumor immunity. The paradigm of Treg-mediated immunosuppression in human cancer was originally defined in epithelial ovarian cancer.⁴² In a detailed analysis of Treg cells in 104 ovarian carcinoma cases, it was shown that human tumor-infiltrating Treg cells suppressed tumor-specific T-cell immunity and contributed to growth of human tumors *in vivo*. At all stages of disease, increased accumulation of Treg cells in tumor was associated with poor OS. In addition, a high CD8⁺/Treg ratio has been associated with favorable prognosis in epithelial ovarian cancer,⁴³ suggesting that an abundance of CD8 effector cells may overcome Treg-mediated suppression. We therefore hypothesize that those immune therapies that enhance CD8⁺ T-cell accumulation and activity while reducing the population of Treg cells will demonstrate anti-tumor activity. Experimental depletion of Treg cells in tumor-bearing mice has been shown to improve immune-mediated tumor clearance, indicating that strong anti-tumor immunity may require breaking Treg-mediated tolerance to tumor antigens.^{44,45 44,4544,45} Activation of the JAK/STAT pathway has been shown to stimulate the recruitment and expansion of negative regulatory cells including myeloid derived suppressor cells and regulatory T-cells. Gritsina et al. showed that the JAK inhibitor AZD1480 significantly reduced tumor growth rate, volume and ascites production in a murine model of human ovarian cancer while decreasing the concentration of suppressor T cells in the peritoneal tumor microenvironment of tumor-bearing mice compared with control mice.⁵ A similar finding was recently reported in an immunocompetent pancreatic cancer *in vivo* model, with enhanced efficacy in combination with checkpoint inhibitors.⁴⁶

Finally, the IL-6/JAK/STAT3 pathway has been implicated in promotion of tumor invasion and metastasis. Silver et al demonstrated that inhibition of STAT3 (a downstream effect of JAK inhibition), reduced the motility of ovarian cancer cells *in vitro*. Activated STAT3 co-localized to focal adhesions in these cells, suggesting that JAK/STAT signaling may contribute to ovarian cancer cell invasiveness.⁴⁷ Gritsina et al. demonstrated a reduction in tumor-associated matrix metalloproteinase (MMP) activity in an *in vivo* murine model of human ovarian cancer.⁵

The above pre-clinical data provide compelling rationale for targeting the IL-6/JAK/STAT3 signaling pathway in ovarian cancer. For this proposal, we have chosen to implement ruxolitinib; an FDA approved inhibitor of JAK1/2 with preliminary evidence of efficacy and tolerability when used in combination with chemotherapy in other solid tumors. The detailed rationale for this agent is detailed below ([section 2.2](#)).

This trial will not only examine the clinical and biologic effectiveness of an agent hypothesized to target key processes hypothesized to drive tumor progression in ovarian cancer, but will also serve as a model by which future biologic agents can be tested. In particular, it will allow determination of 1) whether or not the presumed target is indeed affected by the biologic agent through comparison of pre- and post-treatment tumor specimens; 2) whether efficacy is relatively enhanced in patients with hypothetically predictive biologic features; and 3) whether the biologic therapy adds additional clinical benefit to conventional chemotherapy. The unique features of the phase II randomized design would offer an efficient, resourceful mechanism to transition promising agents to phase III development with a higher likelihood of efficacy in patient populations selected based on predictive tools generated with phase II scientific data.

2.2 Ruxolitinib (10/10/2016)

Ruxolitinib is an oral JAK inhibitor with selectivity for JAK1 and JAK2. It is indicated for the treatment of intermediate or high-risk myelofibrosis. FDA approval for ruxolitinib was based largely on results of a phase III, randomized, placebo-controlled trial (COMFORT-I, NCT00952289) in 304 patients with intermediate to high risk myelofibrosis.⁴⁸ The investigators demonstrated a reduction in spleen size by at least 35% by 24 weeks (primary endpoint) of 41.9% in the ruxolitinib group versus 0.7% for the placebo group, a significant improvement in symptom score and a 50% improvement in survival over the study period. The rate of discontinuation of the study drug because of adverse events was 11.0% in the treatment group versus 10.6% in the placebo group. Anemia and thrombocytopenia were the most common adverse effects related to ruxolitinib. However these patients have hematopoietic compromise at baseline, and these events rarely led to discontinuation of study drug (one patient for each event). The starting dose of ruxolitinib depended on the baseline platelet count: 15 mg twice daily for a platelet count of 100,000/mcl to 200,000/mcl and 20 mg twice daily for a platelet count that exceeded 200,000/mcl.

Although ruxolitinib has yet to be evaluated in patients with epithelial ovarian cancer, there is a clear mechanistic rationale as detailed above, and the combination of ruxolitinib with a variety of cytotoxic chemotherapy regimens has been under investigation in a number of ongoing clinical trials for multiple other solid tumors. Hurwitz et al. recently presented data from a randomized double-blind phase II study of ruxolitinib or placebo with capecitabine as second-line therapy (all had failed gemcitabine) in patients with metastatic pancreatic cancer.⁴⁹ Ruxolitinib or placebo was administered at 15 mg twice daily, days 1 – 21 with capecitabine at 1000 mg/m² twice daily, days 1 – 14. The primary outcome measure was overall survival. For the 127 enrolled, the 12-month survival was 22% for the ruxolitinib group and 11% for the placebo group (hazard ratio 0.79, 95% CI 0.53 – 1.18). Interestingly, a pre-planned Cox regression analysis, adjusting for all other potential prognostic factors, demonstrated that for patients with a high baseline CRP level (> 13 mg/L, n = 60), treatment including ruxolitinib was associated with a statistically significant improvement in overall survival (hazard ratio 0.50, 95% confidence interval 0.26 – 0.96). A preferential clinical benefit was also observed in this subgroup of 60 patients with respect to clinical response, pain control, change in performance status, and

nutritional status.

Adverse effects of ruxolitinib are detailed in [section 7.3](#).

Other trials exploring the combination of ruxolitinib with cytotoxic chemotherapy were initiated. These include: phase I trial of gemcitabine and ruxolitinib with or without nAb paclitaxel in advanced pancreatic cancer (NCT01822756); randomized phase II trial of capecitabine with or without ruxolitinib in breast cancer (NCT02120417); and phase II randomized trial of pemetrexed and cisplatin with or without ruxolitinib in non-small cell lung cancer (NCT02119650). There have been to date no studies evaluating the safety and/or efficacy of ruxolitinib in combination with platinum-taxane combination chemotherapy.

For the ruxolitinib solid tumor clinical development program, Incyte terminated the sub-study of the Phase 2 study, INCB 18424-267, of ruxolitinib or placebo in combination with regorafenib in patients with relapsed or refractory metastatic colorectal cancer (CRC) and high C-reactive protein (CRP) and the Phase 3 study, INCB 18424-362, of ruxolitinib or placebo in combination with capecitabine for the second-line treatment of patients with advanced or metastatic pancreatic cancer. These decisions were taken after planned interim analyses demonstrated that there was an insufficient level of efficacy to warrant continuation. There were no obvious safety issues noted in either study. These decisions were based on recommendations from independent, unblinded Data Monitoring Committees. In addition to these studies, Incyte also took the decision to terminate other ongoing solid tumor studies of ruxolitinib in combination with chemotherapy relying pre-selecting for patients with high CRP levels. These studies included Phase 2 studies in lung and breast cancer, INCB 18424-266 and INCB 18424-268, the other sub-study of INCB 18424-267, and a second Phase 3 study in pancreatic cancer, INCB 18424-363. Incyte is working to close-out these studies, unblind all patients, and further evaluate all available data.

In summary, outcomes for patients with advanced epithelial ovarian, primary peritoneal and fallopian tube cancers treated with standard therapy have been historically poor. Preliminary data indicate the potential of JAK inhibition to decrease pro-inflammatory cytokine mediated signaling, directly target CSC, decrease the infiltration of tumor with negative regulatory T cells and reduce invasive and metastatic potential. We hypothesize that the implementation of a JAK inhibitor in combination with standard chemotherapy may translate into improved disease-related outcomes in women with epithelial ovarian cancer and related malignancies and that subsets of patients may experience enhanced benefit based on biologic characteristics of tumors and their microenvironments. Safety and efficacy of ruxolitinib have been demonstrated in a phase III cancer trial, leading to FDA approval in an oncology indication. Recent results of a phase II trial preliminarily suggested an overall survival advantage for ruxolitinib in combination with second line chemotherapy compared with chemotherapy alone for patients with metastatic pancreatic cancer, with a statistically significant effect in those with evidence of up-regulated pro-inflammatory signaling; treatment in combination with single agent chemotherapy was relatively tolerable with no major safety signals. We therefore propose a phase II

randomized trial to evaluate the efficacy of ruxolitinib in patients with newly diagnosed advanced disease in the context of and following standard cytotoxic therapy and surgery with exploration of biologic characteristics hypothetically predictive of efficacy.

(04/06/2018)

2.3 Reference/backbone chemotherapy regimen

A consideration of relative efficacy and safety was made in the determination of the reference/backbone chemotherapy regimen for this trial. Results of two phase III randomized trials, JGOG 3016⁵⁰ and GOG-0262⁵¹ suggests that intravenous carboplatin with dose-dense weekly paclitaxel would be the most reasonable choice. Long-term outcomes data demonstrated significant improvement in progression-free and overall survival (OS) in JGOG 3016 and in progression-free survival (PFS) in the non-bevacizumab subset within GOG-0262. Furthermore, long-term outcome data from JGOG 3016 demonstrated maximal benefit of weekly dose-dense therapy in patients with more advanced suboptimal disease, reflecting the population to be evaluated in NRG-GY007. From the safety standpoint, due to the concern for possible additive myelosuppression with the addition of ruxolitinib to a platinum-taxane regimen, data related to differential hematologic toxicity of the every three week versus dose-dense regimen in the front-line setting were reviewed. As summarized in Table 1 and Table 2, results from both JGOG 3016 and GOG-0262 demonstrated that though actual percentages in types of clinically significant toxicities differed (most likely due to differences in grading systems), the only grade 3 or greater hematologic toxicity significantly worse for the dose-dense paclitaxel group was anemia. Of note, although clinically impactful myelosuppression was no different between regimens for JGOG 3016, for GOG-0262, grade ≥ 3 neutropenia was significantly greater in the every 3 week paclitaxel cohort (83.1%), than in the weekly dose-dense group (72.0%). In both trials, there was no difference in the rates of febrile neutropenia or in grade ≥ 3 thrombocytopenia.

Table 1. JGOG 3016: Hematologic Toxicity (N = 626)

Type	Q3W	Weekly	P value
Anemia (Grade ≥ 3)	44%	69%	< 0.0001
Neutropenia (Grade ≥ 3)	88%	92%	0.15
Febrile Neutropenia (Grade ≥ 3)	9%	9%	1.00
Thrombocytopenia (Grade ≥ 3)	38%	44%	0.19

Table 2. GOG-0262: Hematologic Toxicity (N = 683)

Type	Q3W	Weekly	Relative Risk 95% CI
Anemia (CTC Grade ≥ 3)	15.7%	36.5%	0.33 – 0.57
Neutropenia (CTC Grade ≥ 3)	83.1%	72.0%	1.06 – 1.25

Febrile Neutropenia (CTC Grade ≥ 3)	4.7%	3.8%	0.60 – 2.50
Thrombocytopenia (CTC Grade ≥ 3)	15.7%	19.7%	0.58 – 1.11

Another advantage of the carboplatin with dose-dense paclitaxel regimen is three times more frequent opportunities for patient safety assessment. From the feasibility standpoint, the dose-dense weekly regimen has become a community standard and is listed in the National Comprehensive Cancer Network (NCCN) guidelines as standard (category 1). In order to control for the potential influence on efficacy outcomes as they related to variations in cytotoxic regimens, the chemotherapy regimen in NRG-GY007 will be held consistent across the study population.

2.4 Evaluation of safety (10/10/2016) NOTE: The Phase I portion of the study is complete. (04/06/2018)

However, because there are no studies yet demonstrating the safety of combining ruxolitinib with platinum-taxane combination chemotherapy, this trial will initially employ a formal phase I component primarily designed to evaluate the safety of ruxolitinib in combination with standard platinum-taxane chemotherapy. Our proposed phase I design is informed by data related to myelosuppression from the two front-line randomized phase III trials examining carboplatin and dose-dense paclitaxel (JGOG 3016 and GOG-0262). The dose-dense regimens in these trials initiated carboplatin at an AUC of 6 IV q 3 weeks with paclitaxel initiated at 80 mg/m² IV weekly. The protocols for these trials utilized systematic dose modification rules for carboplatin (and paclitaxel for GOG-0262) related to neutropenia and for carboplatin related to thrombocytopenia. For GOG-0262, the required dose modification for the first instance of dose-limiting neutropenia and/or thrombocytopenia was a reduction in carboplatin AUC.

Eligibility for both JGOG 3016 and GOG-0262 included a minimum absolute neutrophil count (ANC) of $1.5 \times 10^9/L$ and a minimum platelet count of $100 \times 10^9/L$. In addition, patients were required to have both a minimum ANC of $1.0 \times 10^9/L$ and a minimum platelet count of $75 \times 10^9/L$ to receive treatment on cycle day 1 in subsequent cycles (C2 – C6), and both a minimum ANC of $0.5 \times 10^9/L$ and a minimum platelet count of $50 \times 10^9/L$ to receive paclitaxel on days 8 and 15 during any cycle.

As stated above, for JGOG 3016 and GOG-0262, indications for carboplatin dose reduction based on neutropenia were: febrile neutropenia, absolute neutrophil count (ANC) $< 0.5 \times 10^9/L$ persisting ≥ 7 days, or treatment delay > 7 days. Granulocyte-colony stimulating factor (G-CSF) was implemented for complicated neutropenia or treatment delay based on neutropenia. Rules for holding day 15 of weekly paclitaxel for dose limiting neutropenia were also included. The indications for carboplatin dose reduction based on thrombocytopenia differed slightly between the two trials. For JGOG 3016, carboplatin was dose reduced for a platelet count $< 10 \times 10^9/L$ or for bleeding associated with a platelet count between $10 \times 10^9/L$ and $50 \times 10^9/L$. In GOG-0262, carboplatin was dose reduced for a platelet count $< 25 \times 10^9/L$ (CTC grade 4) or for bleeding associated with a platelet count between $25 \times 10^9/L$ and $50 \times 10^9/L$ (CTC grade

3).

Data related to dose modification and dose intensity for the dose-dense regimen in JGOG 3016 led to the following observations:

- Fewer than 50% of patients completed the regimen without dose modifications, and most dose modifications were made due to neutropenia.
- The frequency of cycle delay (> 7 days) was 76% (compared with 67% in the q 3 week paclitaxel cohort). The vast majority of delays were due to neutropenia.
- Mean dose intensity for carboplatin in AUC (mg/mL per min) in the dose-dense weekly paclitaxel cohort was 4.62 (compared with 5.13 in the q 3 week paclitaxel cohort).
- The mean dose intensities relative to those predicted by initial dose levels for both carboplatin and paclitaxel were 77% and 79%, respectively (compared with 85% and 86%, respectively, for the q 3 week paclitaxel cohort).
- Despite lower overall dose intensity for both standard agents in the dose-dense cohort, the dose-dense regimen was associated with a significant advantage in terms of both PFS and OS.

Data related to dose modification and dose intensity for the 288 women assigned to the dose-dense regimen in GOG-0262 led to the following observations:

- 83% received carboplatin in all 6 cycles (compared with 91% of 314 in the q 3 week paclitaxel cohort).
- 76% received paclitaxel in all 6 cycles (compared with 87% in the q 3 week paclitaxel cohort).
- The cumulative incidence of patients requiring carboplatin dose reduction for dose-limiting neutropenia and/or thrombocytopenia was 24.0% by C3 (based on C1 and C2 hematologic DLT events), with an additional 18% requiring dose reduction by C6. [See section 15.3.2](#) for details.

Given the concern for possible additive myelosuppression with the addition of ruxolitinib to the dose-dense paclitaxel regimen, we have integrated the following elements in the design of the phase I portion of NRG-GY007, in order to provide a rigorous evaluation of safety and toxicity and to maximize protection of trial participants:

- Evaluation of dose-limiting toxicity (DLT) over longer interval. The phase I portion evaluates dose level safety as a function of DLT for more than one cycle, specifically in cycle (C) 1(C1) and C2. No patient may be enrolled at the next higher dose level, until all patients at the previous dose level have been followed through the end of C2.

Patients who do not experience DLT and who do not complete 2 cycles of therapy will be replaced. By including two cycles rather than one, we will improve the resolution in capturing early, potentially cumulative serious impact on DLT related to myelosuppression.

- Dose escalation design, with provision for initial de-escalation of ruxolitinib dose. The standard single agent dose for ruxolitinib as chronic therapy for moderate to severe myelofibrosis (a condition associated with extremely poor marrow reserve and chronic thrombocytopenia) is 25 mg PO bid. Lower doses ranging from 5 mg PO daily to 15 mg PO bid are known to be biologically active (see Investigator Brochure). The dose/schedule incorporated in the majority of completed and ongoing phase I, II and III trials with cytotoxic chemotherapy combined with ruxolitinib is 15 mg/PO bid; this is the target dose/schedule. In the original version of the concept we proposed a dose de-escalation design. We have revised this to primarily a dose escalation design with exception of an initial de-escalation of ruxolitinib dose to account for the possibility that the starting ruxolitinib dose could be too high. In that case, we would re-escalate if a safe ruxolitinib dose is identified, to take into account the possibility that patients could tolerate increase in carboplatin AUC and/or increase in weekly paclitaxel dose with a lowered ruxolitinib dose. The minimum cycle 1 dose for ruxolitinib would be 5 mg PO bid even though a dose as low as 5 mg PO qd is known to be biologically active. In addition, the dose of ruxolitinib is de-escalated at each escalation of carboplatin or paclitaxel is two-fold, given the potential for overlapping myelotoxicity and the potential to compromise the efficacy of the standard agents. For example, if the dose of paclitaxel is escalated from 70 mg/m² to 80 mg/m² with dose of ruxolitinib fixed and that dose level is found to be unacceptable, then we would be missing the opportunity to test whether paclitaxel at 80 mg/m² would be safe with a reduced dose of ruxolitinib. Overall, this approach provides an obvious safety benefit while maintaining at least standard of care treatment; the main potential disadvantages would be inefficiency and cost. In order to maximize the effectiveness of the standard regimen, we have maintained what would be considered standard initiating dose levels for both carboplatin and paclitaxel. The dose levels are shown in section 5.1.1.1.

Dose levels 2 through 1, with carboplatin at AUC 5, can be justified by data from JGOG 3016 related to neutropenia and/or thrombocytopenia-triggered dose reductions of carboplatin in the dose-dense cohort and resultant carboplatin dose intensity. As detailed earlier, these data indicate an intrinsically high rate of neutropenia and thrombocytopenia for carboplatin initiated at AUC 6 that would have equated to a hematologic DLT on NRG-GY007, hence requiring dose reduction. The single most important observation was that mean dose intensity for carboplatin in AUC (mg/mL per min) in the dose-dense weekly paclitaxel cohort was 4.62 (compared with 5.13 in the q 3 week paclitaxel cohort), yet the dose-dense regimen was associated with a significant advantage in terms of both PFS and OS.

Dose levels -2 through 3, with paclitaxel at 70 mg/m², can be justified based on cumulative dose of 210 mg/m² over a three-week period, greater than 175 mg/m²

administered in the every-three-week regimen, and in increased likelihood that the vast majority of patients will be able to receive all three weekly doses. This would in most cases actually increase the cumulative dose delivered per cycle compared to a circumstance in which a weekly dose is omitted, an all too common problem observed in JGOG 3016 and GOG-0262.

- Eight participants per cohort as opposed to standard 3 + 3 design (see [sections 15.1](#) and [15.4](#)). The intrinsic rate of hematologic toxicity requiring dose modifications for the standard regimen required a greater number of participants per dose level than that evaluated using a standard 3 + 3 design, in order to increase the confidence in assessing the likelihood of DLT.
- Hard stop. The protocol requires a hard stop (suspension of accrual) and central (NCI) safety review of all available safety data from the phase I portion, including that related to all chemotherapy cycles and interval tumor reductive surgery, prior to commencing onto the randomized phase II portion of the trial.
- Limited access for phase I portion. The phase I evaluation will be conducted only in a limited number of phase I NRG sites, to assure timely assessment and weekly reporting.

Studies thus far have demonstrated no concern for interactions between ruxolitinib and either carboplatin or paclitaxel.⁵² *In vitro*, ruxolitinib and its M18 metabolite do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Ruxolitinib is not an inducer of CYP1A2, CYP2B6 or CYP3A4 at clinically relevant concentrations. *In vitro*, ruxolitinib and its M18 metabolite do not inhibit the P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 or OAT3 transport systems at clinically relevant concentrations. Ruxolitinib is not a substrate for the P-gp transporter. The major route of elimination of carboplatin is renal excretion. Thus the primary determinant of carboplatin clearance is glomerular filtration rate (GFR). Ruxolitinib has no effect on GFR based on data from the phase III studies. So it is highly unlikely ruxolitinib will affect carboplatin clearance or plasma levels. The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Ruxolitinib does not inhibit any of these enzymes, so there is little chance of an interaction with paclitaxel. Ruxolitinib is metabolized by CYP3A4 and somewhat by CYP2C19. Neither carboplatin nor paclitaxel are inhibitors of either of those enzymes. This information would suggest limited value of a formal pharmacokinetic analysis a priori.

Assuming a safe dose level for ruxolitinib is defined in the phase I portion, the trial also includes two predetermined comparative interim analyses within the randomized phase II portion, evaluating early and intermediate events. The goal of these interim analyses will be to review adverse events in the randomized phase II portion of the study comparing the experimental and reference regimens. Both of these will be conducted by the NRG DSMB. In NRG-GY007, ruxolitinib in cycle 3 is continued only for (not beyond) the 21 days of the cycle. As for GOG-0262, in NRG-GY007, barring evidence of non-response, disease progression or development of medical co-morbidities posing an unacceptable

surgical risk, interval surgery must be performed following cycle 3, as soon as nadir counts permit, but within 6 weeks after the completion of cycle 3. This time window is considered standard. While the likelihood of surgical delay given a 6 week window is extremely low, the interim analyses of safety in the phase II randomized component of the trial will evaluate differences in delay (beyond this window) of interval surgery. In the event that grade 3 or greater hematologic/non-hematologic toxicity or delay of interval tumor reductive surgery for more than 6 weeks after completion of C3 is significantly higher among patients on the ruxolitinib arm, the NRG DSMB may recommend further dose modification or study termination. The first analysis will be conducted after the first 10 patients in each treatment group have completed study therapy. There is a precedent for such an approach in NCI sponsored trials, for example GOG-0219. The second analysis will be conducted at the time of the interim futility analysis related to PFS, the primary endpoint of the trial.

For both the phase I and phase II portions of this trial, given the concern for possible additive myelosuppression with the addition of ruxolitinib to the carboplatin with dose-dense paclitaxel regimen and the notion that the known therapeutic benefit of standard primary platinum-taxane chemotherapy can in no way be compromised at the expense of evaluating the potential for JAK1/2 inhibition to improve long term outcome in trial participants, dose modifications for ruxolitinib based on clinically significant neutropenia and/or thrombocytopenia will be instituted prior to or concurrently with (as would be indicated with standard therapy) dose modifications of the standard therapeutic agents that could adversely affect the efficacy of the standard regimen.

Summary of findings from phase I dose escalation (04/06/2018)

The phase I portion of the study enrolled 17 patients in total, 7 to dose-level 1 (carboplatin AUC 5, paclitaxel 70 mg/m²/week, ruxolitinib 15 mg twice daily) and 10 to dose-level 2 (carboplatin AUC 6, paclitaxel 70 mg/m²/week, ruxolitinib 10 mg twice daily). Neither of the dose levels was associated with dose-limiting non-hematologic toxicity or unexpected toxicities in this patient population. As anticipated from historical data with carboplatin and weekly dose-dense paclitaxel, dose-limiting events were hematologic. A summary of cumulative data from each dose level is included in Table 2.4.1. Based on the pre-defined protocol criteria, dose level 1 was felt to be safe and tolerable, with expected hematologic toxicity, and was selected as the starting dose for the randomized phase II component of the trial. The dose levels for carboplatin (AUC=5) and paclitaxel (70 mg/m² per week) safely achieve generally-accepted dose levels that are appropriate for this high-risk patient population with advanced-stage disease.

Table 2.4.1 DLT summary

Dose Level	Patients Treated	Evaluable for DLT Assessment	Inevaluable for DLT Assessment	DLT	Decision
1	7	7	0	Febrile neutropenia (1 patient)	Safe

				Grade 4 neutropenia > 7 days (1 patient)	
2	10	7	3	Omission day 15 paclitaxel due to neutropenia (2 patients)	Unsafe
				Grade 4 thrombocytopenia and delay of cycle 2 therapy due to neutropenia (1 patient)	

Of 11 evaluable patients, all underwent surgery within 6 weeks of completing cycle 3.

2.5 Treatment modification rules (04/06/2018)

As was the case for the phase I portion of the trial, treatment modification rules for the phase II portion will be as utilized in GOG-0262. The exception to this would be in the case of dose-limiting neutropenia and thrombocytopenia (C3 through C6 for phase I and C1 through C6 for phase II), where modifications of ruxolitinib dose are interdigitated. Please [see section 6.2](#) for details.

While there is evidence of long-term safety with ruxolitinib monotherapy in other populations and while there is a rationale for both ruxolitinib combined with platinum-based chemotherapy and maintenance ruxolitinib in patients with advanced ovarian cancer, the data supporting the implementation of maintenance ruxolitinib in NRG-GY007 is indirect. Single agent anti-tumor activity for a less effective analog of ruxolitinib in pre-clinical *in vivo* models of human ovarian cancer was associated with improved outcome and prevention of metastasis (providing rationale for a maintenance phase to maximize likelihood of overall clinical benefit). In addition, reduction in inflammation as a major mechanism for JAK inhibition suggests that long term treatment may result in enhanced efficacy. There is indirect evidence of safety for long term treatment with ruxolitinib at 25 mg PO bid in patients with bone marrow disease. Despite the fact that these patients have ‘sick marrow’ they tolerate months of therapy with ruxolitinib with minimal side-effects. Nevertheless, there is no preliminary direct evidence of long term safety of maintenance ruxolitinib in humans with advanced/metastatic solid tumors.

2.6 Safety evaluation of maintenance ruxolitinib in Phase I (03/20/2017) (04/06/2018)

Given the above considerations, in the interest of beginning to examine the safety of maintenance therapy in advance of potential future efficacy evaluations, in NRG-GY007 we proposed to examine safety and tolerability of maintenance therapy within only the phase I cohort(s). Specifically, participants who completed all 6 cycles of chemotherapy with ruxolitinib will continue ruxolitinib maintenance at the C6 dose/schedule (see [sections 5.1.1.4](#)) until disease progression, unacceptable toxicity ([see section 6.4](#)), or voluntary withdrawal. Unacceptable toxicity is defined in [section 6.4](#). The primary

endpoint of this maintenance evaluation was safety/tolerability. By focusing on the exact population within the phase I cohort(s) that would theoretically be eligible for maintenance therapy on higher order trials, we will maximize our ability to acquire unique information in an efficient manner.

Safety and tolerability of maintenance ruxolitinib beyond chemotherapy has been demonstrated in 5 of the 17 patients enrolled to the phase I portion of the study who thus far have completed 6 cycles of combination treatment. Based on guidelines in Section 6.2 of the protocol, the starting dose in maintenance was 5 mg BID in 2 patients, 10 mg BID in 2 patients, and 15 mg BID in 1 patient. There were no dose reductions during maintenance. For the 16 cycles of single agent maintenance ruxolitinib administered to these 5 patients, there have been no grade 3 or greater adverse events and no worsening of adverse events after cycle 6. Anemia decreased in severity from grade 2 to grade 1 or 0 for three patients. Alopecia decreased in severity from grade 2 to grade 1 in one patient.

2.7 Other design considerations (04/06/2018)

The phase II portion will be initiated without maintenance ruxolitinib with the objectives of examining relative efficacy and safety with the combination of ruxolitinib and standard chemotherapy versus chemotherapy alone; exploring key mechanistic translational questions; and providing a framework for expanded clinical research, which if successful could potentially lead to examination of the maintenance question.

Based on an FDA approval in December 2018,⁵³ patients enrolled on this trial who have deleterious or suspected deleterious germline or somatic BRCA1 or BRCA2 mutations and who are in complete or partial response to carboplatin and paclitaxel with or without ruxolitinib will be permitted to receive olaparib maintenance after completing the study regimen. Given that the use of olaparib in such patients could affect PFS (the primary endpoint of this trial), PFS will be adjusted statistically (see [section 15.](#)) based on BRCA mutation status. BRCA mutation testing has been considered within standard care for women with epithelial ovarian, tubal and peritoneal cancer since at least 2014.⁵⁴ Therefore, BRCA mutation status (i.e., comprehensive BRCA1 and BRCA2 sequencing, including assessment of gene rearrangements) will be a required on-study data element for participation on this trial (see also [section 3.2.14](#)). (04/05/2019)

With regard to the evaluation of PFS, the primary efficacy endpoint for the phase II randomized component, an active futility rule has been implemented, examining outcome when the study reaches approximately 50% of the planned information-time.

With the understanding that epithelial ovarian cancer and related malignancies are diverse histologically and may reflect key differences in tumor biology, a strong consideration was given to eligibility as it relates specifically to histology. NRG-GY007 includes of all histologic Mullerian duct adenocarcinoma subtypes except for mucinous adenocarcinomas, grade 1 endometrioid adenocarcinomas and low grade serous carcinomas, as women with stage III and IV cancers of these histologic subtypes would be unlikely to benefit from standard platinum-taxane combination chemotherapy or benefit from JAK1/2 inhibition based on the available knowledge, and would be better

suited for rare tumor trials, reflecting the molecular and clinical features of these rare histologic types. Because these cases are rare, exclusion would not jeopardize feasibility of this study. There are supportive preclinical data for JAK inhibition in high grade serous and endometrioid tumors, and IL-6 may be an important driver of tumor progression in clear cell adenocarcinomas. In order to avoid an imbalanced distribution, for the phase II portion of the trial, the population is stratified by clear cell versus the high grade serous/endometrioid prior to randomization.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the NRG Statistical and Data Management Center-Pittsburgh Office: 412-624-2666. **(04/06/2018)**

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential should be willing and able to use medically acceptable forms of contraception during the trial.

3.1.3 Submission of tumor tissue is required for all patients. Investigators should check with their site pathology department regarding release of tissue before approaching patients about participation in the trial. (See [Section 10.4](#) for details.) **(07/30/2018)**

3.2 Eligibility Criteria (10/10/2016)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 Patients must have clinically and radiographically suspected and previously untreated FIGO stage ([Appendix I](#)) III or IV epithelial ovarian, primary peritoneal or fallopian tube cancer, high grade, for whom the plan of management will include neoadjuvant chemotherapy (NACT) with interval tumor reductive surgery (TRS) who have undergone biopsies for histologic confirmation. [See Appendix II](#) for Guidelines to Aid in Classification of Tumor Cell Type.

- 3.2.2** Institutional confirmation of Müllerian epithelial adenocarcinoma on core biopsy (not cytology or fine needle aspiration) or laparoscopic biopsy. (For Phase II of the study FFPE tissue should be available for laboratory analysis.) Patients with the following histologic epithelial cell types are eligible: high grade serous carcinoma, high grade endometrioid carcinoma, clear cell carcinoma, or a combination of these.
- 3.2.3** All patients must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.
- 3.2.4** Appropriate stage for study entry based on the following diagnostic workup:
- History/physical examination within 28 days prior to registration;
 - Radiographic imaging of the chest, abdomen and pelvis within 28 days prior to registration documenting disease consistent with FIGO stage III or IV disease;
 - Further protocol-specific assessments as detailed in [section 4.1](#).
- 3.2.5** Age ≥ 18
- 3.2.6** The trial is open to females only.
- 3.2.7** ECOG/Karnofsky Performance Status of 0, 1, or 2 ([see Appendix III](#)) within 28 days prior to registration.
- 3.2.8** Adequate hematologic function within 14 days prior to registration defined as follows:
- ANC greater than or equal to 1,500/mcl. This ANC cannot have been induced by granulocyte colony stimulating factors.
 - Platelets greater than or equal to 100,000/mcl
 - Hemoglobin greater than 9.0 mg/dl (transfusions are permitted to achieve baseline hemoglobin level)
- 3.2.9** Adequate renal function within 14 days prior to registration defined as follows:
- Estimated CrCl ≥ 50 mL/min according to the Cockcroft-Gault formula. **(07/30/2018)**
- 3.2.10** Adequate hepatic function within 14 days prior to registration defined as follows:
- Bilirubin ≤ 1.5 x ULN
 - ALT and AST ≤ 3 x ULN
 - Alkaline phosphatase ≤ 2.5 x ULN

- 3.2.11** Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE Grade 1.
- 3.2.12** Ability to swallow and retain oral medication.
- 3.2.13** The patient must provide study-specific informed consent prior to study entry.
- 3.2.14** BRCA testing results (i.e., comprehensive BRCA1 and BRCA2 sequencing, including assessment of gene rearrangements) must be submitted for all patients enrolled to Amendment 7 and subsequent amendments. BRCA testing results are optional for all patients enrolled prior to Amendment 7. Please refer to [Section 4.2.2](#) for details. Due to the long acceptance of germline BRCA testing through Myriad, Myriad testing reports will be accepted without additional documentation. If testing for germline BRCA is done by other organizations, in addition to the testing report, documentation from a qualified medical professional (e.g., ovarian cancer specialty physician involved in the field, high risk genetics physician, genetics counselor) detailing the laboratory results is required. Please retain a copy of all reports (positive, VUS, or negative). **(04/05/2019)**
- 3.3 Ineligibility Criteria (10/10/2016)**
Patients with any of the following conditions are NOT eligible for this study.
- 3.3.1** Patients with suspected non-gynecologic malignancy, such as gastrointestinal.
- 3.3.2** Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer and other specific malignancies as noted in [Section 3.3.3](#) and [Section 3.3.7](#) are excluded if there is any evidence of other malignancy being present within the last three years (2 years for breast cancer, [see Section 3.3.3](#)). Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.
- 3.3.3** Patients who have received prior chemotherapy for any abdominal or pelvic tumor within the last three years are excluded. Patients may have received prior adjuvant chemotherapy and radiotherapy for localized breast cancer, provided that it was completed more than 2 years prior to registration, the patient remains free of recurrent or metastatic disease and hormonal therapy has been discontinued.
- 3.3.4** Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis or thoracic cavity within the last three years are excluded. Prior radiation for localized cancer of the head and neck or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.
- 3.3.5** Patients who have received any targeted therapy (including but not limited to vaccines, antibodies, tyrosine kinase inhibitors) or hormonal therapy for management of their epithelial ovarian, fallopian tube or peritoneal primary cancer.

- 3.3.6** Patients with mucinous carcinoma, low grade endometrioid carcinoma, low grade serous carcinoma or carcinosarcoma.
- 3.3.7** Patients with synchronous primary endometrial cancer, or a past history of primary endometrial cancer, unless all of the following conditions are met: Stage not greater than I-A, grade 1 or 2, no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including serous, clear cell or other FIGO grade 3 lesions.
- 3.3.8** Severe, active co-morbidity defined as follows:
- Chronic or current active infectious disease requiring systemic antibiotics, antifungal or antiviral treatment
 - Known brain or central nervous system metastases or history of uncontrolled seizures
 - Clinically significant cardiac disease including unstable angina, acute myocardial infarction within 6 months from enrollment, New York Heart Association Class III or IV congestive heart failure, and serious arrhythmia requiring medication (this does not include asymptomatic atrial fibrillation with controlled ventricular rate).
 - Partial or complete gastrointestinal obstruction
- 3.3.9** Patients who are not candidates for major abdominal surgery due to known medical comorbidities.
- 3.3.10** Patients with any condition that in the judgment of the investigator would jeopardize safety or patient compliance with the protocol.
- 3.3.11** Patients who are unwilling to be transfused with blood components.
- 3.3.12** Concurrent anticancer therapy (e.g. chemotherapy, radiation therapy, biologic therapy, immunotherapy, hormonal therapy, investigational therapy).
- 3.3.13** Receipt of an investigational study drug for any indication within 30 days or 5 half-lives (whichever is longer) prior to Day 1 of protocol therapy.
- 3.3.14** Patients who, in the opinion of the investigator, are unable or unlikely to comply with the dosing schedule and study evaluations.
- 3.3.15** Patients who are pregnant or nursing. The effects of ruxolitinib on the developing human fetus are unknown. For this reason, women of child-bearing potential (WOCBP) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. WOCBP must have a screening negative serum or urine pregnancy test within 14 days of registration. A second pregnancy test must be done within 24 hours prior to the start of the first cycle of study treatment. Women must not be breastfeeding. (01/09/2017)

Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile) do not require contraception.

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy and/or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 month amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level greater than 40mIU/mL.

- 3.3.16** Known history of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection or known history of tuberculosis.
(This exclusion criterion is necessary because the treatments involved in this protocol may be immunosuppressive.)

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP**4.1 PRE-TREATMENT ASSESSMENTS**

Assessments	Prior to Registration (calendar days)	Prior to Treatment (Cycle 1) (calendar days) (03/20/2017)
History and Physical	≤ 28 days	≤ 28 days
Vital Signs (Blood Pressure, Heart Rate, Temperature)	≤ 28 days	≤ 28 days
Performance Status	≤ 28 days	≤ 28 days
Toxicity Assessment	≤ 14 days	≤ 14 days
Concurrent Medications	≤ 14 days	≤ 14 days
CBC/Differential/Platelets	≤ 14 days	≤ 14 days
Electrolytes, including BUN, creatinine, Ca, and magnesium	≤ 14 days	≤ 14 days
CrCl by the Cockcroft-Gault Formula	≤ 14 days	≤ 14 days
Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin	≤ 14 days	≤ 14 days
Pregnancy Test (if childbearing potential exists)	≤ 14 days	≤ 24 hours ¹ (01/09/2017)
EKG	≤ 28 days	≤ 28 days
FSH	X ⁵	
Audiogram ²	≤ 28 days	≤ 28 days
CA-125		≤ 28 days
Radiographic Tumor Measurement ³	≤ 28 days	≤ 28 days
Biopsy for Histologic Diagnosis ⁴		

¹ The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of hCG.

² Although not required, should be considered at baseline and repeated as clinically necessary during the treatment period with carboplatin for patients with a history of hearing loss.

³ Radiographic tumor measurements should be obtained via imaging of the chest, abdomen and pelvis to establish the location and extent of disease. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline (and subsequent assessments). Contrast CT is the preferred modality.

⁴ Core biopsy (not cytology or fine needle aspiration) or laparoscopic biopsy must have been performed (within standard clinical care) prior to enrollment to confirm diagnosis (see section 3.2.2). (10/10/2016)

⁵ FSH if needed to determine menopausal status per 3.3.16

4.2 ASSESSMENTS DURING TREATMENT**4.2.1 ASSESSMENTS DURING TREATMENT – PHASE I NOTE: The Phase I portion of the study is complete. (04/06/2018)**

Assessments	Prior to Cycles 2-6 (03/20/2017)	During Cycles 1 – 6 of Carboplatin/Paclitaxel/ Ruxolitinib		During Maintenance Ruxolitinib		
		Days 8 & 15	TRS ¹	Prior to Each Cycle (Cycles 7- 12)	Prior to Every Other Cycle (Cycles ≥ 13)	Timed (Treatment Cycle Independent)
History and Physical	≤ 1 day of treatment		Prior to TRS ⁴	≤ 1 day of treatment	≤ 1 day of treatment	
Vital Signs (Blood Pressure, Heart Rate, Temperature)	Day of treatment	Day of treatment	Prior to TRS ⁴	Day of treatment	Day of treatment	
Performance Status	≤ 1 day of treatment		Prior to TRS ⁴	≤ 1 day of treatment	≤ 1 day of treatment	
Toxicity Assessment	≤ 1 day of treatment ¹	≤ 1 day of treatment ²	Prior to TRS ⁴	≤ 1 day of treatment	≤ 1 day of treatment	
Concurrent Medications	≤ 1 day of treatment			≤ 1 day of treatment	≤ 1 day of treatment	
CBC/Differential/ Platelets	≤ 3 days of treatment	≤ 1 day of treatment	Prior to TRS ⁴	≤ 3 days of treatment	≤ 3 days of treatment	
Electrolytes, including, BUN, creatinine, Ca, and magnesium	≤ 3 days of treatment		Prior to TRS ⁴	≤ 3 days of treatment	≤ 3 days of treatment	
CrCl by the Cockcroft-Gault Formula (10/10/2016)	≤ 3 days of treatment			≤ 3 days of treatment	≤ 3 days of treatment	
Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin	≤ 3 days of treatment		Prior to TRS ⁴	≤ 3 days of treatment	≤ 3 days of treatment	
CA-125	≤ 3 days of treatment		Prior to TRS ⁴	≤ 3 days of treatment	≤ 3 days of treatment	
Radiographic Tumor Measurement ³			Prior to TRS ⁶			X ⁶
Documentation of Gross Residual Disease			At time of TRS			
Patient Pill Calendar ⁵	≤ 1 day of treatment		Prior to TRS ⁴	≤ 1 day of treatment	≤ 1 day of treatment	

¹ TRS = Tumor Reductive Surgery. See [section 5.3](#) and [Appendix VIII](#) for guidelines.

² Toxicity assessment should occur weekly during Cycles 1 and 2. Beginning in Cycle 3, toxicity assessments will occur prior to each cycle for Cycles 3-6.

³ Radiographic tumor measurements should be obtained via imaging of the chest, abdomen and pelvis to re-assess disease using the same modality as for pre-treatment baseline imaging ([see section 4.1](#)), until disease progression is confirmed according to guidelines in [section 13.1.3](#); at the investigator's discretion, they can be repeated any other time if clinically indicated based on symptoms, physical signs or rising CA-125 levels suggestive of new or progressive disease. A tool is provided to calculate dates of re-imaging.

⁴ Within 3 weeks after completing cycle 3. Prior to TRS.

⁵ [See Appendix VI](#).

⁶ Within 3 weeks of completing Cycle 6, prior to initiating Cycle 7 (maintenance ruxolitinib); then every 12 weeks (+/- 7 days) following cycle 7, day 1 (regardless of delays and/or changes in treatment schedule) for the first 2 years; then every 24 weeks for the next 3 years; then annually.

4.2.2 ASSESSMENTS DURING TREATMENT – PHASE II (04/06/2018)

Assessments	Prior to Cycles 2-6 (03/20/2017)	During Cycles 1 – 6 of Carboplatin/Paclitaxel/ +/- Ruxolitinib		Post-Treatment Visit ⁷
		Days 8 & 15	TRS ¹	
History and Physical	≤ 1 day of treatment			Day of visit
Vital Signs (Blood Pressure, Heart Rate, Temperature)	Day of treatment	Day of treatment	Prior to TRS ⁴	Day of visit
Performance Status	≤ 1 day of treatment		Prior to TRS ⁴	Day of visit
Toxicity Assessment	≤ 1 day of treatment ²	≤ 1 day of treatment ²	Prior to TRS ⁴	Day of visit
Concurrent Medications	≤ 1 day of treatment			
CBC/Differential/ Platelets	≤ 3 days of treatment	≤ 1 day of treatment	Prior to TRS ⁴	≤ 3 days of visit
Electrolytes, including, BUN, creatinine, Ca, and magnesium	≤ 3 days of treatment		Prior to TRS ⁴	≤ 3 days of visit
CrCl by the Cockcroft-Gault Formula (10/10/2016)	≤ 3 days of treatment			
Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin	≤ 3 days of treatment		Prior to TRS ⁴	≤ 3 days of visit
CA-125	≤ 3 days of treatment		Prior to TRS ⁴	≤ 3 days of visit
Radiographic Tumor Measurement ³			Prior to TRS	≤ 7 days of visit
Documentation of Gross Residual Disease			At time of TRS	
Patient Pill Calendar (for patients receiving Ruxolitinib) ⁵	≤ 1 day of treatment		Prior to TRS ⁴	Day of visit
Tissue Samples for Histologic Diagnosis ⁶			At time of TRS ⁶	
BRCA1/2 Testing ⁸ (04/05/2019)				

¹ TRS = Tumor Reductive Surgery. See [section 5.3](#) and [Appendix VIII](#) for guidelines.

² Toxicity assessment should occur weekly during Cycles 1 and 2. Beginning in Cycle 3, toxicity assessments will occur prior to each cycle for Cycles 3-6.

³ Radiographic tumor measurements should be obtained via imaging of the chest, abdomen and pelvis to re-assess disease using the same modality as for pre-treatment baseline imaging (see [section 4.1](#)), until disease progression is confirmed according to guidelines in [section 13.1.3](#); at the investigator's discretion, they can be repeated any other time if clinically indicated based on symptoms, physical signs or rising CA-125 levels suggestive of new or progressive disease. A tool is provided to calculate dates of re-imaging.

Radiographic tumor measurement should be obtained at the following time points: prior to TRS at 11 weeks (+/- 14 days) following cycle 1, day 1; and at 26 weeks (+/- 14 days) following cycle 1, day 1 [at 20 weeks (+/- 14 days) for patients who do not undergo TRS due to evidence of non-response or medical contraindication].

- 4 Within 3 weeks after completing cycle 3. Prior to TRS.
- 5 [See Appendix VI.](#)
- 6 See section 5.3 for guidelines related to TRS. Gross tumor tissue should be analyzed histologically per standard anatomic pathology procedures. In the absence of gross tumor tissue, tissue from the required specimens removed surgically in accordance with [section 5.3](#) guidelines should be assessed histologically. There must be sufficient FFPE tissue representative of microscopic tumor available for laboratory analysis (see [section 10](#) for requirements); the only exception to this requirement would be evidence of pathologic complete response. For patients that do not undergo TRS (in the case of disease progression, failure to respond to first 3 cycles of protocol therapy or TRS medically contraindicated), imaging guided core biopsies should be obtained which fulfill basic requirements for tissue studies as detailed in [Section 10](#).
- 7 3 weeks +/- 7 days following Cycle 6, Day 1 treatment.
- 8 Comprehensive BRCA1/2 testing results (i.e., comprehensive BRCA1 and BRCA2 sequencing including assessment of gene rearrangements) must be submitted for all patients enrolled to Amendment 7 and subsequent amendments. BRCA testing results are optional for all patients enrolled prior to Amendment 7. Patients with prior BRCA1/2 testing should provide a formal copy of BRCA1/2 testing results, consisting of both the official BRCA1/2 testing report and, if appropriate, per [Section 3.2.14](#), documentation by an appropriate qualified medical professional. The BRCA Status Form must also be completed in Rave. **(04/05/2019)**

4.3 ASSESSMENTS IN FOLLOW UP**4.3.1 ASSESSMENTS IN FOLLOW UP – PHASE I (04/06/2018) NOTE: The Phase I portion of the study is complete.**

Assessments	Schedule
Toxicity Assessment	X ¹
Radiographic tumor measurement	X ²

- ¹ Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. For reporting of delayed toxicity, [see Section 7](#).
- ² In the case that protocol directed therapy is discontinued for reasons other than disease progression, follow radiographic tumor measurement schedule as defined under [section 4.2.1](#), until disease progression documented by RECIST 1.1 ([see section 13.1.3](#)) or until patient initiates a subsequent cancer therapy.

4.3.2 ASSESSMENTS IN FOLLOW UP – PHASE II (04/06/2018)

Assessments	Schedule
History and Physical	X ¹
Serum CA-125 Level	X ¹
Vital Status	X ²
Toxicity Assessment	X ³
Radiographic tumor measurement ⁴	X ¹

- ¹ Every 12 weeks (+/- 7 days) for the first 2 years; then every 24 weeks (+/- 7 days) for the next 3 years until disease progression or patient initiates a subsequent cancer therapy except for olaparib maintenance therapy as indicated in women with deleterious or suspected deleterious BRCA1 or BRCA2 mutations who are in complete or partial response to carboplatin and paclitaxel with or without ruxolitinib. **(04/05/2019)**
- ² Vital Status should be reported every 3 months for 2 years and then every 6 months for 3 years. Follow-up forms are collected for the 5-year follow-up period or until study termination.
- ³ Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. For reporting of delayed toxicity, [see Section 7](#).
- ⁴ Radiographic tumor measurements should be obtained via imaging of the chest, abdomen and pelvis to re-assess disease using the same modality as for pre-treatment baseline imaging ([see section 4.1](#)), until disease progression is confirmed according to guidelines in [section 13.1.3](#); at the investigator's

discretion, they can be repeated any other time if clinically indicated based on symptoms, physical signs or rising CA-125 levels suggestive of new or progressive disease. A tool is provided to calculate dates of re-imaging.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

Study sites must follow General Chemotherapy Guidelines in Appendix IV. Note that the maximum dose of carboplatin will be 750 mg at an AUC of 5 and 900 mg at an AUC of 6.

Protocol treatment must begin within 7 days after registration.

Cycles are 21 days in duration.

Treatment will be given in the outpatient setting. (10/10/2016)

5.1 Treatment Regimens

5.1.1 Phase I Component (04/06/2018)

NOTE: The Phase I portion of this study is complete. Please proceed to [Section 5.1.2](#) for the Phase II Component.

Limited access for phase I component. The phase I component will be conducted only in a limited number of phase I NRG sites, to assure timely assessment and weekly reporting.

5.1.1.1 Chemotherapy - Cycles 1-3: (10/10/2016)

Ruxolitinib (see dose levels Table below) orally (PO) twice daily (BID), continuously on Days 1 – 21. The first dose of ruxolitinib will be taken at least 1 hour prior to the first dose of paclitaxel on Cycle 1, Day 1. The dose of ruxolitinib will be assigned according to the dose escalation Table below at the time of patient enrollment.

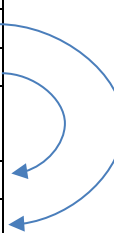
Ruxolitinib will be self-administered by the study patient orally (PO) without regard to food in an outpatient setting twice daily (BID) approximately 12 hours apart, generally after the morning and evening meal. If the patient is more than 4 hours late in taking a dose, the dose should be skipped.

Ruxolitinib dose should not be replaced in the event of emesis. (03/20/2017)

Paclitaxel 70 mg/m² or 80 mg/m² IV (see Table below) over 1 hour on Days 1, 8 and 15

Carboplatin AUC 5 or 6 (see Table below) IV over 30 min on Day 1.

Phase I Dose Levels				
Dose Level	Patients (range)	Agent		
		Carboplatin (AUC)	Paclitaxel mg/m ² /wk	Ruxolitinib (mg)
-2	4-7	5	70*	5 bid
-1	4-7	5	70*	10 bid
1 (Starting Dose Level)	4-7	5	70*	15 bid
2	4-7	6	70*	**RD5.70 -1
3	4-7	6	70*	**RD5.70
4	4-7	6	80	***RD6.70 -1
5	4-7	6	80	***RD6.70



* If no DLT is encountered through the first 2 cycles of therapy, the dose of paclitaxel may be escalated to 80 mg/m² per discretion of the site investigator.

**RD5.70 = Recommended dose of ruxolitinib with carboplatin AUC=5 and paclitaxel 70 mg/m²/wk

***RD6.70 = Recommended dose of ruxolitinib with carboplatin AUC=6 and paclitaxel 70 mg/m²/wk

In general, once RD5.70 is established, carboplatin and paclitaxel will be escalated sequentially, in an attempt to define RD6.70 and RD6.80, de-escalating ruxolitinib at each escalation of carboplatin or paclitaxel, unless ruxolitinib is already at the minimum dose of 5 bid, in which case that dose will be maintained. The rationale for this design is detailed in [section 2.4](#).

The starting dose level (Dose Level 1) will consist of carboplatin AUC 5, paclitaxel 70 mg/m²/wk and ruxolitinib at 15 mg bid.

If Dose Level 1 is considered safe, then will escalate in a linear fashion to Dose Level 2 (in this case carboplatin AUC 6, paclitaxel 70 mg/m²/wk, ruxolitinib 10 mg bid), then Dose Level 3 (in this case carboplatin AUC 6, paclitaxel 70 mg/m²/wk, ruxolitinib 15 mg bid), then Dose Level 4 (in this case carboplatin AUC 6, paclitaxel 80 mg/m²/wk, ruxolitinib 10 mg bid), then Dose Level 5 (in this case carboplatin AUC 6, paclitaxel 80 mg/m²/wk, ruxolitinib 15 mg bid). If Dose Level 5 is considered safe, then Dose Level 5

will be considered the phase II regimen. If any dose level beyond Dose Level 1 is deemed too toxic, then the previous dose level will be declared the phase II regimen.

If Dose level 1 is deemed too toxic, then this could be secondary to ruxolitinib dose. In that case, will dose de-escalate to Dose Level -1.

If Dose Level -1 is deemed too toxic, this could be secondary to ruxolitinib dose. In that case, will Dose de-escalate to Dose Level -2.

- Arrows indicate re-escalation to levels with higher Carboplatin AUC and/or higher weekly paclitaxel dose, but with lower ruxolitinib dose, in order to control for the possibility that dose limiting toxicity had been dependent on ruxolitinib dose (however, the dose level of ruxolitinib will not be de-escalated below 5 bid):
 - If Dose Level -1 is considered safe, then will escalate to Dose Level 2 (in this case carboplatin AUC 6, paclitaxel 70 mg/m²/wk, ruxolitinib 5 mg bid). In that case, if Dose Level 2 is considered safe, then will escalate to Dose Level 3 (in this case carboplatin AUC 6, paclitaxel 70 mg/m²/wk, ruxolitinib 10 mg bid). If Dose Level 3 is considered safe, then will escalate to Dose Level 4 (in this case carboplatin AUC 6, paclitaxel 80 mg/m²/wk, ruxolitinib 5 mg bid). If Dose Level 4 is considered safe, then will escalate to Dose Level 5 (in this case carboplatin AUC 6, paclitaxel 80 mg/m²/wk, ruxolitinib 10 mg bid). If Dose Level 5 is considered safe, then Dose Level 5 will be considered the phase II regimen. If any dose level beyond Dose Level -1 is deemed too toxic, then the previous dose level will be declared the phase II regimen.
 - If Dose Level -1 is deemed too toxic but Dose Level -2 is considered safe, then will escalate to Dose Level 3 (in this case carboplatin AUC 6, paclitaxel 70 mg/m²/wk, ruxolitinib 5 mg bid). If Dose Level 3 is considered safe, then will escalate to Dose Level 4 (in this case carboplatin AUC 6, paclitaxel 80 mg/m²/wk, ruxolitinib 5 mg bid). If Dose Level 4 is considered safe, then Dose Level 4 will be considered the phase II regimen, since the ruxolitinib dose will not be re-escalated above 5 mg bid in this scenario. If any dose level beyond Dose Level -2 is deemed too toxic, then the previous dose level will be declared the phase II regimen.
 - If Dose Level -2 is deemed too toxic, it will be considered unsafe to proceed to phase II.

During the Phase I portion, in which the dose limiting toxicities of the study agents will be assessed over cycles 1 and 2, enrollment to a dose level will be staggered so that no more than 4 participants will be at risk at any given time. All enrolling sites will be required to participate in a regularly scheduled teleconference with the Study Chair and

Phase I Subcommittee Chair, and their assigned delegates.

5.1.1.1.1 Pre-Medication:

Paclitaxel

Due to the risk of immediate hypersensitivity reaction, paclitaxel should always be infused before carboplatin.

For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed prior to the treatment regimen, to reduce the risk associated with hypersensitivity reactions to this drug.

This regimen should include standard dose(s) of dexamethasone (either IV or PO), an anti-histamine H1 (diphenhydramine 25-50 mg IV or orally, or an equivalent dose of an alternate H1 blocker such as loratadine or fexofenadine), and a standard dose of anti-histamine H2 IV (such as cimetidine, ranitidine, or famotidine).

5.1.1.1.2 Dosing of Carboplatin

[See Appendix V](#) for current dosing instructions.

Note that carboplatin dose will be recalculated if patient has weight change $\geq 10\%$ from baseline.

5.1.1.1.3 Assessment of Compliance with Ruxolitinib

Patients will be required to maintain a pill calendar ([see Appendix VI](#)) to be reviewed by the investigator or designee at study visits according to [section 4.2](#). Patients will also be instructed to bring their ruxolitinib bottles with them to each study visit. Pill counts will be conducted to assess medication compliance.

Compliance with ruxolitinib will be calculated, by SDMC, based on the drug accountability documented by the investigator or designee and monitored by SDMC by review of pill calendars.

5.1.1.2 Interval Tumor Reductive Surgery

Barring evidence of non-response, disease progression or medical contraindication, the 3 cycles of chemotherapy will be followed by interval tumor reductive surgery (TRS) within 6 weeks after completion of cycle 3, as soon as nadir counts permit and surgery deemed safe by investigator. Disease progression by RECIST (see section 13.1) is an absolute contraindication to proceeding with TRS. Relative contraindications to proceeding with TRS would include either stable disease or development of medical comorbidities that would put a patient at high surgical risk. Relative contraindications to

proceeding with TRS require discussion with the Study Chair or Study Co-Chair prior to omitting TRS. [See section 5.3](#) and [Appendix VIII](#) for details regarding TRS.

5.1.1.3 Chemotherapy Cycles 4-6

Barring disease progression or unacceptable toxicity, resume treatment with Paclitaxel, Carboplatin and Ruxolitinib (same dose level as for cycles 1-3) as soon as investigator deems safe, within 6 weeks of surgery.

If TRS is not performed due to non-response or medical contraindications (see [section 5.1.1.2](#)) and criteria for discontinuation of protocol therapy have not been met, Cycle 4 of protocol therapy should be initiated with no treatment break.

5.1.1.4 Chemotherapy - Maintenance Ruxolitinib (Phase I portion Only) (10/09/2017)

Patients who complete all cycles of chemotherapy will continue Ruxolitinib alone at the C6 dose/schedule until disease progression, unacceptable toxicity or voluntary withdrawal. Maintenance therapy will be initiated after completing C6. Day 1 treatment during maintenance therapy will not be given until the ANC is $\geq 1,000$ cells/mcl and the platelet count is $\geq 75,000$ /mcl. Treatment with ruxolitinib will be delayed for a maximum of 3 weeks beyond completion of C6 (6 weeks from day 1 of C6) until these values are achieved. Patients who fail to recover adequate counts within this time frame will no longer receive any protocol-directed therapy.

During the maintenance phase of therapy with ruxolitinib, the dose of ruxolitinib should be initiated based on platelet count at the conclusion of cycle 6 of chemotherapy after recovery of platelet count to $\geq 75,000$ /mcl, as follows: For platelet count $\geq 100,000$ /mcl, initiate at dose level as administered during cycle 6 with chemotherapy. For platelet count of $75,000$ /mcl to less than $100,000$ /mcl, reduce one dose level (see Table A).

Following subsequent hematologic evaluations specified in [section 4.2](#), the dose of ruxolitinib should be modified according to the following rules, using dose levels specified in [Section 6 Table A](#) and the following platelet count ranges:

- $\geq 100,000$ /mcl
- $75,000$ /mcl to less than $100,000$ /mcl
- $50,000$ /mcl to less than $75,000$ /mcl.

If subsequent platelet count decreases into the next lower range, reduce one dose level. No dose level re-escalation is permitted. Discontinue study therapy for platelet count $< 50,000$ /mcl.

5.1.1.5 Definition of Dose-Limiting Toxicity (DLT) (10/10/2016)

DLT is defined as either hematologic or non-hematologic toxicity (assessed in accordance with the CTEP CTCAE Version 4.0), which cause any of the following:
Any Toxicity:

- Dose delay > 7 days related to any toxicity (treatment related adverse event).
- Omission of day 8 or day 15 paclitaxel
- Any treatment related death.

Hematologic Toxicity:

- Study treatment-related febrile neutropenia.
- Grade 4 neutropenia lasting > 7 days.
- Study treatment-related Grade 4 thrombocytopenia or bleeding associated with Grade 3 thrombocytopenia.

Non-Hematologic Toxicity:

- Study treatment-related Grade 3 or Grade 4 non-hematological toxicity (excluding alopecia, paclitaxel hypersensitivity reaction; and excluding fatigue, other hypersensitivity reaction, pain, depression, dyspepsia, nausea, vomiting, dehydration, hypotension, constipation, diarrhea, dizziness, extremity edema, peripheral ischemia, hypokalemia, hyperkalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia, and infusion reaction responsive to medical management and supportive care).

5.1.1.6 Dose Escalation Design (10/10/2016) (03/20/2017)

At each dose level, DLT will be based on cycle 1 and 2 of therapy, though the phase II dose could be modified after evaluation of cumulative data. Patients who experience DLT will be treated as per standard care based on the judgment of the investigator, without ruxolitinib, but will continue on study to evaluate whether or not such patients undergo interval tumor reductive surgery within 6 weeks of completing cycle 3 therapy for reasons other than non-response, disease progression, or medical contraindications. Patients who do not experience DLT and who do not complete 2 cycles of therapy will be replaced. Patients who miss more than 25% of ruxolitinib doses in the first two cycles of therapy (based on pill diary review) without medical justification would also be replaced.

For all dose levels, 4 participants will be enrolled initially, per cohort. If no DLTs are observed through 2 cycles of therapy in these 4 participants, then the dose level would be considered safe and escalation to the next higher dose level. Otherwise, the dose level will be expanded to up to 3 additional participants. Out of 7 participants, a dose level with 2 or fewer participants experiencing DLT events over the first 2 cycles of therapy would be considered safe. As indicated previously, enrollment to a dose level will be staggered so that no more than 4 participants are at risk at any given time. There are two dose de-escalation levels for ruxolitinib (see table in [section 5.1.1.1](#)) should the starting

dose level (1) be considered too toxic (≥ 3 participants experiencing a DLT). If one of these dose levels is considered safe, then re-escalation to successive levels is permitted, increasing first carboplatin AUC, then weekly paclitaxel dose.

No intra-patient dose escalations will be allowed.

No patient may be enrolled at the next higher dose level until all patients at the previous dose level have been followed through the end of the second cycle.

As the initial treatment of ovarian cancer and related malignancies with paclitaxel and carboplatin is known to require treatment modifications to maintain dose-intensity and cumulative dose-delivery, treatment modification will be allowed as specified in [Section 6](#).

5.1.2 **PHASE II Component**

5.1.2.1 Chemotherapy Cycles 1-3

Pre-Medication:

Paclitaxel

Due to the risk of immediate hypersensitivity reaction, paclitaxel should always be infused before carboplatin.

For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed prior to the treatment regimen, to reduce the risk associated with hypersensitivity reactions to this drug.

This regimen should include standard dose(s) of dexamethasone (either IV or PO), an anti-histamine H1 (diphenhydramine 25-50 mg IV or orally, or an equivalent dose of an alternate H1 blocker such as loratadine or fexofenadine), and a standard dose of anti-histamine H2 IV (such as cimetidine, ranitidine, or famotidine).

5.1.2.1.1 **Reference Regimen - Treatment Arm 1 (07/30/2018)**

Paclitaxel 80 mg/m² IV over 1 hour on Days 1, 8 and 15.

Carboplatin AUC 6 IV over 30 min on Day 1.

5.1.2.1.2 **Experimental/Ruxolitinib Regimen - Treatment Arm 2 (04/06/2018) (07/30/2018)**

Ruxolitinib 15 mg PO BID, continuously on Days 1 – 21. The first dose of ruxolitinib will be taken at least 1 hour prior to the first dose of paclitaxel on Cycle 1, Day 1. If the patient is more than 4 hours late in taking a dose, the dose should be skipped.

Paclitaxel 70 mg/m² IV over 1 hour on Days 1, 8 and 15.

Carboplatin AUC 5 IV over 30 min on Day 1.

5.1.2.2 Interval Tumor Reductive Surgery (TRS)

Barring evidence of non-response, disease progression or medical contraindication, the 3 cycles of chemotherapy will be followed by interval tumor reductive surgery (TRS) within 6 weeks after completion of cycle 3, as soon as nadir counts permit and surgery deemed safe by investigator. Disease progression by RECIST (see section 13.1) is an absolute contraindication to proceeding with TRS. Relative contraindications to proceeding with TRS would include either stable disease or development of medical comorbidities that would put a patient at high surgical risk. Relative contraindications to proceeding with TRS require discussion with the Study Chair or Study Co-Chair prior to omitting TRS. [See section 5.3](#) and [Appendix VIII](#) for details regarding TRS.

5.1.2.3 Chemotherapy Cycles 4-6 (04/06/2018)

Barring disease progression or unacceptable toxicity, resume protocol therapy as soon as investigator deems safe but within 4 weeks of surgery.

If TRS is not performed due to non-response or medical contraindications (see [section 5.1.2.2](#)) and criteria for discontinuation of protocol therapy have not been met, Cycle 4 of protocol therapy should be initiated with no treatment break. As noted in Section 5.9, inability to resume protocol therapy within 3 weeks after the completion of Cycle 3 for patients who do not undergo TRS due to non-response or medical contraindications would require discontinuation of protocol therapy.

5.1.2.3.1 Reference Regimen

Paclitaxel and Carboplatin as in [section 5.1.2.1.1](#)

5.1.2.3.2 Experimental/Ruxolitinib Regimen (04/06/2018)

Paclitaxel, Carboplatin and Ruxolitinib as in [Section 5.1.2.1.2](#)

5.2 Radiation Therapy

Not Applicable

5.3 Tumor Reductive Surgery (TRS)

Barring evidence of non-response, disease progression or medical contraindication, tumor reductive surgery (TRS) will be performed within 6 weeks after the completion of Cycle 3 of protocol therapy. The goals of surgery are documentation of the extent of disease at exploration and total resection of all macroscopic and palpable tumor. The purpose and details of the procedure are described in [Appendix VIII](#)

5.4 Device

Not Applicable.

5.5 Imaging (for imaging-focused study)

Not Applicable.

5.6 Integral Assay/Biomarker

Not Applicable.

5.7 Intervention Not Otherwise Categorized

Not Applicable.

5.8 General Concomitant Medication and Supportive Care Guidelines

5.8.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the investigator within the parameters of the protocol and documented on each site's source documents as concomitant medication.

5.8.1.1 Antiemetics (10/10/2016)

It is anticipated that nausea and vomiting may be a significant side effect of each regimen. Follow institution, ASCO or NCCN guidelines for high emetic risk intravenous chemotherapy (acute and delayed emesis prevention). NOTE: as moderate inhibitors of CYP3A4, aprepitant and other neurokinin 1 (NK1) receptor antagonists can increase plasma concentrations of ruxolitinib, NK1 receptor antagonists should be avoided if possible. If use of NK1 receptor antagonists is unavoidable, follow [section 5.8.2](#) for guidance.

5.8.1.2 Anticoagulants - Use at discretion of investigator. No specific contraindication.

5.8.1.3 Blood products – Use at discretion of investigator. No specific contraindication.

5.8.1.4 Antidiarrheals - Use at discretion of investigator. No specific contraindication.

5.8.1.5 Analgesics - Use at discretion of investigator. No specific contraindication.

5.8.1.6 Hematopoietic Growth Factors – [see section 6.1](#)

5.8.1.7 Nutritional supplementation - Use at discretion of investigator. No specific contraindication.

5.8.2 Prohibited Therapies

- Amifostine
- Inducers of CYP3A4 ([Appendix VII](#)) may be used with caution, and investigators should seek other options if available.
- Use of potent inhibitors of CYP3A4 (ketoconazole, clarithromycin, itraconazole, nefazodone or telithromycin, voriconazole or posaconazole, see [Appendix VII](#)) and use of fluconazole should be avoided; any intended use should be discussed with the Study Chair or Study Co-Chair prior to co-administration. If approved by the Study Chair or Study Co-Chair, dose modifications of ruxolitinib will be made according to section 2.3 of the Jakafi (ruxolitinib) Prescribing Information (<https://www.jakafi.com/pdf/prescribing-information.pdf>), with frequent complete blood count monitoring during the period of co-administration. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole in the study. (10/10/2016)
- Moderate CYP3A4 inhibitors ([Appendix VII](#)) may be used with caution. Differences in individual sensitivity and variation in potency of inhibition of various CYP enzymes may result in the need for a reduced dose of ruxolitinib during a period of concomitant medication use. Any intended use should be discussed with the Study Chair or Study Co-Chair prior to co-administration. If used, the ruxolitinib dose may be reduced from BID to QD with frequent complete blood count monitoring during the period of co-administration.
- Use of any concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, or tumor embolization) other than those specified in the Protocol.
- Concomitant use of a JAK inhibitor.
- Use of any investigational medication within 30 days or 5 half-lives, whichever is longer, prior to Cycle 1, Day 1 of study treatment is prohibited.
- St John's wort and rifampin are not permitted at any time during participation in the study.

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements can be found in [Appendix X](#).

5.8.3 Participation in Other Trials

Not applicable.

5.9 Duration of Therapy (04/06/2018)

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of protocol therapy
- Unacceptable adverse event(s), as described in [Section 6](#)
- Inability to resume protocol therapy within 6 weeks following TRS or within 3 weeks

after the completion of Cycle 3 for patients who do not undergo TRS due to non-response or medical contraindications (see [sections 5.1.1.2](#) and [5.1.2.2](#)). (10/09/2017)

- Dose-limiting toxicity ([Section 5.1.1.5](#)) during Cycle 1 or Cycle 2 of the Phase I component.
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Phase I Only: Patients who discontinue protocol therapy during Cycle 1 through Cycle 6 for reasons other than disease progression will be treated as per standard care based on the judgment of the investigator, without ruxolitinib, but will continue on study to evaluate whether or not such patients undergo interval tumor reductive surgery within 6 weeks of completing cycle 3 therapy for reasons other than non-response, disease progression, or medical contraindications. (03/20/2017)

6. TREATMENT MODIFICATIONS/MANAGEMENT (04/06/2018)

This section specifies treatment modifications/management in patients enrolled in the phase I component of the trial.

In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. No dose escalation is planned for this study.

Table A defines Phase I dose reduction increments for each agent as specified in sections [6.2](#) and [6.3](#).

NOTE: The Phase I portion of the study is complete.

USE TABLE B for Phase II Dosing Instructions.

Table B defines Phase II dose reduction increments for each agent as specified in sections 6.2 and 6.3.

Table A: Intra-patient Dose Reduction Increments for Toxicity in Patients Receiving Experimental Regimen (for Phase I portion Only)

Drug	Maximum Starting Dose	First Incremental Reduction	Second Incremental Reduction	Third Incremental Reduction	Fourth Incremental Reduction
Carboplatin (AUC, mg/mL/min)	6	5*	4	Discontinue study therapy	
Paclitaxel	80*	70	60	Discontinue	

(mg/m ²)				study therapy	
Ruxolitinib (mg AM/mg PM)	15/15	10/10*	5/5	5/0	Discontinue study therapy

*Starting doses in dose level 1 of phase I portion

For the Phase I component, protocol therapy will be discontinued for development of a DLT (as defined in Section 5.1.1.5) during Cycle 1 or Cycle 2. The definition of DLT as defined in [Section 5.1.1.5](#) and as it relates to the Phase I component should be distinguished from references to and definitions of DLT-ANC and DLT-PLT in [Section 6.2](#).

Table B: Intra-Patient Dose Reduction Increments for Toxicity for **Phase II** portion

Drug	Starting Dose	First Incremental Reduction	Second Incremental Reduction	Third Incremental Reduction
Reference Regimen				
Carboplatin (AUC, mg/mL/min)	6	5	4	Discontinue carboplatin
Paclitaxel (mg/m ²)	80	70	60	Discontinue paclitaxel
Experimental/Ruxolitinib Regimen				
Carboplatin (AUC, mg/mL/min)	5	4	Discontinue carboplatin	
Paclitaxel (mg/m ²)	70	60	Discontinue paclitaxel	
Ruxolitinib (mg AM/mg PM)	15/15	10/10	5/5	Discontinue ruxolitinib

6.1 Treatment modifications based on hematologic toxicity

Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

Lower Limits for ANC and Platelet Count

- Subsequent cycles of treatment for Cycles 2 - 6 will not be initiated until the ANC is $\geq 1,000$ cells/mcl and the platelet count is $\geq 75,000$ /mcl. Patients who fail to recover adequate counts within a 3-week delay will no longer receive protocol-directed therapy.
- The Day 8 and 15 paclitaxel dose will not be administered unless the ANC is ≥ 500 cells/mcl and the platelet count is $\geq 50,000$ /mcl. If not given, these doses are omitted and not made up.
- For patients receiving the experimental regimen, ruxolitinib will be held until ANC and platelets recover to allow administration of chemotherapy (paclitaxel and/or carboplatin) as specified by the protocol.

During ruxolitinib maintenance (Phase I component only), Day 1 treatment will not be given until the ANC is $\geq 1,000$ cells/mcl and the platelet count is $\geq 75,000$ /mcl. Treatment with ruxolitinib will be delayed for a maximum of 3 weeks beyond completion of C6 (6 weeks from day 1 of C6) until these values are achieved. Patients who fail to recover adequate counts within this time frame will no longer receive any protocol-directed therapy. See also Section 5.1.1.4. (10/09/2017)

Use of Hematopoietic Cytokines and Protective Agents:

Myeloid growth factor support. It is anticipated that myelosuppression may be a significant adverse effect of protocol therapy. In general, patients will NOT receive prophylactic myeloid growth factors unless they experience complicated neutropenia, treatment delays due to neutropenia, or dose omissions due to neutropenia. In particular, myeloid growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. Granulocyte-colony stimulating factor (G-CSF) support with filgrastim will be implemented for febrile neutropenia and for dose-limiting neutropenia as specified in [section 6.2](#). When G-CSF is used prophylactically in subsequent chemotherapy cycles after dose-limiting neutropenia has been documented, it is recommended that filgrastim (dose according to institutional standard) will be administered daily subcutaneously starting 24-72 hours after the last dose of chemotherapy and continuing through hematopoietic recovery. Administration of growth factors on the same day as chemotherapy is not recommended. Pegfilgrastim is not recommended for chemotherapy regimens given less than every 2 weeks.

Note: JAK inhibition by ruxolitinib may reduce the effectiveness of growth factor support. Ruxolitinib will be held when chemotherapy is also held for low ANC (see above); this will coincide with situations where filgrastim is used for the active management of complicated neutropenia. However, ruxolitinib may be administered

concomitantly with prophylactic filgrastim during subsequent chemotherapy cycles after dose-limiting neutropenia has been documented in a prior cycle(s). Filgrastim will not be administered prophylactically during cycles of ruxolitinib maintenance therapy (applies to phase I component only).

Patients will NOT receive prophylactic thrombopoietic agents.

Given the mechanism of action of ruxolitinib, which may inhibit or diminish the efficacy of erythropoiesis-stimulating agents (ESAs), and the thromboembolic risk associated with ovarian cancer and related malignancies, the **use of ESAs is not permitted**. **Patients may receive** iron supplements, vitamin B supplementation and/or transfusions as clinically indicated for management of anemia.

Patients may NOT receive amifostine or other protective reagents.

6.2 **Modifications for Hematologic Toxicity (Nadirs) (10/10/2016) (04/06/2018)**

Dose-limiting neutropenia (DLT-ANC, defined in [section 6.2](#)) or dose limiting thrombocytopenia (DLT-PLT, defined in [section 6.2](#)) will be handled according to **Tables B and C**.

DLT-ANC is defined by the occurrence of febrile neutropenia, Grade 4 neutropenia lasting > 7 days, delay of treatment for more than 7 days because of neutropenia, ANC < 1000 cells/mcl on Day 1, or omission of day 8 or day 15 paclitaxel because of neutropenia.

Febrile neutropenia is defined within the CTCAE as a disorder characterized by an ANC <1000/mcl and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour.

DLT-PLT is defined as a platelet count < 25,000/mcl (CTC grade 4), bleeding associated with a platelet count between 25,000/mcl and 50,000/mcl (CTC grade 3), delay of treatment on Day 1 of a cycle > 7 days because of thrombocytopenia, platelet count < 75,000/mcl on Day 1, or inability to administer day 8 or day 15 paclitaxel due to thrombocytopenia.

Anemia: No dose modifications will be made for anemia. Patients may receive red blood cell transfusions, and/or iron and vitamin B supplementation using standard supportive care guidelines.

Tables B and C delineate the dose-modification rules based on the occurrence of DLT-ANC and/or DLT-PLT. Refer to Table B for dose reduction increments. Study therapy will be discontinued in the event that any agent is discontinued based on an incremental dose reduction.

Table C: Dose Modification Rules for Dose-Limiting Hematologic Toxicity,

DLT ANC	DLT PLT	1 st Occurrence	2 nd Occurrence	3 rd Occurrence
Yes	No	Reduce ruxolitinib (if on experimental regimen) one dose increment. Administer GCSF starting after day 8 paclitaxel	Reduce ruxolitinib (if on experimental regimen) one dose increment. Reduce carboplatin one dose increment, discontinue day 15 paclitaxel dose, and administer GCSF starting after day 8 paclitaxel	Discontinue study therapy
Yes	Yes	Reduce ruxolitinib (if on experimental regimen). Reduce carboplatin one dose increment and administer GCSF starting after day 8 paclitaxel	Discontinue study therapy	
No	Yes	Reduce ruxolitinib (if on experimental regimen). Reduce carboplatin one dose increment	Discontinue study therapy	

During the maintenance phase of therapy with ruxolitinib (**Phase I Component only**), the dose of ruxolitinib should be initiated based on platelet count at the conclusion of cycle 6 of chemotherapy and following recovery of platelet count to $\geq 75 \times 10^9/L$ with maximum delay of 3 weeks, as follows: For platelet count $> 100 \times 10^9/L$, initiate at dose level as administered during cycle 6 with chemotherapy. For platelet count of $75 \times 10^9/L$ to less than $100 \times 10^9/L$, reduce one dose level (see Table A). Following subsequent hematologic evaluations specified in section 4.2, the dose of ruxolitinib should be modified according to the following rules, using dose levels specified in Table A and the following platelet count ranges: $> 100 \times 10^9/L$, $75 \times 10^9/L$ to less than $100 \times 10^9/L$, $50 \times 10^9/L$ to less than $75 \times 10^9/L$. This includes the provision to re-escalate ruxolitinib dose with recovery of platelet counts. If subsequent platelet count decreases into the next lower range, reduce one dose level; conversely, if subsequent platelet count increases into the next higher range, increase one dose level. In any case, discontinue study therapy for platelet count $< 50 \times 10^9/L$. (03/20/2017)

6.3 Modifications for Non-Hematologic Toxicity (10/10/2016) (04/06/2018)

Table B above should be used for dose level modifications for non-hematologic toxicity only as indicated specifically in the sections below. In general, dose modifications are to be made only after maximal medical management has been implemented.

Peripheral Neuropathy. Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level in paclitaxel and delay in all subsequent protocol-directed therapy for a maximum of three weeks until recovered to Grade 1. If peripheral neuropathy fails to recover to Grade 1 by a maximum delay of three weeks from time therapy is due, or recurs, then paclitaxel should be withheld from all subsequent chemotherapy cycles.

Renal toxicity (associated with reduction in GFR) is not expected as a direct complication of chemotherapy or ruxolitinib in this untreated patient population using the prescribed dose and schedule of each regimen. As such, there are no specific dose modifications for renal toxicity. However, the target AUC dose of carboplatin must be recalculated each cycle in any patient who develops renal insufficiency, defined by serum creatinine greater than 1.5 x institutional upper limit normal (ULN). In addition, ruxolitinib should be reduced one dose level for estimated CrCl (see [section 4.2.1](#)) of between 30 and 49 and two dose levels for CrCl between 15 and 29. Ruxolitinib should be discontinued for CrCl below 15. Should there be a concomitant indication for dose level reduction of ruxolitinib due to a drop in CrCl and hematologic toxicity, only one dose level decrease would apply at that time.

Hepatic toxicity is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule for each regimen. However, the development of Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level in paclitaxel and delay in subsequent therapy for a maximum of three weeks until recovered to Grade 1.

There will be no dose modifications for **alopecia, nausea, constipation, hypokalemia, hypocalcemia, or hypomagnesemia**. It is recommended that routine medical measures be employed to manage these adverse events. Grade 3 diarrhea on day of planned treatment will require holding of paclitaxel in patients on weekly paclitaxel. Any grade 3 diarrhea will mandate a one dose level reduction of paclitaxel in future cycles. In addition, since ruxolitinib has been associated with diarrhea, though usually grade 1 to 2, ruxolitinib should be held for grade 3 diarrhea until resolution to grade 2 or less. If the diarrhea is clearly infectious and has resolved, the above mandated dose reductions do not apply.

In general, the occurrence of a **hypersensitivity reaction** to paclitaxel is not considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments in infusion rates should be made. However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study.

Potential modifications for **other non-hematologic toxicities with an impact on organ function** of Grade 2 (or greater) require discussion with one of the study co-chairs except where noted below.

Special Modifications of Study Treatment

For any CTCAE Grade 3 non-hematologic adverse event (except controllable nausea/emesis) considered to be at least possibly related to study treatment, protocol directed treatment should be held until symptoms resolve to \leq CTCAE Grade 1. If a CTCAE Grade 3 adverse event persists for > three weeks or recurs after resumption of therapy, the patient may be taken off protocol directed treatment after consulting with the Study Chair.

For any CTCAE Grade 4 non-hematologic adverse event (except controllable nausea/emesis), the patient may be taken off protocol directed treatment therapy after consulting with the Study Chair.

6.4 Criteria for Discontinuation of Ruxolitinib Maintenance Therapy (Phase I Component Only) (10/10/2016)

During the maintenance phase of the phase I component, ruxolitinib will be discontinued for unacceptable toxicity defined as grade 3 or greater toxicity; for symptomatic grade 2 toxicity requiring continuous medical management for 2 weeks; or for asymptomatic grade 2 toxicity persisting for two consecutive 3-week cycles.

6.5 Interruption and Restart of Ruxolitinib for Other Reasons

Except for the hematologic criteria specified in Section 6.2 (and in the case of DLT in Cycle 1 or Cycle 2 of the Phase I component, defined in Section 5.1.1.5), interruption of ruxolitinib for safety reasons is at the discretion of the investigator. In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse experiences that may have an unclear relationship to study drug. Except for cases otherwise specified, restart of ruxolitinib should occur at the most recently administered dose. If the same AE recurs following restart of study drug the investigator should consider reducing the study drug dose for any subsequent restart after recovery and after discussing with Study Chair or Study Co-Chair.

Procedures for Interruption of Ruxolitinib

In the case of ruxolitinib interruption, the patient should be provided written instructions at the study visit, or should be notified by phone with written follow-up as soon as possible. Dose modification, interruption, and restart should be recorded by the investigator or designee in the patient's medical record and recorded in the CRF.

6.6 Guidelines for Use of Cytotoxic Therapy, After Discontinuation of Protocol Directed Cytotoxic Therapy and Prior to Disease Progression In Phase II Component (28-FEB-2020)

In the absence of disease progression, in the Phase II component of the trial, if treatment is delayed more than 21 days for adverse events (as directed specifically in [section 6.](#)), protocol-directed therapy is discontinued. In that case, a patient may, at discretion of the investigator, continue non-protocol directed carboplatin and/or paclitaxel therapy (including dose reductions and growth factor support) for up to 6 total cycles of cytotoxic therapy, according to best clinical practice standards. There are no specific guidelines in this situation for dose modifications, laboratory testing, or use of growth factor support. In such situations, treatment data should still be submitted via Rave.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-GY007 is ruxolitinib, which is being made available under an IND sponsored by NRG Oncology. For patients receiving ruxolitinib, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in [section 7.52](#) of the protocol.

Ruxolitinib: IND #129988; IND Sponsor: NRG Oncology

Commercial Agents

The commercial agents in NRG-GY007 are carboplatin and paclitaxel. For patients receiving carboplatin and paclitaxel, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in [Section 7.52](#) of the protocol

7.2 Adverse Events and Serious Adverse Events

7.2.1 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. (04/06/2018)

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug 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 (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Adverse Events for Investigational Study Agents Not Provided by CTEP

The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoietic proliferation attributable to the inhibition of growth factor pathways associated with JAK inhibition. Dose-dependent, reversible thrombocytopenia, anemia, and neutropenia were the most frequent treatment-emergent AEs (TEAEs) observed during the Phase 3 clinical studies of ruxolitinib in patients with myelofibrosis. Increased rates of infection and anemia are potential risks of myelosuppression. In healthy volunteers, patients with rheumatoid arthritis, and patients with pancreatic cancer or hormone-refractory prostate cancer, the effects on hematopoietic proliferation have been less pronounced, presumably because of greater bone marrow reserve. The most frequent non-hematologic AEs in clinical trials have been mild, reversible increases in ALT and AST, bruising, hypercholesterolemia, dizziness, headache, and urinary tract infections.

For a thorough assessment of the risks of ruxolitinib, see the IB.⁵²

7.4 Adverse Events for Commercial Study Agents Refer to the package insert for detailed pharmacologic and safety information

7.5 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, <https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613>

Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.5.1 Expedited Reporting Methods

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS24-hour notification must be followed by a complete report within 3 days.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Regulatory Affairs at 215-854-0716.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as “an action *not* recommended” must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the “NOT recommended” assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.5.2 Expedited Reporting Requirements for Adverse Events

7.5.2.1 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention ¹

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
 An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

<p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> ○ “24-Hour; 5 Calendar Days” - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. ○ “10 Calendar Days” - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.
<p>¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: Expedited 24-hour notification followed by complete report within 5 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 3, 4, and Grade 5 AEs <p>Expedited 10 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 AEs resulting in hospitalization or prolongation of hospitalization <p>Effective Date: May 5, 2011</p>

7.5.2.2 Phase 1, 2 and 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a non-IND/IDE within 30 Days of the Last Administration of the Commercial Agent/Intervention ^{1,2} (10/09/2017)

<p>FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)</p> <p>NOTE: Investigators MUST immediately report to the sponsor (NCI) ANY Serious Adverse Events, whether or not they are considered related to the commercial agent(s)/intervention</p> <p>An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ul style="list-style-type: none"> 7) Death 8) A life-threatening adverse event 9) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 10) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 11) A congenital anomaly/birth defect. 12) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to NRG via CTEP-AERS within 24 hours of learning of the AE, followed by a complete report within 3 calendar days of the initial 24-hour report.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	24-Hour 3 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- “24-Hour; 3 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.

¹Serious adverse events that occur more than 30 days after the last administration of commercial agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs
- Grade 1 and 2 AEs resulting in hospitalization or prolongation of hospitalization

² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered.

Footnote “1” above applies after this reporting period.

7.5.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.4 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.5.5 Reporting to the Pharmaceutical Company: The CTEP-AERS report will be sent directly to Incyte via the CTEP-AERS system upon submission to NCI. **(10/10/2016)**

7.5.6 Reporting to the FDA: The NRG Oncology Regulatory Department will submit an IND safety report to the FDA and all participating investigators no later than 15 calendar days after determining that the suspected adverse reaction or other information qualifies for reporting (21 CFR 312.32(c)(1)). Any unexpected fatal or life-threatening suspected adverse reaction will be reported to the FDA no later than 7 calendar days after initial receipt of the information by GOG (21 CFR 312.32(c)(2)). Each report will be submitted on FDA Form 3500A (21 CFR 320.31(d)(3)).

8. REGISTRATION AND STUDY ENTRY PROCEDURES (04/06/2018)

8.1 CTEP Registration Procedures (04/06/2018)

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
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

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>.

8.1.1 Requirements for NRG-GY007 Site Registration (01/09/2017) (03/20/2017) (04/06/2018)

Before patient enrollment, submit the following documents to the NRG Oncology Regulatory Department ([See Section 8.1.2.2](#)):

- IRB approval letter (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 a combination is accepted)
- IRB-approved informed consent
- IRB Membership list or IRB assurance number
- FDA Form 1572 for institution PI (study-specific)
- Current CV (signed and dated within 2 years) for institution PI and all sub-investigators listed on FDA Form 1572
- Medical License for institution PI and sub-investigators listed on FDA Form 1572
- Lab license, certificates, and Normal Lab Values (NLV) for labs listed on FDA Form 1572
- Signed Investigator Signature Page
- Signed financial Disclosure Form for all investigators listed on FDA Form 1572
- Pharmacy Information Form
- Signed Trial and Toxicity Management Training Certificate of Review*

***Trial and Toxicity Management Training**

All institutions participating in this trial will be required to participate in a Trial and Toxicity Management Training. This training will focus on the toxicities and the toxicity management around ruxolitinib. The institution PI and one study coordinator/nurse from each site must review the Trial and Toxicity Management slides and submit a signed Certificate of Review to satisfy this regulatory requirement. This is an institution-specific requirement to participate in this trial. Training slides will be provided by NRG and details for participation are on the NRG-GY007 NRG Oncology web site. NRG Oncology will notify CTSU when an institution has satisfied this requirement.

The NRG Oncology Regulatory Department Administrative Office will receive, review, and approve all regulatory documents. **Please allow 7-10 days for review and approval of all documents prior to screening first patient.**

8.1.2 IRB Approval (01/09/2017) (04/06/2018)

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 separate 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 IRBManager 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.

8.1.2.2 Submitting Regulatory Documents:

The required regulatory documents can be submitted electronically or via mail to the NRG Oncology Regulatory Department.

NRG Oncology Regulatory Department
ATTN: NRG-GY007
1600 JFK Blvd., Suite 1020
Philadelphia, PA 19103
E-mail: NRG-GY-Regulatory@NRGOncology.org

8.1.2.3 Checking Your Site's Registration Status: (01/09/2017) (03/20/2017)

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

- Go to <https://www.ctsuo.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.

8.2 Patient Enrollment (04/06/2018)

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

NOTE: The Phase I portion is complete.

For the Phase I portion, the SDMC-Buffalo Office web-based patient reservation system will be used, in which slots for particular patients are reserved. Reservations are not transferrable to other patients, and if the patient is not enrolled within the required timeframe, the reservation is cancelled and the slot is then made available to other patients and sites. If all slots are reserved, patients can be added to a waiting list. (10/10/2016)

The URL for the Phase I reservation system can be found at <https://nrg42.nrgoncology.org/phaseireservations>. (03/20/2017)

8.2.1 Oncology Patient Enrollment Network (OPEN) (04/06/2018)

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 position in the Rave database. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' web site <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 ctscontact@westat.com.

8.3 Data Submission / Data Reporting (04/06/2018)

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/index.jsp> >) 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 hold the 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 ctscontact@westat.com.

9. DRUG INFORMATION

9.1 Ruxolitinib Phosphate, IND# 129988

9.1.1 Chemical Name: 1*H*-Pyrazole-1-propanenitrile, β -cyclopentyl-4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-, (β R)-, phosphate (1:1)

9.1.2 Molecular Formula: C₁₇H₁₈N₆.H₃PO₄

9.1.3 M.W.: 404.36

9.1.4 Mode of Action: Ruxolitinib is an oral JAK inhibitor with selectivity for JAK1 and JAK2.

9.1.5 Formulation: Round curved white to almost white 5 mg tablets

9.1.6 Route of Administration: Oral

9.1.7 How Supplied: Ruxolitinib will be supplied in HDPE bottles containing 60 tablets. (10/10/2016)

9.1.8 Ordering/Accountability:

Initial Supply: Following submission and approval of all required regulatory documents (as stated in section 8.1.2), an initial supply may be requested by emailing the drug request form to NRG-GY-Regulatory@NRGOncology.org.

Subsequent Supply: If additional drug is needed, please email the drug request form to NRG-GY-Regulatory@NRGOncology.org

Drug Accountability: All study drug must be accounted for during the course of this study. Site must maintain an NCI Drug Accountability Record Form (DARF).

Drug Destruction: At the conclusion of the study, remaining inventory is documented on the DARF and unused drug is to be destroyed as per institution policy and recorded on the DARF. The final DARF must be forwarded to the NRG Oncology Regulatory Department via email to NRG-GY-Regulatory@NRGOncology.org

9.1.9 Drug Distribution: All drug orders are shipped via FedEx Priority Overnight delivery for shipments to US sites by Incyte. Each shipment will contain 3 cycles worth of drug.

9.1.10 Stability/Storage: Ruxolitinib has been shown to be stable for up to 6 months at 40°C and up to 24 months when stored at 25°C.

9.1.11 Concomitant dosing with CYP3A4 substrates⁵²

Co-administration of ruxolitinib with midazolam increased midazolam C_{max} by 14% while minimally increasing overall exposure AUC by 9% suggesting that co-administration of midazolam with ruxolitinib does not lead to clinically meaningful increases in the peak known to undergo extensive hepatic as well as intestinal metabolism. Thus it was concluded that ruxolitinib did not show any potential to inhibit CYP3A4 enzymes and hence no dose adjustment is necessary when ruxolitinib is co-administered with CYP3A4 substrates.

9.1.12 Interactions Between Ruxolitinib and Either Carboplatin or Paclitaxel⁵²

Studies thus far have demonstrated no concern for interactions between ruxolitinib and either carboplatin or paclitaxel.⁵² *In vitro*, ruxolitinib and its M18 metabolite do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Ruxolitinib is not an inducer of CYP1A2, CYP2B6 or CYP3A4 at clinically relevant concentrations. *In vitro*, ruxolitinib and its M18 metabolite do not inhibit the P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 or OAT3 transport systems at clinically relevant concentrations. Ruxolitinib is not a substrate for the P-gp transporter. The major route of elimination of carboplatin is renal excretion. Thus the primary determinant of carboplatin clearance is glomerular filtration rate (GFR). Ruxolitinib has no effect on GFR based on data from the phase III studies. So it is highly unlikely ruxolitinib will affect carboplatin clearance or plasma levels. The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Ruxolitinib does not inhibit any of these enzymes, so there is little chance of an interaction with paclitaxel. Ruxolitinib is metabolized by CYP3A4 and somewhat by CYP2C19. Neither carboplatin nor paclitaxel are inhibitors of either of those enzymes.

9.1.13 Adverse Effects Please refer to the Ruxolitinib IB for complete AE information.

9.1.14 Investigator Brochure⁵²:

To supplement the toxicity information contained in this document, investigators must obtain the current version of the investigator brochure for comprehensive pharmacologic and safety information. The IB can be requested by sending a request to NRG-GY-Regulatory@NRGOncology.org. In the subject line of the request, please state, "NRG-GY007 IB Request". The following information must be stated in the request:

Institution Name
CTEP Institution Code
Principal Investigator

9.2 Commercial Agents
Carboplatin (NSC #241240)
Paclitaxel (NSC #673089)

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.2.1 Adverse Events

Please refer to the package insert for complete discussion of adverse events.

9.2.2 Administration:

Please see [Sections 5.1.1.1](#) and [5.1.2.1.2](#) for administration instructions. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

10. PATHOLOGY/BIOSPECIMEN

10.1 Central Pathology Review Guidelines

Not Applicable.

10.2 Tissue Selection for Integral Marker Testing

Not Applicable.

10.3 Tissue Selection for Integrated marker testing

Not Applicable.

10.4 Biospecimen Submission Tables (04/06/2018) (07/30/2018) (04/05/2019)

Biospecimens listed below should not be submitted until after patient registration and Bank ID assignment. **(10/10/2016)**

A detailed description of the biospecimen procedures can be found in Appendix IX.

If biospecimen availability is limited, the mandatory biospecimens listed in section 10.4.1 should be submitted before the optional biospecimens listed in section 10.4.2.

10.4.1 Mandatory Biospecimen Submissions (Phase II only) (01/09/2017) (04/06/2018) (07/30/2018) (04/05/2019)

The patient must give permission to participate in this **mandatory** study component. Participating sites are required to submit the patient’s biospecimens as outlined below.

MANDATORY BIOSPECIMENS		
Required Biospecimen (Biospecimen Code)	Collection Time Point	Sites Ship Biospecimens To
PRE-TREATMENT		
Pre-treatment Serum (SB01) prepared from 7-10mL of blood drawn into plain red top tube(s)	Prior to study treatment	NRG BB-Columbus within 16 weeks of registration ³
FFPE Primary Tumor (FP01) ¹	Prior to all treatment	NRG BB-Columbus within 8

1 st Choice: block 2 nd Choice: 35 unstained slides (30 charged, 5µm & 5uncharged, 10µm) ²		weeks of registration ³
FFPE Metastatic Tumor (FM01) ¹ 1 st Choice: block 2 nd Choice: 35 unstained slides (30 charged, 5µm & 5 uncharged, 10µm)	Prior to all treatment (<i>Optional if FP01 is submitted</i>)	
TUMOR REDUCTIVE SURGERY		
FFPE Interval Primary Tumor (FP02) ¹ 1 st Choice: block 2 nd Choice: 35 unstained slides (30 charged, 5µm & 5 uncharged, 10µm) ²	During interval Tumor Reductive Surgery (TRS) or image-guided biopsy	NRG BB-Columbus within 16 weeks of registration ²³
FFPE Interval Metastatic Tumor (FM02) ¹ 1 st Choice: block 2 nd Choice: 35 unstained slides (30 charged, 5µm & 5 uncharged, 10µm) ²	During interval Tumor Reductive Surgery (TRS) or image-guided biopsy (<i>Optional if FP02 is submitted</i>)	

- 1 A copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the NRG BB-Columbus
- 2 If tumor tissue is limited, priority should be given to the 30 charged, 5µm sections. If less than the requested number of slides are available, contact the NRG BB-Columbus (BPCBank@nationwidechildrens.org).
- 3 NRG BB-Columbus / Protocol NRG GY007, Nationwide Children’s Hospital, 700 Children’s Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

10.4.2 Optional Biospecimens (04/06/2018) (07/30/2018) (04/05/2019)

If the patient gives permission to participate in this optional study component, then participating sites are required to submit the patient’s biospecimens as outlined below.

Note: Collection materials and shipping labels are **not** provided for some optional biospecimens. Refer to [Appendix IX](#) for details.

OPTIONAL BIOSPECIMENS		
Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens To
PRE-TREATMENT		
Snap Frozen Primary (RP01) <i>or</i> Metastatic (RM01) Tumor ^{1,2} ≥0.2g total weight in cryovials ³	At the time of biopsy for histologic confirmation. Tumor tissue should be processed in the following order of priority: 1. Snap Frozen (1-5 segments) 2. Cryopreserved (one segment) 3. OCT Frozen (two segments) <i>Submit one of each type - Primary preferred; submit metastatic if primary not available. If tissue is limited, submit at least one segment processed in order of priority (above).</i>	NRG BB-Columbus within 16 weeks of registration ⁴
Snap Frozen Adjacent Normal (RN01) Tissue ^{1,2} ≥0.05g total weight in cryovials ³		
Cryopreserved Primary (RP02) <i>or</i> Metastatic (RM02) Tumor ^{1,2} ≥0.2g total weight in cryopreservation media ³		
OCT Frozen Primary (RP03) <i>or</i> Metastatic (RM03) Tumor ^{1,2} ≥0.2g total weight in OCT ³		
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to receiving any study treatment.	

Whole Blood for Cell-Free DNA (WB02) 10mL drawn into a Streck (cell-free DNA) tube		NRG BB-Columbus the day the specimen is collected ⁴
TUMOR REDUCTIVE SURGERY		
Snap Frozen Primary (RP04) <i>or</i> Metastatic (RM04) Tumor ^{1,2} ≥0.2g total weight in cryovials ³	During interval Tumor Reductive Surgery (TRS) or image-guided biopsy. Tumor tissue should be processed in the following order of priority: 1. Snap Frozen (1-5 segments) 2. Cryopreserved (one segment) 3. OCT Frozen (two segments) <i>Submit one of each type - Primary preferred; submit metastatic if primary not available. If tissue is limited, submit at least one segment processed in order of priority (above).</i>	NRG BB-Columbus within 16 weeks of registration ⁴
Cryopreserved Primary (RP05) <i>or</i> Metastatic (RM05) Tumor ^{1,2} ≥0.2g total weight in cryopreservation media ³		
OCT Frozen Primary (RP06) <i>or</i> Metastatic (RM06) Tumor ^{1,2} ≥0.2g total weight in OCT ³		
Whole Blood (WB03) 7-10mL drawn into purple top (EDTA) tube(s)	After receiving the first three cycles of study treatment; at the time of interval	
Whole Blood for Cell-Free DNA (WB04) 10mL drawn into a Streck (cell-free DNA) tube	Tumor Reductive Surgery (TRS) or image-guided biopsy.	NRG BB-Columbus the day the specimen is collected ⁴

- 1 A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the NRG BB-Columbus.
- 2 If a pathology report is not available for frozen tissue, a copy of the radiology report or operative report from the tissue removal procedure must be sent to the NRG BB-Columbus, along with a completed copy of the Pathology Verification (Appendix XII).
- 3 Total dimension of each segment should not exceed 1.0x1.0x0.5cm. Each segment should be frozen in a separate cryovial.
- 4 NRG BB-Columbus / Protocol NRG GY007, Nationwide Children’s Hospital, 700 Children’s Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

10.5 Laboratory Testing

Note: Testing of banked biospecimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

10.5.1 Cancer Stem Cells (Exploratory Biomarker)

Pending review and approval in accordance with NCTN policies, unstained sections of FFPE will be batch shipped to Drs. Buckanovich and Powell for exploratory biomarker analysis including (1) CD8:FOXP3 immunohistochemistry (IHC), (2) tumor CD3, CD4, TAI-1, HLA class I and II, and CD68 IHC, and (3) AQUA immunofluorescence and quantitative PCR analysis of ALDH, CD133, CD24, and CK19.

10.5.2 C-Reactive Protein and IL-6 (Exploratory Biomarker)

Pending review and approval in accordance with NCTN policies, aliquots of frozen

serum will be batch shipped to Drs. Buckanovich and Powell for analysis of C-reactive protein and IL-6.

10.5.3 Optional Biospecimens (04/06/2018) (07/30/2018) (04/05/2019)

The purpose of the optional biospecimen collection is to support CPTAC efforts.

11. SPECIAL STUDIES (NON-TISSUE)

Not applicable.

12. MODALITY REVIEWS

Not Applicable.

13. ASSESSMENT OF EFFECT

13.1 Definition of Disease Assessments

Disease progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).⁵³ 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 the RECIST criteria.

13.1.1 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 ≥ 10 mm with CT scan, as ≥ 20 mm by chest x-ray, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are

considered as non-measurable.

Notes:

Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

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 that can be reproducibly measured 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 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, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

13.1.2 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 the beginning of the treatment.

The same method of assessment and the same technique should 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 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), but NOT lung.

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 should 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, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

NRG will not allow PET-CT use for RECIST 1.1 response criteria.

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.

CA-125 (Ovarian, fallopian tube and primary peritoneal cancer trials): CA-125 alone cannot be used to determine progression in this study.

13.1.3 Criteria for Determining Disease Progression

Determination of disease progression should take into consideration all target ([see Section 13.1.4](#)) and non-target lesions ([see section 13.1.5](#)).

13.1.4 Evaluation of Target Lesions

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).

13.1.5 Evaluation of Non-Target Lesions

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. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only “non-target” lesions 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 Study Chair or Study Co-Chair).

13.1.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first.

13.1.7 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

13.1.8 Total Gross Resection

At the time of TRS, total gross resection is defined as no visible or palpable tumor remaining after completion of surgery and no evidence of disease on radiographic imaging outside of the surgical field at the time of radiographic tumor measurement just prior to TRS ([see section 4.2](#)).

13.1.9 Complete Pathologic Response

At the time of TRS, complete pathologic response is defined as no evidence of disease on radiographic imaging at the time of radiographic tumor measurement just prior to TRS ([see section 4.2](#)), no visible or palpable tumor at the time of surgical exploration, and no pathologic evidence of disease in tissue specimens obtained at TRS ([see section 5.3](#) for details regarding TRS).

14. DATA AND RECORDS

14.1 Data Management/Collection

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS (Regulatory Support System). To access iMedidata/Rave, the site user must have an active CTEP-IAM account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization rosters at the enrolling site. Each person responsible for data management must be on the NRG roster in order to receive access to Medidata 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 (iMedidata-Notification@mdsol.com) to activate their account. 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 will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts also will 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 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.

14.2 NRG Data Management Forms (10/10/2016) (04/06/2018) (07/30/2018) (04/05/2019)

The following forms must be completed for all patients registered and submitted to the NRG Oncology Statistics and Data Management Center (SDMC) in Buffalo, NY according to the schedule below. Electronic case report forms must be submitted through the Medidata Rave Electronic Data Entry System (www.imedidata.com). All amendments to forms must also be submitted through Medidata Rave. The operative report, discharge summary and pathology reports can be sent to the NRG Oncology SDMC in Buffalo, NY via postal mail or uploaded in Medidata Rave. The upload option is an alternative method for submitting paper reports.

Form	Comments
Baseline Folder <i>(Forms due within 2 weeks of registration)</i>	
Baseline/History Forms: <ul style="list-style-type: none"> - Visit Information – Baseline Form - Registration Form - Pre-Treatment Summary Form - On Study History Surgery Form - Pre-Study History Chemotherapy Information Form - Pre-Study Radiation Therapy Information Form - Concomitant Medications Form - Vitals Form - Specimen Consent* - Vitals Form - ECG Information Form - Medical History Form - Bio-Marker Information Form - BRCA Status Form** Baseline Adverse Event Reporting <ul style="list-style-type: none"> - Baseline Adverse Event-Terms - Baseline Adverse Event AE Grades 	The appropriate forms will load in the Baseline Folder based on the answers reported on the corresponding Baseline Visit Information form. *Phase II only **Required for patients enrolled to Amendment 7 and subsequent amendments. Requested, but not required, for patients entered before Amendment 7.
Visit Folder <i>(Forms due within 2 weeks of the completion of each cycle*)</i>	
Cycle Information and Treatment Forms: <ul style="list-style-type: none"> - Visit Information Form - Post-Treatment Weekly Lab loader** - Cycle Drug Information Form - Labs and Chemistries Form - Lab Loader - Dose Limiting Toxicity Form - Vitals Form - Physical Exam 	The appropriate forms will load in the Visit Folder based on the answers reported on the corresponding Visit Information forms. *Patients on the Phase 1 portion – the forms will be due within 72hrs from the start of the subsequent cycle.

<ul style="list-style-type: none"> - - ECG Information Form - Biomarker Information <p>Toxicity Forms:</p> <ul style="list-style-type: none"> - Toxicity Report-Section 1 Form - Toxicity Report – AEs Toxicity Report -AE Grades 	<p>**Labs and Chemistries Forms will be collected prior to each dose of study drug.</p>
<p>Solid Tumor Evaluation Folder <i>(Forms due within 2 weeks of disease evaluation)</i></p>	
<p>Solid Tumor Evaluation Forms:</p> <ul style="list-style-type: none"> - Target Lesions Form - No Target Lesions Form - Non-Target Lesions Form - New Target Lesions Form - Status and Response Form 	<p>This protocol uses the STE loader. Please report STE forms at specified time points as required per protocol. A tool is provided to calculate dates of re-imaging.</p>
<p>Pathology Folder <i>(Reports and slides due within 6 weeks of registration)</i></p>	
<p>Primary disease:</p> <ul style="list-style-type: none"> - Pathology Report (initial core biopsy report) - Tumor Reductive Surgery Report - Image guided core biopsy report (submit if TRS is not performed) 	<p>Submit one copy of the pathology reports to SDMC in Buffalo, NY via postal mail or upload the pathology report online via RAVE.</p>
<p>Surgery Folder (forms due within 8 weeks of Surgery) <u>This folder will load only for patients who have undergone surgery</u></p>	
<ul style="list-style-type: none"> - Surgery Visit Information Form - Operative Report - Pathology Report - Discharge Summary Report - Surgical Reporting Form - Summary of Operative Findings-Bowel - Summary of Operative Findings-Mesentery - Summary of Operative Findings Abdominal Organs Form - Summary of Operative Findings Pelvis Form - Summary of Operative Findings Peritoneum 	<p>Submit one copy of the Pathology, Operative, and Discharge Summary reports to SDC via postal mail or upload the pathology report online via RAVE.</p> <ul style="list-style-type: none"> ◆ Appropriate forms will load based on the answers reported on the corresponding Surgery Visit Information form.

<ul style="list-style-type: none"> - Summary of Operative Findings Nodes Primary Disease Description Form ♦ - Post-Operative Complications Form ♦ 	
Translational Research Folder (Phase II only)	
<p>TR Forms:</p> <p><u>Pre-Treatment - Mandatory</u></p> <ul style="list-style-type: none"> - Pre-Treatment Serum (SB01) - FFPE Primary Tumor (FP01) - FFPE Metastatic Tumor (FM01) <i>optional</i> <p><u>Tumor Reductive Surgery - Mandatory</u></p> <ul style="list-style-type: none"> - FFPE Interval Primary Tumor (FP02) - FFPE Interval Metastatic Tumor (FM02) <i>optional</i> <p><u>Pre-Treatment - Optional</u></p> <ul style="list-style-type: none"> - Snap Frozen Primary (RP01) - Snap Frozen Metastatic (RM01) <i>optional</i> - Snap Frozen Adjacent Normal (RN01) - Cryopreserved Primary (RP02) - Cryopreserved Metastatic (RM02) <i>optional</i> - OCT Frozen Primary (RP03) - OCT Frozen Metastatic (RM03) <i>optional</i> - Whole Blood (WB01) - Whole Blood for Cell-Free DNA (WB02) <p><u>Tumor Reductive Surgery - Optional</u></p> <ul style="list-style-type: none"> - Snap Frozen Primary (RP04) - Snap Frozen Metastatic (RM04) <i>optional</i> - Cryopreserved Primary (RP05) - Cryopreserved Metastatic (RM05) <i>optional</i> - OCT Frozen Primary (RP06) - OCT Frozen Metastatic (RM06) <i>optional</i> - Whole Blood (WB03) - Whole Blood for Cell-Free DNA (WB04) 	<p>The appropriate forms will load in the Translational Research Folder based on the answers reported on the Specimen Consent form.</p> <p>An electronically completed copy of Form TR must accompany each biospecimen shipped to the NRG BB-Columbus. Handwritten forms will not be accepted. (01/09/2017)</p> <p>SB01, RP01-03, RM01-03, RN01, and WB01-02 is due one week from registration</p> <p>FP01 or FM01 are due 8 weeks from registration.</p> <p>FP02 or FM02, RP04-06, and WB03-04 are due 16 weeks from registration.</p>
Treatment Completion Folder (Forms due within 2 weeks of treatment completion)	
<p>Treatment Completion Form</p>	
Follow-up Visit Folder (Forms due within 2 weeks of follow-up visits, disease progression or death)	
<p>Visit Information Follow-Up Form</p> <p>Follow-Up Form</p> <p>Follow-Up Period Adverse Event:</p>	<p>Follow-up visits should be scheduled every 3 months for 2 years, and then every 6 months for 3 years for a total of</p>

<ul style="list-style-type: none"> - Follow-Up Adverse Event – Part 1 - Follow-Up Adverse Event –Terms - Follow-Up Adverse Event – AE Grades <p>Solid Tumor Evaluation:</p> <ul style="list-style-type: none"> - Target Lesions Form - Non-Target Form - New Target Lesions Form - Status and Response Form 	<p>5 years or until study terminations.</p> <p>The appropriate forms will load in the Follow-up Visit Folder based on the answers reported on the corresponding Follow-up Visit Information forms.</p>
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14.3 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. [See Section 7.5](#) for information about expedited and routine reporting.

For reporting of second primary cancers or other report forms available in Rave: Indicate form for reporting in Rave, timeframes, add if loading of the pathology report is required.

14.4 Global Reporting/Monitoring

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, either by FTP burst of data or via the CDS web application. 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>)

15. STATISTICAL CONSIDERATIONS

15.1 Study Design (04/06/2018) (04/05/2019)

Phase I Study:

The phase I study will escalate dose-levels until an MTD is estimated or the maximum dose-level is determined to be safe. The selected dose-level for the phase II study will be the dose-level that estimates the MTD or the maximum dose-level in the study (whichever is lower). The selected dose will be called “the recommended phase II dose.” All patients on this part of the study will receive the experimental regimen. The minimum number of patients studied in this part of the study will be 8 (perhaps 4 if the accrual is unusually slow). The maximum number of patients studied in the phase I study is not expected to exceed 32 patients. Safety will be evaluated by dose-limiting toxicities in cycles 1 and 2.

Phase II Study:

The study will prospectively stratify patients before randomization by initial performance status (0 or 1 versus 2) and cell type (clear cell versus the high grade serous/Endometrioid). Randomization will be 2:1 with approximately twice as many patients randomized to the experimental regimen as to the reference regimen. Patients with BRCA mutation are anticipated to receive further therapy to delay disease progression. The primary analysis will include BRCA status as a post-randomization stratification factor. BRCA strata will be BRCA mutated versus not BRCA mutated or BRCA status unknown. The total number of patients randomized is expected to be about 130 in a single stage of accrual. An interim futility analysis will be conducted at approximately 1/2 the information time. If the interim futility analysis does not recommend further accrual, the study will suspend accrual after consultation with the DMC. An analysis of toxicity will be conducted as well. The study will use PFS as the primary endpoint to compare the experimental regimen to the reference regimen using a log-rank test stratified by performance status, cell type, and BRCA status.

15.2 Study Endpoints**15.2.1 Primary Endpoints:**

Phase I Endpoint: Whether or not a patient experiences a dose-limiting toxicity (DLT) in cycles 1 or 2 (see section 5.1.1.5).

Phase II Endpoint: Progression-free survival (PFS).

15.2.2 Secondary Endpoints:

Phase I Secondary Endpoint:

- The frequency and severity of adverse events for all cycles of therapy, including those for maintenance ruxolitinib.
- The frequency of patients who could not receive surgery within the defined timeframe for reasons other than non-response, disease progression, or medical contraindications will be given by the dose-level administered.
- The number of patients who discontinue ruxolitinib in the first 3 months of maintenance therapy. **(10/10/2016)**

Phase II Secondary Endpoints:

- Subset analyses within categorized, important exploratory laboratory parameters that examine the treatment effect on PFS.
- A log-rank test utilizing the categorized values of the exploratory laboratory parameters or a Cox proportional hazards (PH) model to estimate of the hazard ratio for progression or death in PFS and overall survival (OS). If feasible, the PH model will examine the effect of continuous measures.
- Patients will be dichotomized by total gross resection. Differences in the proportion who have total gross resection by treatment arm will be examined with Fisher's Exact Test. Multivariate logistic modeling will be conducted if feasible.
- Patients will be dichotomized by complete pathologic response. Differences in the proportion who have complete pathologic response by treatment arm will be examined with Fisher's Exact Test. Multivariate logistic modeling will be

- conducted if feasible.
- Overall survival (OS) by treatment arm. Log-rank test and Cox PH estimate of the HR.

15.3 Primary Objectives Study Design

15.3.1 Primary Hypothesis and Endpoints

Phase I Study Primary Endpoint: Whether or not a patient experiences a dose-limiting toxicity (DLT) in cycles 1 or 2.

Phase I Primary Hypotheses: The regimen is considered safe if the probability of a patient experiencing a DLT in cycles 1 or 2 is 35% or less for the experimental regimens examined on this study. The regimen is considered too toxic if the probability of a patient experiencing a DLT in cycles 1 or 2 is 55% or more. (10/10/2016)

Phase II Primary Endpoint: Progression-free survival (PFS).

Phase II Primary Hypotheses: The null hypothesis is that $S_0(t) \geq S_1(t)$ for all t where $S_0(t)$ is the survival function of PFS for the reference arm and $S_1(t)$ is the survival function of PFS for the experimental regimen. The alternative hypothesis is that $S_0(t) < S_1(t)$ for some t.

15.3.2 How Primary Endpoints Will Be Analyzed (10/10/2016)

Phase I Historical Data Analysis:

An analysis of GOG 262 toxicity data showed that approximately 13 of patients on the weekly regimen experienced treatment related non-hematological toxicities in cycles 1 or 2. The original study did not include paclitaxel dose omissions and required a delay of greater than 14 days. The current study includes dose omissions and delays of greater than 7 days to declare DLT events. Approximately 20% had dose reductions in cycles 1 or 2 due to hematological toxicities or infections, and about 7% had delays of administering the regimen for cycle 2 or 3 due to protocol adverse events for more than 7 days. About 19% had an omission of paclitaxel on either day 8 or day 15 of cycles 1 or 2. Overall, the estimated probability of a patient experiencing a DLT in cycles 1 or 2 is about 34% to 37%, depending in part on the proportion of patients who have grade 4 neutropenia lasting longer than 7 days and those with the excluded adverse events that cannot be controlled with maximal medical management. The 95% CI for the probability of a patient experiencing a DLT is approximately 29.7 ~ 41.8%. Therefore, the null hypothesis for tolerable regimens based on the historical data and definitions of DLT will be $H_0: p = 0.35$ where p is the probability of a DLT. The alternative hypothesis is $H_a: p = 0.60$.

Phase I Study Design

The study will accrue patients to each dose-level in cohorts of size 4-7. Enrollment to a dose level will be staggered so that no more than 4 participants are at risk at any given

time. Patients must be considered evaluable for toxicity in cycles 1 and 2 to be included in the analysis. The regimen will be evaluated for safety in cycles 1 and 2 (noting delays in starting cycle 3). Patients who do not experience DLT and who do not complete 2 cycles of therapy will be replaced. Patients who miss more than 25% of ruxolitinib doses in the first two cycles of therapy (based on pill diary review) without medical justification would also be replaced. Patients will be classified as having no DLTs in cycles 1 and 2 (i.e. not experiencing a DLT) or having at least 1 DLT in either cycle 1 or cycle 2. If no more than 2 patients experience at least 1 DLT out of 7 evaluable patients, then the current dose-level will be deemed safe and the study will escalate up to the next dose-level. If 3 or more patients out of 7 experience DLTs, then the current dose-level will be considered too toxic, and a lower dose-level may be considered for the recommended phase II study. Escalation/de-escalation will continue until a dose-level is considered too toxic/safe, the highest dose-level is evaluated and deemed safe, or the lowest level is deemed too toxic.

To increase the efficiency of the study, patients will be entered in two cohorts per dose-level. Instead of the typical 3+3 design, we will enter patients onto the study in a 4+3 manner. If 0 patients have DLTs in the first set of 4, then escalation will proceed immediately. If 1 or 2 patients have DLTs in the first set of 4, then the dose-level will be expanded to 7 in total. If the total number of patients experiencing DLTs is 2 or less, then escalation will continue. If 3 or more patients are observed to have DLTs at a particular dose-level, then that dose-level will be deemed too toxic, and consideration will be given to a lower dose-level.

Before beginning the phase II study, the number of patients who could not receive their tumor reductive surgery within the specified timeframe for reasons other than non-response, disease progression, or medical contraindications will be examined.

Phase II Analysis (04/05/2019)

Approximately 130 patients will enroll onto the study in a single stage. The analysis will be an intent to treat analysis of all enrolled patients. Patients will be randomized in a 2:1 fashion to the experimental to reference regimen. Treatment randomization will be balanced on cell type (clear cell versus high grade serous/Endometrioid) and performance status (0 or 1 versus 2). The analysis will also include BRCA status as a post-randomization, stratification factor. An interim safety analysis will be conducted once there are 10 participants enrolled and treated on the experimental arm. Tabulations of toxicities will be reviewed by the study chair and phase I chair. Patients will be monitored for disease progression or death (PFS endpoint). Time at risk will be assessed from the date of randomization. Patients who start another therapy prior to progression will continue to be followed for PFS. The data will be frozen approximately at one-half the information time for futility (after 46 PFS events) and a toxicity assessment. If there are still patients entering the study, and if the log-rank statistic for the hazard of progression or death favors the reference arm (i.e. indicates a higher hazard of progressing or dying on the experimental arm), then the study will recommend study suspension. Otherwise, the study will recommend continued accrual based on efficacy interim results. A final analysis will be conducted after 93 PFS events.

15.4 Sample Size and Power Calculations: (10/10/2016)

Phase I Study (10/10/2016)

Up to seven patients will be evaluated at each dose level. Patients will be enrolled to each dose-level in two cohorts. The probability mass function for the number of DLTs is provided below:

$$p(x_i = j) = \binom{n_i}{j} \pi^j (1 - \pi)^{n_i - j}$$

where $n_1 = 4$, $n_2 = 3$, $i = 1, 2$ for first and second cohort respectively, and π is the probability of DLT.

In order to proceed to a higher dose-level, it is necessary that:

$$P(X_1 = 0) + P(X_1 = 1)P(X_2 \leq 1) + P(X_1 = 2)P(X_2 \leq 0)$$

The chances of escalating after examining only 4 patients is 17.9% and 4.1% when the true DLT is 35% and 55%, respectively.

The dose-level will be considered too toxic (that is, to have exceeded the maximum tolerated dose (MTD)) if $x_1 + x_2 \geq 3$. Otherwise, it will be considered safe. The goal of the study will be to identify doses that do not exceed the MTD for administration in the phase II study. The dose-level operating characteristics for this decision rule is a 46.0% probability of declaring a safe regimen as being too toxic when the probability of a DLT is 35% ($\pi = 0.35$). If the probability of a DLT is 55% ($\pi = 0.55$), then the chances of declaring the regimen safe is 16%.

For comparison purposes, the 3+3 design has about a 34.5% probability of declaring a safe regimen (cycle 1 $p=0.20$) as being too toxic and a 23.3% probability of declaring a toxic regimen (cycle 1 $p=0.40$) as being safe when 6 patients are evaluated at that dose-level. Many dose escalating designs contain a (-1) and (-2) dose-level.

Table of the distribution of the recommended phase II dose (RP2D) for various probabilities of DLT across different dose-levels is not provided because of complex escalation rules.

Phase II Study

The number of PFS events required to achieve the desired operating characteristics can be approximated with Schoenfeld's equation:

$$D = \frac{(Z_\alpha + Z_\beta)^2}{\pi(1 - \pi)\theta^2}$$

Where $\alpha = \beta = 0.15$ are the type I and type II errors, respectively, π (not to be confused with the same character in the phase I study) is the probability of being randomized to the

experimental treatment ($\pi = 2/3$), and $\theta = \ln(HR) = \ln(0.625) = -0.47$. $Z_\alpha = Z_\beta = 1.0364$, so under the alternative hypothesis where the HR=0.625, the total number of required events is 87.52 or 88. However, an interim futility analysis is to be performed at one-half the information time (about 47 PFS events), so a correction to the distribution of the final test statistic is used. Note from Jennison and Turnbull (p49, eq. 3.1) that we will use the standardized test statistics, related to the log-rank test statistics (before squaring in the common Chi-square test) at the interim and final analyses, which will be designated by Z_1 and Z_2 , respectively. According to Jennison and Turnbull, the standardized statistics for the log-rank test will be distributed as a multivariate normal distribution with the following parameters:

$$\begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix} \sim MVN \left(\begin{pmatrix} \theta\sqrt{I_1} \\ \theta\sqrt{I_2} \end{pmatrix}, \Sigma = \begin{pmatrix} 1 & \sqrt{I_1/I_2} \\ \sqrt{I_1/I_2} & 1 \end{pmatrix} \right)$$

where I_k is the information obtained at the k^{th} stage of the design with $I_k = 2d_k/9$ and d_k being the total number of observed events at that time. $I_k = 2d_k/9$ (instead of $I_k = d_k/4$ in this case because the randomization is 2:1). Since the use of Wei and et al. plans on observing Z_1 at 50% information time, the covariance between Z_1 and Z_2 is about 0.707. The cumulative distribution function of Z_1 and Z_2 is provided below by $F(\cdot)$:

$$P(Z_1 \leq z_1, Z_2 \leq z_2) = F(z_1, z_2 | \theta, I_1, I_2)$$

The design will reject the null hypothesis $H_0: \theta \geq 0$ only if $Z_1 < 0$ and $Z_2 < c_2$. Since $\alpha = 0.15$, we wish to find c_2 so that $F(0, c_2 | \theta = 0, I_1, I_2) = 0.15$. Searching algorithms can quickly find the value of $c_2 = -0.9805$ which deviates slightly from the usual value of -1.036 obtained with a single stage test.

The required number of events to obtain 85% power is 93 PFS events with the interim analysis. That is to say:

$$F(0, -0.9805 | \theta = -0.47, I_1 = 10.3, I_2 = 20.7) = 0.85$$

It is unlikely that the interim analysis will be conducted at precisely 50% of the information time. The realized information at the interim and final analyses will be used to determine the critical value of c_2 under the null hypothesis so that the probability of a type I error does not exceed 15%. The probability of early termination under the alternative hypothesis is 6.5%. The probability of early termination under the null hypothesis is 50%.

GOG protocol data 0262 was used to estimate the median time of PFS and to project the times of analysis for the interim and final analysis.

In order to obtain the required number of events in a suitable timeframe, we will accrue 130 patients. We anticipate an accrual rate of 5 patients per month. The period of active

accrual is expected to be 26 months. We expect an interim analysis about 24 months after trial activation and a final analysis 40 months after trial activation (assuming a 14 month median PFS time with an exponential survival distribution). Using GOG-0262 survival distribution data did not significantly impact these estimates.

15.5 Study Monitoring of Primary Objectives

During the phase I portion of the study, all enrolling sites will be required to participate in a regularly scheduled teleconference including the Study Chair, and Phase I Subcommittee Chair and his/her assigned delegates.

Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an “as needed” basis.

15.6 Accrual/Study Duration Considerations

As stated above, we anticipate an accrual rate of 5 patients per month. The period of active accrual is expected to be 26 months. We expect an interim analysis about 24 months after trial activation and a final analysis 40 months after trial activation (assuming a 14 month median PFS time with an exponential survival distribution).

15.7 Dose Level Guidelines

An escalation/de-escalation design enrolling single cohorts of 8 patients will be used for regimens on this study. See above for further design details.

See section 5.1.1.1 for the dose-levels and section 5.1.1.5 for the definition of DLTs.

15.8 Secondary or Exploratory Endpoints (10/10/2016)

15.8.1 Secondary Hypotheses and Endpoints for the Phase I Study (10/10/2016)

1. There is no hypothesis to be tested for the frequency and severity of adverse events in the phase I study. They will be collected mostly for descriptive purposes. Tables of the maximum grade by patient and organ (or organ system) will be made.
2. The null hypothesis relating the probability of a patient failing to undergo interval tumor reductive surgery is 15% or less, i.e. $H_0: p \leq 0.15$. The alternative hypothesis is that the probability is 40% or more, i.e. $H_1: p \geq 0.40$.
3. The null hypothesis relating the probability of a patient discontinuing ruxolitinib in the first 3 months of maintenance therapy for toxicity is 10% or less, i.e. $H_0: p \leq 0.10$. The alternative hypothesis is that the probability is 30% or more, i.e. $H_1: p \geq 0.30$.

15.8.2 Secondary Hypotheses and Endpoints:

1. Subset analyses within categorized, important exploratory laboratory parameters that examine the treatment effect on PFS. The null hypothesis is that the survival functions by treatment are the same against the alternative hypothesis that says the survival functions are different.
2. A log-rank test utilizing the categorized values of the exploratory laboratory parameters or a Cox proportional hazards (PH) model to estimate of the hazard ratio for progression or death in PFS and overall survival (OS). If feasible, the PH model will examine the effect of continuous measures. One set of null hypotheses is that the survival functions by the lab parameters are the same. Another set of null hypotheses is that the hazard ratio (HR) is equal to 1.0. The alternative hypotheses are that the survival functions are different or that the $HR \neq 1.0$, respectively.
3. Patients will be dichotomized by total gross resection (Yes/No). Differences in the proportion who have total gross resection by treatment arm will be examined with Fisher's Exact Test. Multivariate logistic modeling will be conducted if feasible.
4. Patients will be dichotomized by complete pathologic response. Differences in the proportion who have complete pathologic response by treatment arm will be examined with Fisher's Exact Test. Multivariate logistic modeling will be conducted if feasible.
5. Overall survival (OS) by treatment arm. Log-rank test and Cox PH

15.8.3 Definitions of Secondary Endpoints and How These Will Be Analyzed in the Phase I Study (10/10/2016)

1. Adverse event described by severity (grade) and organ (or organ system) effected.
2. Whether or not a patient fails to undergo interval tumor reductive surgery. We expect about 85% of patients to undergo cytoreductive surgery in the prescribed timeframe in the absence of progressive disease and comorbidities. Historical data are limited, but in the 44 patients from GOG-0262 who underwent neoadjuvant chemotherapy with carboplatin plus dose-dense weekly paclitaxel (as proposed for NRG-GY007), only 4 patients did not undergo interval surgery. On the other hand, within the context of a dose-escalating phase I cohort that could include between 8 and 32 patients, it would be challenging to determine, with precision, the true rate of proceeding to interval cytoreductive surgery in NRG-GY007. Therefore, we would propose to set the lower bar at less than or equal to 60% as unacceptable (during the phase I dose-escalating component), and we would not proceed to the phase II component until a more tolerable regimen was defined. In addition, the proportion of patients eligible for interval cytoreduction would be monitored as a secondary endpoint in the randomized phase II portion, with an increased number of patients treated in a more uniform manner.

Let X = The number of patients who fail to undergo interval tumor reductive surgery. The study will be stopped if X is equal to or exceeds a threshold, x .

Sample Size	x	$P(X \geq x p = 0.15)$	$P(X \geq x p = 0.4)$
8	4	2.1%	40.6%
16	6	2.4%	67.1%
24	8	2.0%	80.8%
32	8	4.1%	94.3%

A final dose-level with 4 or more patients failing to receive reductive tumor surgery in the appropriate timeframe will be examined more closely by the DMC for consideration of not proceeding with the phase II portion of the study.

- Let X = The number of patients who discontinue ruxolitinib due to toxicity in the first 3 months in of the maintenance phase. Maintenance ruxolitinib will not be included in the phase II portion of the study if X is equal to or exceeds a threshold, x .

Sample Size	x	$P(X \geq x p = 0.10)$	$P(X \geq x p = 0.3)$
8	3	3.8%	44.8%
16	5	1.7%	55.0%
24	6	2.8%	77.1%
32	7	3.6%	88.7%

A final dose-level with 3 or more patients out of 8 requiring discontinuation of ruxolitinib due to toxicity in the first 3 months of the maintenance phase will be examined more closely by the DMC for consideration of eliminating ruxolitinib maintenance in the phase II study. Furthermore, if the study proceeds into the phase II study with maintenance ruxolitinib, then the first 32 evaluable patients randomized to the ruxolitinib arm will be examined. If 7 or more of the first 32 patients experience DLTs in maintenance, then the regimen will be examined again by the DMC for modification.

15.8.4 Definitions of Secondary Endpoints and How These Will Be Analyzed

- Often continuous laboratory biomarkers are dichotomized at the median. If many values are below the threshold of detection, they may be dichotomized as being positive (i.e. > 0) or negative (less than the threshold of detection). Sometimes they are inherently ordered (e.g. cell staining intensity). Ordinal categorical data may be dichotomized in a manner that splits the number of observations into two equally sized groups. Alternatively, the analysis may be done directly to look for evidence of trends in the hazard of PFS. More generally, the effect of treatment on PFS will be examined within each of these subsets using a log-rank test or a Cox PH model. Since treatment assignment is random, it is anticipated that about two thirds of the patients will belong to the experimental therapy. Interest will center

on whether the hazard of PFS changes from one group to another. Inferences may be feasible with as little as 10 events within each treatment group. If the hazards of PFS depend on the group examined, then the variable may be predictive of treatment effect, or to put it another way, an interaction term may be significant in a larger study.

2. These analyses will be done strictly with patients assigned to the reference arm (they can also be done in the experimental arm as well). The biomarkers will be categorized using the same techniques as discussed above. The impact of the biomarkers on PFS or OS will be assessed using log-rank tests or Cox PH models. In some instances, Cox modelling will be conducted on the continuous measure and checked for model adequacy.
3. The total gross tumor resection is defined as the removal of all visible tumor at the time of surgery. The simplest analysis to examine whether or not treatment has an impact of total resection will be Fisher's Exact Test. The results of this analysis will be presented in terms of the odds ratio (MLEs and CIs). If there are a sufficient number with responses in each group to allow for asymptotic analyses, then the analysis may be adjusted for prognostic factors using logistic models.

The total gross tumor resection at the time of surgery is a continuous variable, and the sample sizes are expected to be sufficiently large to assure that the central limit theorem applies to sample means of each arm. Therefore, simple Z tests should be adequate for testing the equivalencies of tumor mass resected between the experimental and reference arms. Differences in treatment arms are expected to be characterized using normal distribution theory. More complex linear models may be used if the data warrant.

4. This analysis will use the same techniques as the one used to analyze patients with total gross resection.
5. Overall survival is defined as the time from randomization until death or date last seen. The endpoint for OS is death. The effect of treatment on OS will be conducted with the log-rank statistic and characterized with a Cox PH model. If there are significant prognostic factors, then the analysis may be stratified on them or explicitly included in the model.

15.8.5 Interim Analysis for All Other Endpoints (Goals):

The analysis of the severity of toxicity by treatment arm (dichotomized into severe versus not severe) will be presented to the DMC at the time of the interim futility analysis.

15.8.6 Power Calculations:

If the median overall survival (not PFS) is 28 months, then we anticipate 70 deaths in 45 months of study accrual and monitoring. This gives about 79% power of detecting a 37.5% reduction in the hazard of death when testing at the 15% level of significance. Power drops to 58.3% when testing at the 5% level of significance. The probability of

detecting a 30% reduction in the hazard of death is only 41% ($\alpha=5\%$).

15.9 Exploratory Hypothesis and Endpoints

Toxicity will be characterized by the frequency and severity of adverse events in the phase I study for the experimental regimen. Toxicity will be characterized by the frequency and severity of adverse events according to treatment arm in the phase II study. They will be dichotomized as severe or not severe for each category of toxicity, and the hypothesis of equal proportions of severe toxicities to the reference arm will be assessed using an exact Chi-square test (or Fisher's Exact Test). If a 95% CI for the risk ratio or odds ratio is strictly greater than 1.5, then the study will highlight such a category as being potentially problematic.

Effects of Treatment on Stemness and C-reactive protein (CRP):

A multivariate linear model will be used to determine the effect of treatment on the number of cancer stem cells (CSCs) observed in tissue obtained from the patient after 3 cycles of therapy. The model will be adjusted with the patients' pre-treatment count of CSC, which will be log transformed to reduce the amount of right skewness. Treatment with ruxolitinib is expected to reduce the amplification of CSC during therapy.

The prognostic value of CSC will be assessed with the pre-therapy values. Landmark analyses will be conducted to see if changes in CSC are associated with PFS. The predictive value of CSC will be formally examined with a Cox model using an interaction term with treatment. Subset analyses will be conducted as well in the event that a formal analysis fails to reject the null hypothesis.

Similar analyses can be conducted on the measurements taken for serum C-reactive protein (CRP). Linear models can examine the effect of therapy on CRP values, adjusting for baseline levels. The impact of baseline values on PFS and OS can be assessed for prognostic and predictive significance with log-rank statistics and Cox models. Finally, the impact of changes in CRP values on PFS and OS can be examined with landmark analyses or as time dependent covariates.

15.10 Gender/Ethnicity/Race Distribution (04/06/2018)

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	2	0	0	0	2
Asian	2	0	0	0	2
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	7	0	0	0	7
White	128	0	7	0	135
More Than One Race	0	0	0	0	0
Total	140	0	7	0	147

16. REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA: a cancer journal for clinicians* 2015;65:5-29.
2. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 2015.
3. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010;363:943-53.
4. Burke WM, Jin X, Lin HJ, et al. Inhibition of constitutively active Stat3 suppresses growth of human ovarian and breast cancer cells. *Oncogene* 2001;20:7925-34.
5. Gritsina G, Xiao F, O'Brien SW, et al. Targeted Blockade of JAK/STAT3 Signaling Inhibits Ovarian Carcinoma Growth. *Molecular cancer therapeutics* 2015.
6. Vainchenker W, Dusa A, Constantinescu SN. JAKs in pathology: role of Janus kinases in hematopoietic malignancies and immunodeficiencies. *Seminars in cell & developmental biology* 2008;19:385-93.
7. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncol* 2010;6:149-63.
8. Whatcott CJP, R.G.; Von Hoff, D.D.; Han, H. Desmoplasia and chemoresistance in pancreatic cancer. In: Grippo PJM, H.G., ed. *Pancreatic Cancer and Tumor Microenvironment*. Trivandrum (India): Transworld Research Network; 2012.
9. Fearon KC, Barber MD, Falconer JS, McMillan DC, Ross JA, Preston T. Pancreatic cancer as a model: inflammatory mediators, acute-phase response, and cancer cachexia. *World journal of surgery* 1999;23:584-8.
10. Falconer JS, Fearon KC, Ross JA, et al. Acute-phase protein response and survival duration of patients with pancreatic cancer. *Cancer* 1995;75:2077-82.
11. Ueno H, Okada S, Okusaka T, Ikeda M. Prognostic factors in patients with metastatic pancreatic adenocarcinoma receiving systemic chemotherapy. *Oncology* 2000;59:296-301.
12. Nixon AB, Pang H, Starr MD, et al. Prognostic and predictive blood-based biomarkers in patients with advanced pancreatic cancer: results from CALGB80303 (Alliance). *Clin Cancer Res* 2013;19:6957-66.
13. Nozoe T, Matsumata T, Kitamura M, Sugimachi K. Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. *American journal of surgery* 1998;176:335-8.
14. Kodama J, Miyagi Y, Seki N, et al. Serum C-reactive protein as a prognostic factor in patients with epithelial ovarian cancer. *European journal of obstetrics, gynecology, and reproductive biology* 1999;82:107-10.
15. Nozoe T, Saeki H, Sugimachi K. Significance of preoperative elevation of serum C-reactive protein as an indicator of prognosis in esophageal carcinoma. *American journal of surgery* 2001;182:197-201.
16. Hashimoto K, Ikeda Y, Korenaga D, et al. The impact of preoperative serum C-reactive protein on the prognosis of patients with hepatocellular carcinoma. *Cancer* 2005;103:1856-64.
17. Ito K, Asano T, Yoshii H, Satoh A, Sumitomo M, Hayakawa M. Impact of thrombocytosis and C-reactive protein elevation on the prognosis for patients with renal cell carcinoma. *International journal of urology : official journal of the Japanese Urological Association*

- 2006;13:1365-70.
18. Polterauer S, Grimm C, Tempfer C, et al. C-reactive protein is a prognostic parameter in patients with cervical cancer. *Gynecol Oncol* 2007;107:114-7.
 19. Schmid M, Schneitter A, Hinterberger S, Seeber J, Reinthaller A, Hefler L. Association of elevated C-reactive protein levels with an impaired prognosis in patients with surgically treated endometrial cancer. *Obstetrics and gynecology* 2007;110:1231-6.
 20. Hefler LA, Concin N, Hofstetter G, et al. Serum C-reactive protein as independent prognostic variable in patients with ovarian cancer. *Clin Cancer Res* 2008;14:710-4.
 21. Koike Y, Miki C, Okugawa Y, et al. Preoperative C-reactive protein as a prognostic and therapeutic marker for colorectal cancer. *Journal of surgical oncology* 2008;98:540-4.
 22. Wang CY, Hsieh MJ, Chiu YC, et al. Higher serum C-reactive protein concentration and hypoalbuminemia are poor prognostic indicators in patients with esophageal cancer undergoing radiotherapy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2009;92:270-5.
 23. Shimura T, Kitagawa M, Yamada T, et al. C-reactive protein is a potential prognostic factor for metastatic gastric cancer. *Anticancer research* 2012;32:491-6.
 24. Chen R, Alvero AB, Silasi DA, Mor G. Inflammation, cancer and chemoresistance: taking advantage of the toll-like receptor signaling pathway. *American journal of reproductive immunology* 2007;57:93-107.
 25. Chen R, Alvero AB, Silasi DA, Steffensen KD, Mor G. Cancers take their Toll--the function and regulation of Toll-like receptors in cancer cells. *Oncogene* 2008;27:225-33.
 26. Kelly MG, Alvero AB, Chen R, et al. TLR-4 signaling promotes tumor growth and paclitaxel chemoresistance in ovarian cancer. *Cancer Res* 2006;66:3859-68.
 27. Leizer AL, Alvero AB, Fu HH, et al. Regulation of inflammation by the NF-kappaB pathway in ovarian cancer stem cells. *American journal of reproductive immunology* 2011;65:438-47.
 28. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. *Br J Cancer* 2003;89:1028-30.
 29. Sharma R, Hook J, Kumar M, Gabra H. Evaluation of an inflammation-based prognostic score in patients with advanced ovarian cancer. *European journal of cancer* 2008;44:251-6.
 30. Garbers C, Aparicio-Siegmund S, Rose-John S. The IL-6/gp130/STAT3 signaling axis: recent advances towards specific inhibition. *Current opinion in immunology* 2015;34C:75-82.
 31. Plante M, Rubin SC, Wong GY, Federici MG, Finstad CL, Gastl GA. Interleukin-6 level in serum and ascites as a prognostic factor in patients with epithelial ovarian cancer. *Cancer* 1994;73:1882-8.
 32. Ginestier C, Hur MH, Charafe-Jauffret E, et al. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. *Cell Stem Cell* 2007;1:555-67.
 33. Dylla SJ, Beviglia L, Park IK, et al. Colorectal cancer stem cells are enriched in xenogeneic tumors following chemotherapy. *PLoS One* 2008;3:e2428.
 34. Huang EH, Hynes MJ, Zhang T, et al. Aldehyde dehydrogenase 1 is a marker for normal and malignant human colonic stem cells (SC) and tracks SC overpopulation during colon tumorigenesis. *Cancer Res* 2009;69:3382-9.
 35. Silva IA, Bai S, McLean K, et al. Aldehyde dehydrogenase in combination with CD133 defines angiogenic ovarian cancer stem cells that portend poor patient survival. *Cancer Res*

- 2011;71:3991-4001.
36. Marotta LL, Almendro V, Marusyk A, et al. The JAK2/STAT3 signaling pathway is required for growth of CD44(+)CD24(-) stem cell-like breast cancer cells in human tumors. *J Clin Invest* 2011;121:2723-35.
 37. Lin L, Liu A, Peng Z, et al. STAT3 is necessary for proliferation and survival in colon cancer-initiating cells. *Cancer Res* 2011;71:7226-37.
 38. Liu S, Ginestier C, Ou SJ, et al. Breast cancer stem cells are regulated by mesenchymal stem cells through cytokine networks. *Cancer Res* 2011;71:614-24.
 39. Dave B, Landis MD, Tweardy DJ, et al. Selective small molecule Stat3 inhibitor reduces breast cancer tumor-initiating cells and improves recurrence free survival in a human-xenograft model. *PLoS One* 2012;7:e30207.
 40. McLean K, Gong Y, Choi Y, et al. Human ovarian carcinoma-associated mesenchymal stem cells regulate cancer stem cells and tumorigenesis via altered BMP production. *J Clin Invest* 2011;121:3206-19.
 41. Abubaker K, Luwor RB, Escalona R, et al. Targeted Disruption of the JAK2/STAT3 Pathway in Combination with Systemic Administration of Paclitaxel Inhibits the Priming of Ovarian Cancer Stem Cells Leading to a Reduced Tumor Burden. *Frontiers in oncology* 2014;4:75.
 42. Curiel TJ, Coukos G, Zou L, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat Med* 2004;10:942-9.
 43. Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. *Proc Natl Acad Sci U S A* 2005;102:18538-43.
 44. Jones E, Dahm-Vicker M, Golgher D, Gallimore A. CD25+ regulatory T cells and tumor immunity. *Immunology letters* 2003;85:141-3.
 45. Abrams SI. Role of anti-CTLA-4 therapies in the treatment of cancer. *Current opinion in molecular therapeutics* 2004;6:71-7.
 46. Koblisch HH, M.; Wang, L-C.S.; Yang, G.; Huang, T.; Xue, C-B.; Li, Y-L.; Yue, E.; Combs, A.; Yao, W.; Huber, R.; Scherle, P. Novel immunotherapeutic activity of JAK and PI3Kδ inhibitors in a model of pancreatic cancer. American Association for Cancer Research. Philadelphia2015.
 47. Silver DL, Naora H, Liu J, Cheng W, Montell DJ. Activated signal transducer and activator of transcription (STAT) 3: localization in focal adhesions and function in ovarian cancer cell motility. *Cancer Res* 2004;64:3550-8.
 48. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med* 2012;366:799-807.
 49. Hurwitz HI, Uppal N, Wagner SA, et al. Randomized, Double-Blind, Phase II Study of Ruxolitinib or Placebo in Combination With Capecitabine in Patients With Metastatic Pancreatic Cancer for Whom Therapy With Gemcitabine Has Failed. *J Clin Oncol* 2015;33:4039-47.
 50. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009;374:1331-8.
 51. Chan JB, M.; Penson, R.; Monk, B.; Boente, M.; Walker, J.; Davidson, S.; DiSilvestro, P.; O'Malley, D.; Morgan, M.; Pearl, M.; De Geest, K.; Michael, H. Every 3-week vs. dose-dense weekly paclitaxel combined with carboplatin +/- bevacizumab in advanced epithelial

ovarian, peritoneal or fallopian tube cancer. GOG 0262: A phase III randomized trial of the Gynecologic Oncology Group. European Society of Gynecologic Oncology. Liverpool, United Kingdom 2013.

52. Ruxolitinib Investigator's Brochure, Edition 13. 2014.

53. FDA approves olaparib for first-line maintenance of BRCA-mutated advanced ovarian cancer. 2018. at

<https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm628876.htm>.)

54. Oncology SoG. SGO Clinical Practice Statement: Genetic Testing for Ovarian Cancer. 2014.

APPENDIX I - FIGO OVARIAN CANCER STAGING 2014

STAGE I: Tumor confined to ovaries

- IA Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.
- IB Tumor involves both ovaries otherwise like 1A.
- IC Tumor limited to 1 or both ovaries
 - IC1 Surgical spill
 - IC2 Capsule rupture before surgery or tumor on ovarian surface
 - IC3 Malignant cells in the ascites or peritoneal washings

STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer

- IIA Extension and/or implant on uterus and/or Fallopian tubes
- IIB Extension to other pelvic intraperitoneal tissues

STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

- IIIA Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis
 - IIIA1 Positive retroperitoneal lymph nodes only
 - IIIA1(i) Metastasis \leq 10 mm
 - IIIA1(ii) Metastasis $>$ 10mm
 - IIIA2 Microscopic, extrapelvic (above the brim) peritoneal involvement \pm positive retroperitoneal lymph nodes
- IIIB Macroscopic, extrapelvic, peritoneal metastasis \leq 2 cm \pm positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
- IIIC Macroscopic, extrapelvic, peritoneal metastasis $>$ 2 cm \pm positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.

STAGE IV: Distant metastasis excluding peritoneal metastasis

- IVA Pleural effusion with positive cytology

IVB Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity).

Other major recommendations are as follows:

- Histologic type including grading should be designated at staging
- Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible
- Tumors that may otherwise qualify for stage I but involved with dense adhesions justify upgrading to stage II if tumor cells are histologically proven to be present in the adhesions

APPENDIX II - GUIDELINES FOR PATHOLOGIC CLASSIFICATION OF TUMOR CELL TYPE

Histologic features for determination of Tumor Cell Type and Tissue of Origin are imperfect and subject to lack of specificity, resulting in significant lack of agreement by expert pathologists. This lack of agreement is most problematic when small biopsy material is evaluated in the clinical context of advanced stage cancer or with tumor recurrence. Nevertheless, a consensus is developing that immunohistologic phenotypes are associated with common genetic features of tumors and thus form a rational basis for meaningful classification of cell type (Soslow, Kobel). These features are mutational pattern of expression of p53 antigen and diffuse nuclear WT-1 antigen expression in high grade serous mullerian adenocarcinoma, lack of diffuse nuclear estrogen receptor (ER) expression in clear cell carcinomas, and the expression of ER and lack of significant WT-1 expression in endometrioid carcinomas. These immunohistologic features do not define cell type but are useful criteria to consider when attempting to classify tumors--especially for poorly differentiated tumors. For example, a tumor with a solid growth pattern (lacking histologically evident glandular differentiation) that shows a mutational pattern of p53 staining by immunohistochemistry (diffuse strong nuclear p53 expression or complete lack of p53 expression in tumor cells) should be classified as a high grade serous cancer (diffuse nuclear WT-1 expression will also likely be present). Conversely, lack of mutational p53 pattern by immunohistochemistry would most consistent with high grade endometrioid adenocarcinoma, including carcinosarcoma (malignant mixed mullerian tumor). Diffuse nuclear ER expression is uncommon in clear cell carcinoma and thus is useful for distinguishing poorly differentiated endometrioid carcinoma (with areas of “clear” cells) from clear cell carcinoma. These features are summarized in the following table:

Immunophenotypes of Common Epithelial Ovarian Carcinoma Cell Types – GY007

High Grade Serous Adenocarcinoma	p53mut	WT-1nuclear	ERvariable
Endometrioid Adenocarcinoma	p53wt	WT-1negative	ERpositive
Clear Cell Adenocarcinoma	p53wt	WT-1negative	ERnegative

P53mut: diffuse strong nuclear immunoreactivity or complete lack of nuclear immunoreactivity in tumor cells

P53wt: Wild type p53 expression. Variable nuclear immunoreactivity of tumor cells, often expressed with the same tissue distribution (similar pattern) as Ki-67 antigen expression (because both p53 and Ki-67 antigen are expressed in normal dividing cells). In poorly differentiated rapidly dividing tumors p53 antigen is commonly prominent and strong but lacks the constitutive (every tumor cell) pattern of expression associated with mutation.

WT-1nuclear: nuclear expression of WT-1

ERnuclear: nuclear expression of Estrogen Receptor

Refs: Soslow RA, *Int J Gynecol Pathol*. 2008, 27:161-74.

Kobel, M et al . *American Journal of Surgical Pathology*, 2009, 33:14-21

APPENDIX III - PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (<i>e.g.</i> , light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX IV - GENERAL CHEMOTHERAPY GUIDELINES

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual chemotherapy doses to be delivered within a “24-hour window before and after the protocol-defined date” for “Day 1” treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a “24-hour window,” for example; “Day 8 chemotherapy” can be delivered on Day 7, Day 8, or Day 9 and “Day 15 chemotherapy” can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be “rounded” according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

APPENDIX V - CARBOPLATIN DOSE CALCULATION INSTRUCTIONS

- 1) The Cockcroft-Gault formula will be used in NRG trials
- 2) Conversion of IDMS creatinine levels to “non-IDMS” values will not be permitted.
- 3) A carboplatin calculation tool is available on the GOG website (Web Menu, Tools).

Dosing of Carboplatin:

- 1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.
- 2) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.
- 3) Carboplatin doses should be recalculated if the patient has a weight change of greater than or equal to 10%.
- 4) At the time of dose modification, if the patient’s age has changed (the patient has had a birthday), the site can use the current age.
- 5) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a **minimum value of 0.7 mg/dl**.
- 6) For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC x (GFR + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.

Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed doses of carboplatin are:

AUC 6 = 900 mg

AUC 5 = 750 mg

AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\text{Creatinine Clearance (mL/min)} = \frac{[140 - \text{Age (years)}] \times \text{Weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dl)}}$$

Notes:

1) Weight in kilograms (kg):

- a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: <http://www.nhlbisupport.com/bmi/>
- b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
- c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.
- d. Adjusted weight calculation:

$$\text{Ideal weight (kg)} = (((\text{Height (cm)} / 2.54) - 60) \times 2.3) + 45.5$$

$$\text{Adjusted weight (kg)} = ((\text{Actual weight} - \text{Ideal weight}) \times 0.40) + \text{Ideal weight}$$

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity:

If the serum creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

APPENDIX VI - PATIENT PILL CALENDAR- RUXOLITINIB (03/20/2017)

NRG-GY007 – A PHASE I/II STUDY OF RUXOLITINIB WITH FRONT-LINE NEOADJUVANT AND POST-SURGICAL THERAPY IN PATIENTS WITH ADVANCED EPITHELIAL OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CANCER

Today’s date _____

Patient Name _____ Patient Study ID _____
(initials acceptable for patient’s name)

Cycle # _____

INSTRUCTIONS TO THE PATIENT:

This is a calendar on which you are to record the number of pills you take each day.

1. Complete one form for each cycle (21 days).
2. Unless otherwise instructed, you will take ___ tablets of Ruxolitinib each morning (AM Dose) and ___ tablets of Ruxolitinib each evening (PM Dose), about 12 hours apart. Tablets may be taken with or without food. It is generally best to take the tablets after the morning and evening meal.
3. Record the date, the number of tablets you took, and when you took the.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your tablet bottle and this form to your physician when you go for your next appointment.
6. If you miss a dose of Ruxolitinib, take it as soon as you remember. If you are more than 4 hours late in taking a dose, the dose should be skipped. Please call your doctor’s office for instruction if you skip or miss a dose or at any other time if you have questions.
7. Do NOT take another dose of ruxolitinib beyond what is instructed for any reason, even including vomiting any time after a dose.

Date	Day	AM Dose		PM Dose		Comments
		# Tablets	Time Taken	# Tablets	Time Taken	
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					

	10						
	11						
	12						
	13						
	14						
	15						
	16						
	17						
	18						
	19						
	20						
	21						
		Patient's Signature: _____				Date: _____	

APPENDIX VII - INHIBITORS AND INDUCERS OF CYP3A4 (10/10/2016)**A list of CYP3A4 inhibitors and inducers**

This list is not comprehensive. Please refer to a frequently-updated drug information reference for strong CYP3A4 inducers and inhibitors:

http://www.uptodate.com/contents/image?imageKey=CARD/76992&topicKey=HEME%2F1370&source=outline_link&utdPopup=true

Strong Inhibitors	Moderate Inhibitors	Strong Inducers	Moderate Inducers
Atazanavir	Amiodarone [¶]	Carbamazepine	Bexarotene
Boceprevir	Aprepitant	Enzalutamide	Bosentan
Ceritinib	Cimetidine [¶]	Fosphenytoin	Dabrafenib
Clarithromycin	Conivaptan	Lumacaftor	Dexamethasone [¶]
Cobicistat and cobicistat containing coformulations	Crizotinib	Mitotane	Efavirenz
Darunavir	Cyclosporine [¶]	Phenobarbital	Eslicarbazepine
Idelalisib	Diltiazem	Phenytoin	Etravirine
Indinavir	Dronedarone	Primidone	Modafinil
Itraconazole	Erythromycin	Rifabutin	Nafcillin
Ketoconazole	Fluconazole	Rifampin (rifampicin)	St. John's wort
Lopinavir	Fosamprenavir	Rifapentine	
Nefazodone	Fosaprepitant [¶]		
Nelfinavir	Grapefruit juice		
Ombitasvir-paritaprevir-ritonavir	Imatinib		
Ombitasvir-paritaprevir-ritonavir plus dasabuvir	Isavuconazole (isavuconazonium sulfate)		
Posaconazole	Mifepristone		
Ritonavir and ritonavir containing coformulations	Netupitant		
Saquinavir	Nilotinib		
Telaprevir	Tibolone		
Telithromycin	Verapamil		
Voriconazole			

APPENDIX VIII– INTERVAL TUMOR REDUCTIVE SURGERY(TRS) (04/06/2018)

The guidelines for TRS are adapted in part from the Gynecologic Oncology Group Surgical Procedures Manual (2010 revision).

Note: These guidelines for surgery are within standard care. The components of the surgical procedure outlined below should be performed only when benefits outweigh risks.

Purpose 1) Documentation of the extent of disease at exploration

- 2) Maximal resection of all gross (macroscopic and palpable) tumor
- 3) Documentation of the extent of disease at completion of surgery

Content of Procedure

- 1) Exposure must be adequate to explore the entire abdominal cavity and allow safe cytoreductive surgery. The surgical approach for this procedure is at the discretion of the treating surgeon and can be either via laparotomy or minimally invasive techniques. If a primarily minimally invasive technique is utilized, conversion to laparotomy should be performed if the minimally invasive surgical techniques do not allow for adequate exposure, are contraindicated for reasons related to patient safety or are limited in their ability to access known disease sites for maximal tumor resection. On the other hand, for a patient initially explored via a minimally invasive approach, if in the opinion of the surgeon total gross tumor resection would be technically impossible regardless of approach, conversion to laparotomy could be avoided.
- 2) If free peritoneal fluid is identified it should be aspirated for cytology. If no free peritoneal fluid is present and if no macroscopic or palpable tumor is identified, peritoneal washings should be obtained. Every effort should be made to lavage the peritoneal cavity in its entirety. .
- 3) Exploration to document the extent of gross disease by palpation and inspection (when applicable), including evaluation of the ovaries, fallopian tubes, uterus, all abdominal and pelvic peritoneal surfaces (including the under surface of the diaphragms, and the serosa and mesentery of the entire gastrointestinal tract), and omentum.
 - a. If gross evidence of tumor is identified, then a maximal attempt to resect all gross tumor should be made, with surgical procedures that may include but are not limited to:
 - i. Bilateral salpingo-oophorectomy
 - ii. Hysterectomy (extrafascial or modified radical)
 - iii. Omentectomy
 - iv. Removal of tumor implants along visceral and parietal peritoneal surfaces
 - v. Retroperitoneal lymphadenectomy
 - vi. Bowel resection
 - vii. Other (e.g. splenectomy, partial hepatic resection, diaphragmatic resection), as clinically indicated
 - b. If no gross evidence of tumor is identified, then the minimum procedure should be:
 - i. Bilateral salpingo-oophorectomy
 - ii. Hysterectomy (total or supracervical)
 - iii. Omentectomy
 - iv. Peritoneal biopsies

1. Right and left pelvic wall
 2. Cul-de-sac
 3. Bladder
 4. Right and left paracolic
 5. Right diaphragm (scraping of surface for cytology may substitute for biopsy)
- v. Biopsies of adhesive bands and abnormally scarred areas
 - vi. One sample of cytologic washings in the absence of ascites
 - vii. Removal of any suspicious lymph nodes

APPENDIX IX – TRANSLATIONAL SCIENCE BIOSPECIMEN PROCEDURES (01/09/2017) (04/06/2018) (07/30/2018) (04/05/2019)

1. Obtaining a Bank ID for Translational Science Biospecimens

Only one Bank ID (#### - ## - G ####) is assigned per patient. All translational science biospecimens and accompanying paperwork must be labeled with this coded patient number.

A Bank ID is automatically assigned once the Specimen Consent is completed and indicates that a patient has agreed to participate in the translational science component. If a patient has previously been assigned a Bank ID, please ensure the Bank ID appearing in Rave is the same as the previously assigned Bank ID.

Please contact Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@nrgoncology.org).

2. Requesting Translational Science Biospecimen Kits (03/20/2017)

2.1 Frozen Biospecimens

One single chamber kit will be provided per patient for the shipment of frozen biospecimens. Collection supplies will only be provided for pre-treatment serum biospecimens. Sites must use their own supplies for the collection of frozen tissue and whole blood biospecimens.

Sites can order kits online via the Kit Management link (<https://ricapps.nationwidechildrens.org/KitManagement>). Each site may order two kits per protocol per day (daily max = 6 kits).

Please contact the NRG BB-Columbus if you need assistance (Email: BPCBank@nationwidechildrens.org; Phone: 866-464-2262).

Be sure to plan ahead and allow time for kits to be shipped by ground transportation. Kits should arrive within 3-5 business days.

Unused materials and kits should be returned to the NRG BB-Columbus. A pre-paid shipping label for the return of unused supplies and kits may be obtained via the Kit Management system. Select “Empty Kit” for package contents when returning unused kits.

2.2 Whole Blood for Cell-Free DNA (Collected in Streck Tubes)

Collection materials and shipping labels are **not** provided for the optional whole blood for cell-free DNA biospecimens. Sites must utilize their own materials for collection and shipment of these biospecimens. Shipment will be at the site’s expense.

3. Tissue Biospecimens Shipped to the NRG BB-Columbus

3.1 General Information for Tissue Biospecimens

3.1.1 Collection of Surgical Suite Data

The designated operating room staff should record the time the tissue is removed from the patient. For frozen tissue biospecimens, the time tissue is removed from the patient to the start

of freeze time must be documented on Form TR as Estimated Processing Time.

3.1.2 Transport of Tissue from the Surgical Suite to the Gross Pathology Suite

Tissue should be transported in a closed container (sterile container or tray covered in plastic wrap). Do not use ice or wrap tissue biospecimens in gauze.

3.1.3 Receipt of Tissue in the Gross Pathology Suite

All tissue must first undergo gross pathology evaluation and the collection of appropriate samples for patient diagnosis. Once the appropriate review and clinical sample collection has been completed, the residual tissue may be released for research purposes and should be processed in the following order:

1. FFPE (*mandatory* - tumor: one segment; section 3.2 below),
2. Snap Frozen (*optional* - tumor: 1-5 segments, adjacent normal [pre-treatment only]: 1-3 segments; section 3.3 below),
3. Cryopreserved (*optional* - tumor: one segment; section 3.4 below), and
4. OCT Frozen (*optional* - tumor: two segments; section 3.5 below).

If tissue is limited, submit at least one segment processed in the order of priority.

3.2 FFPE Tumor Tissue

Only one block may be submitted per tissue type. All FFPE tissue must be submitted with the corresponding pathology report.

3.2.1 Mandatory FFPE Biospecimen Requirement

3.2.1.1 Tumor Tissue Type

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the required type:

- **Primary (FP01)** and **metastatic (FM01)** tumor should be collected prior to all treatment.
- **Interval primary (FP02)** and **interval metastatic (FM02)** tumor should be collected during the interval Tumor Reductive Surgery (TRS) or image-guided biopsy.

FFPE Type

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 35 unstained slides (30 charged, 5µm, and 5 uncharged, 10 µm) should be submitted. All slides must be cut sequentially from one block. If tumor tissue is limited, priority should be given to the 30 charged, 5µm sections. If less than the requested number of slides are available, contact BPCBank@nationwidechildrens.org.

3.2.2 Labeling FFPE Tissue

A waterproof permanent marker or printed label should be used to label each translational science tissue biospecimen with:

Bank ID (##### - ## - G ###)
protocol number (NRG-GY007)
specimen code (see section 3.2.1.1 above)

collection date (mm/dd/yyyy)
surgical pathology accession number
block number

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

3.2.3 Completing Form TR for FFPE Biospecimens

The type of biospecimen (block or slides) should be specified on Form TR. If submitting slides, the slide type, thickness, and count should also be specified.

The time the tissue was in formalin (i.e., fixation time) should be entered as Estimated Processing Time.

3.3 Snap Frozen Tumor and Adjacent Normal Tissue

Sites must use their own supplies for the collection of frozen tissue biospecimens.

Note: This procedure requires access to a CryoCooler (Ops Diagnostics, CG 08-07) or equivalent. **If your site does not have access to this equipment, frozen tissue biospecimens should not be collected.**

3.3.1 Optional Snap Frozen Biospecimen Requirements

Note: To minimize the risk of cross-contamination, always use clean, disposable scalpels and forceps when cutting different types of tissue (i.e., tumor and normal) from the same patient and tissues from different patients.

3.3.1.1 Tumor Tissue

- Snap frozen tissue should be the most representative of the required type:
 - Pre-treatment **snap frozen primary (RP01)** or **metastatic (RM01)** tumor should be collected at the time of biopsy for histologic confirmation.
 - Interval **snap frozen primary (RP04)** or **metastatic (RM04)** tumor should be collected at the time of interval tumor reductive surgery (TRS).
- The total time from surgical removal to start of freeze must be no more than 30 minutes (≤ 15 minutes preferred). This total time must be entered on Form TR as Estimated Processing Time.
- A minimum of one and a maximum of five segments of tumor should be submitted. Total tumor tissue volume should be ≤ 200 mg. Each segment should measure no greater than 1.0x1.0x0.5cm and frozen in a separate cryovial.
- Tumor segments need not be contiguous, but must be collected from the same tumor nodule and be as close in proximity to each other as possible.

3.3.1.2 Adjacent Normal Tissue

- Snap frozen tissue should be the most representative of the required type:
 - Pre-treatment **adjacent normal (RN01)** tissue should be collected at the time of biopsy for histologic confirmation.

- The total time from surgical removal to start of freeze must be no more than 35 minutes (≤ 15 minutes preferred). This total time must be entered on Form TR as Estimated Processing Time.
- A minimum of one and a maximum of three segments of adjacent normal tissue should be submitted. Total adjacent normal tissue volume should be ≤ 50 mg (≤ 200 mg preferred). Each segment should measure no greater than 1.0x1.0x0.5cm and be frozen in a separate cryovial.
- In general, adjacent normal tissue should be collected from a perilesional, grossly uninvolved tissue adjacent to tumor.

3.3.2 Processing Snap Frozen Tissue

Note: To minimize tumor tissue ischemic time, process the tumor tissue prior to processing the adjacent normal tissue.

1. At least 30 minutes prior to tissue procurement:
 - a. Storage boxes should be pre-labeled and pre-chilled, either on dry ice or within a -80°C freezer.
 - b. Prepare a commercially available CryoCooler (Ops Diagnostics, CG 08-07) or equivalent as per the manufacturer's instructions. Warming of the cooler should be minimized by always keeping the lid closed and locked when not actively adding or removing biospecimens.
 - c. Label cryovials as described below. Use 2mL cryovials as tissue biospecimens will be shipped to the NRG BB-Columbus.
2. Using a clean Petri dish, weigh one tissue segment and record the weight on a cryovial. Place the tissue segment in the pre-chilled, pre-labeled cryovial.
3. Freeze the tissue segment within the cryovial for 3 to 5 minutes. Record the start of freeze time. The time tissue is removed from the patient to the start of freeze time must be documented on Form TR as Estimated Processing Time.
4. Repeat steps 2 and 3 for all tissue segments.
5. Once all tumor and normal tissue segments have been frozen, place properly labelled cryovials in a pre-chilled storage box and transfer to a liquid nitrogen freezer until shipment. Ship frozen on dry ice.

3.3.3 Labeling Snap Frozen Biospecimens

A waterproof permanent marker or printed label should be used to label each translational science snap frozen tumor and normal tissue biospecimen with:

Bank ID (### - ## - G ###)
protocol number (NRG-GY007)
specimen code (see section 3.3.1.1 above)
collection date (mm/dd/yyyy)
surgical pathology accession number (on corresponding pathology report for FFPE)
tissue weight

3.3.4 Completing Form TR for Snap Frozen Biospecimens

The type of biospecimen (snap frozen) should be specified on Form TR.

The time tissue is removed from the patient to the start of freeze time must be documented on Form TR as Estimated Processing Time.

3.4 Cryopreserved Tumor Tissue

Sites must use their own supplies for the collection of frozen tissue biospecimens.

Note: This procedure requires access to a CoolCell LX freezing unit (Catalog # BCS-405, Biocon) or equivalent, as well as cryopreservation media. **If your site does not have access to these supplies, frozen tissue biospecimens should not be collected.**

3.4.1 Optional Cryopreserved Biospecimen Requirements

3.4.1.1 Tumor Tissue Type

Cryopreserved tissue should be the most representative of the required type (e.g., primary or metastatic tumor).

- Pre-treatment **cryopreserved primary (RP02)** or **metastatic (RM02)** tumor should be collected at the time of biopsy for histologic confirmation.
- Interval **cryopreserved frozen primary (RP05)** or **metastatic (RM05)** tumor should be collected at the time of interval tumor reductive surgery (TRS).

3.4.2 Processing Cryopreserved Tumor

1. Prior to tissue procurement:

- a. Label two cryovials as described below.
 - b. Using sterile technique, fill the labeled cryovials with 1mL of cryopreservation media.
 - c. *The first time the CoolCell LX freezing unit (or equivalent) is used*, fill additional unlabeled cryovials with 1mL of cryopreservation media. Unlabeled tubes with cryopreservation media are used to fill the empty slots of the unit that are not occupied by cryovials containing tissue in cryopreservation media. These “placeholders” may be saved and reused for each cryopreservation procedure. If the vials appear grossly contaminated, they should be replaced with fresh placeholder cryovials.
2. Place the tumor tissue segment in the pre-labeled cryovial containing 1mL of ambient preservation media.
 3. Ensure each cryovial (actual tumor biospecimens and placeholders) is closed tightly and place into the CoolCell LX freezing unit (or equivalent). The unit and cryopreservation media in all cryovials should be at ambient temperature. Carefully close the lid to the unit.
 4. Place unit in a -80°C freezer for *at least* 18 hours.
 5. After *at least* 18 hours in a -80°C freezer, the cryovials containing tumor biospecimens may be transported to liquid nitrogen vapor storage or shipped immediately to the NRG BB-Columbus on dry ice.

3.4.3 Labeling Cryopreserved Biospecimens

A waterproof permanent marker or printed label should be used to label each translational science cryopreserved tumor tissue biospecimen with:

Bank ID (#### - ## - G ####)
protocol number (NRG-GY007)
specimen code (see section 3.4.1.1 above)

collection date (mm/dd/yyyy)

surgical pathology accession number (of corresponding pathology report)

3.4.4 Completing Form TR for Cryopreserved Biospecimens

The type of biospecimen (Other; specify, “Cryopreserved”) should be specified on Form TR.

The time the tissue is removed from the patient to the start of freeze time must be documented on Form TR as Estimated Processing Time.

3.5 OCT Frozen Tumor Tissue

Sites must use their own supplies for the collection of frozen tissue biospecimens.

3.5.1 Optional OCT Biospecimen Requirements

3.5.1.1 Tumor Tissue Type

OCT tissue should be the most representative of the required type (e.g., primary or metastatic tumor).

- Pre-treatment **OCT primary (RP03)** or **metastatic (RM03)** tumor should be collected at the time of biopsy for histologic confirmation.
- Interval **OCT frozen primary (RP06)** or **metastatic (RM06)** tumor should be collected at the time of interval tumor reductive surgery (TRS).

3.5.2 Processing OCT Frozen Tumor

1. At least 30 minutes prior to tissue procurement:
 - a. Prepare for freezing tissue in an OCT mold:
 - i. Ensure access to a freezing plate on a pathology cryostat, **or**
 - ii. Ensure access to the flat surface of a dry ice block, **or**
 - iii. Prepare a commercially available CryoCooler (Ops Diagnostics, CG 08-07) or equivalent.

The objective of any appropriate method is to provide a flat surface colder than -30°C to rapidly freeze tissue embedded in OCT media. **Do not** freeze tissue in OCT media by placing warm tissue in a -70°C to -90°C freezer, dry ice ethanol bath, or submersion in an isopentane cryobath.
 - b. Label one tissue cryomold and zip bag as described below.
2. Using a clean Petri dish, weigh one tissue segment and record the weight on the cryomold and zip bag.
3. Place a thin layer of OCT in the mold to cover the bottom surface.
4. Working quickly, gently place (“float”) the tissue on the surface of the bottom layer of OCT. Ensure that the largest dimension of the tissue is facing upward. Lay needle core biopsy biospecimens length-wise in the mold.
5. Working quickly, fill the remainder of the mold with approximately 4mL of OCT (completely cover the tissue). Carefully dispense the OCT to avoid generating bubbles in the media. Ensure the tissue is laying flat in the mold and the OCT completely covers the tissue in a level plane.
6. Quickly place the cryomold on the level cold plate or flat, level surface of dry ice. Allow the tissue and OCT to freeze for 3 to 5 minutes. When the tissue and OCT are completely frozen, the block will turn white.

7. Once frozen, quickly wrap the mold in pre-chilled foil and place the block in the corresponding labeled zip bag. Maintain the tissue block buried in dry ice, in a -70°C to -90°C freezer, or in liquid nitrogen vapor (not liquid phase) until shipment. Ship frozen on dry ice.

3.5.3 Labeling OCT Frozen Biospecimens

A waterproof permanent marker or printed label should be used to label each translational science OCT frozen tumor tissue biospecimen with:

Bank ID (#### - ## - G ###)
protocol number (NRG-GY007)
specimen code (see section 3.5.1.1 above)
collection date (mm/dd/yyyy)
surgical pathology accession number (of corresponding pathology report)
tissue weight

3.5.4 Completing Form TR for OCT Frozen Biospecimens

The type of biospecimen (OCT) should be specified on Form TR.

The time tissue is removed from the patient to the start of freeze time must be documented on Form TR as Estimated Processing Time.

4. Serum Shipped to the NRG BB-Columbus

4.1 Mandatory Serum Biospecimen Requirements

Serum should be collected pre-treatment (SB01).

4.2 Processing Serum Biospecimens

1. Label cryovials and a 15mL conical tube as described below. Use 2mL cryovials as serum will be shipped to the NRG BB-Columbus.
2. Draw 7-10mL of blood into red top tube(s).
3. Allow the blood to clot at 4°C (or in a bucket with ice) for at least 30 minutes but no longer than 3 hours.
4. Centrifuge the blood at 1000g for 15 minutes at 4°C (preferred) or room temperature to separate the serum (top, straw-colored layer) from the red blood cells (bottom, red layer).
5. Transfer the serum into a 15mL conical tube and gently mix.
6. Quickly, evenly dispense (aliquot) the serum into the pre-labeled cryovials and cap the tubes securely. Place at least 0.25mL into each cryovial.
7. Immediately freeze the serum in an upright position in a -70°C to -80°C freezer or by direct exposure with dry ice until ready to ship. If a -70°C to -80°C freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

4.3 Labeling Serum Biospecimens

A waterproof permanent marker or printed label should be used to label each translational science serum biospecimen with:

Bank ID (#### - ## - G ###)

protocol number (NRG-GY007)
specimen code (SB##; see section 4.1 above)
collection date (mm/dd/yyyy)

5. Whole Blood (in EDTA) Shipped to the NRG BB-Columbus

Sites must use their own supplies for the collection of frozen whole blood biospecimens.

5.1 Optional Whole Blood Biospecimen Requirements

Whole blood should be collected prior to receiving study treatment (**WB01**) and after receiving the first three cycles of study treatment at the time of interval tumor reductive surgery (**WB03**).

5.2 Processing Whole Blood Biospecimens

1. Label the lavender/purple top (EDTA) collection tube(s) as described below. Multiple tubes may be used to collect the required amount. **Do not use glass blood collection tubes.**
2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.
4. Immediately **freeze the whole blood in an upright position** in a -70°C to -80°C freezer or by direct exposure with dry ice until ready to ship. If a -70°C to -80°C freezer is not available for storage, store and ship on dry ice within 24 hours of collection at the institution's expense.

5.3 Labeling Whole Blood

A waterproof permanent marker or printed label must be used to label each translational science whole blood biospecimen with:

Bank ID (##### - ## - G ###)
protocol number (NRG-GY007)
specimen code (WB##; see section 5.1 above)
collection date (mm/dd/yyyy)

6. Whole Blood for Cell-Free DNA Shipped to the NRG BB-Columbus

*Sites must utilize their own materials for collection and shipment of whole blood for cell-free DNA biospecimens. Collection materials and shipping labels are **not** provided and shipment will be at the site's expense.*

Note: This collection requires Streck (cell-free DNA) blood collection tubes and an ambient shipper. **If your site does not have access to Streck tubes and ambient shippers, then this biospecimen should not be collected.**

6.1 Optional Whole Blood for Cell-Free DNA Biospecimen Requirements

Whole blood for cell-free DNA should be collected prior to receiving study treatment (**WB02**) and after receiving the first three cycles of study treatment at the time of interval tumor reductive surgery (**WB04**).

6.2 Special Notes Regarding the Collection of Blood in Streck (Cell-Free DNA) Tubes

- Heparin should be avoided in pre-collection flush procedures.
- All other blood biospecimens should be drawn *before* the Streck (cell-free DNA) tube when multiple blood biospecimens are collected on the same day.
- Over or under filling a Streck (cell-free DNA) tube will result in an incorrect blood-to-additive ratio.
- No other tube may be substituted for a Streck (cell-free DNA) tube.

6.3 Collecting Streck (Cell-Free DNA) Whole Blood

1. Label the **Streck** (cell-free DNA) collection tube as described below.
2. Draw **10mL** of blood into the labeled tube.
3. Immediately after collection, gently invert the tube 5-10 times.
4. Ship whole blood to the NRG BB-Columbus the day the biospecimen is collected. If the whole blood **absolutely** cannot be shipped the day it is collected, the tube must remain at **room temperature** until shipment.

6.4 Labeling Cell-Free Streck Whole Blood

A waterproof permanent marker or printed label must be used to label each translational science cell-free Streck whole blood biospecimen with:

Bank ID (#### - ## - G ###)
protocol number (NRG-GY007)
specimen code (WB##; see section 6.1 above)
collection date (mm/dd/yyyy)

7. Submitting Form TR

A specimen transmittal form (i.e., Form TR) for each biospecimen will be available in the **Translational Research Folder in Rave**, once the Specimen Consent (located in the Baseline Folder) has been completed.

An electronically (i.e., Rave) completed copy of Form TR must accompany each biospecimen shipped to the NRG BB-Columbus. Handwritten forms will not be accepted.

Note: A copy does not need to be sent to the NRG BB-Columbus if biospecimens are not collected.

Form TR should be printed from the Translational Research Form screen in Rave using the **“PDF File” link at the top of the form**. Clicking this link will generate a single page PDF. Do not use the “Printable Version” or “View PDF” links at the bottom of the form or any other method to print the form, as these formats will not be accepted.

Retain a printout of the completed form for your records.

Please contact Support if you need assistance (Email: support@nrگونcology.org).

8. Shipping Translational Science Biospecimens

8.1 General Information for Shipping Biospecimens to the NRG BB-Columbus

- Translational science biospecimens should not be shipped until after patient registration and Bank ID assignment.
- An electronically completed copy of Form TR must be included for each translational science biospecimen.
- All translational science biospecimens should be shipped to:

NRG BB-Columbus / Protocol NRG-GY007

Nationwide Children's Hospital

700 Children's Dr, WA1340

Columbus, OH 43205

Phone: 614-722-2865

FAX: 614-722-2897

Email: BPCBank@nationwidechildrens.org

8.2 FFPE Tissue Shipped to the NRG BB-Columbus

FFPE tissue and a copy of the corresponding pathology report should be shipped using your own container at your own expense to the NRG BB-Columbus (address in section 8.1).

Do not ship FFPE tissue for Saturday delivery.

8.3 Frozen Biospecimens Shipped to the NRG BB-Columbus

All frozen biospecimens (i.e., serum, tissue, whole blood in EDTA) should be shipped using the **one** specimen kit provided to the NRG BB-Columbus (address in section 8.1).

*Note: **All** frozen biospecimens from a given patient must be shipped together in the **one** biospecimen kit provided. If all biospecimens from a given patient are not shipped together in one kit, then your institution must provide the additional shipping materials (e.g., kits, biohazard bags, etc.) and ship at your institution's expense.*

Frozen biospecimens should be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship frozen biospecimens on Friday or the day before a holiday. Note: Saturday delivery is not available for frozen biospecimens.

Frozen biospecimens should be stored in an ultra-cold freezing/storage space (i.e., ultra-cold \leq -70°C freezer, liquid nitrogen, or direct exposure with dry ice) until the biospecimens can be shipped.

8.3.1 Shipping Frozen Translational Science Biospecimens in a Single Chamber Kit

*Note: **All** frozen biospecimens from a given patient must be shipped together in the **one** biospecimen kit provided. If all biospecimens from a given patient are not shipped together in one kit, then your institution must provide the additional shipping materials (e.g., kits, biohazard bags, etc.) and ship at your institution's expense.*

1. Pre-fill the kit chamber about 1/3 full with dry ice.
2. Place the frozen biospecimens from each time point in a separate zip-lock bag.

3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes.
4. Place the Tyvek envelope containing the frozen biospecimens into the kit and fill the chamber to the top with dry ice.
5. Insert a copy of Form TR for each biospecimen.
6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber.
7. Print a pre-paid FedEx air bill using the Kit Management link (<https://ricapps.nationwidechildrens.org/KitManagement>). Attach the air bill. **(03/20/2017)**
8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.
9. Arrange for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

8.4 Whole Blood in Streck Tubes Shipped to the NRG BB-Columbus

Whole blood in Streck tubes must be kept at room temperature until processed at the NRG BB-Columbus. An ambient shipper with a SAF-T-TEMP Gel Pak or an insulated shipper must be used when shipping whole blood in Streck tubes. These shippers are not provided.

Whole blood in Streck tubes should be shipped Priority Overnight at the site's expense to the NRG BB-Columbus (address in section 8.1).

Whole blood in Streck tubes can be shipped to the NRG BB-Columbus **Monday through Friday for Tuesday through Saturday delivery**. Do not ship whole blood the day before a holiday. Use your own shipping container to ship specimens via **FedEx priority overnight**.

When shipping whole blood in Streck tubes, **your site must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the NRG BB-Columbus at BPCBank@nationwidechildrens.org or by phoning 866-464-2262.

8.4.1 Shipping Whole Blood Using Your Own Shipping Container

1. Place the whole blood biospecimen in a biohazard envelope containing absorbent material.
2. Expel as much air as possible before sealing the bag.
3. Wrap the biohazard envelope in bubble wrap or another padded material.
4. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.
5. Place the Tyvek envelope in either an ambient shipper or an insulated shipping container.
 - a. If using an ambient shipper, prepare the SAF-T-TEMP Gel Pak for shipment and place it in the bottom of the ambient shipper before adding the specimens. If contents of the Gel Pak are crunchy, place the Gel Pak in a warm water bath until the gel is smooth. Do not refrigerate, freeze, or microwave.
6. Insert a copy of Form TR for each biospecimen.
7. Attach an Exempt Human Specimen sticker to the outside of the shipping container.
8. Attach a completed FedEx air bill. **Shipping expenses are not covered**. Shipping costs must be paid by your site.
9. Arrange for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

9. Banking Translational Science Biospecimens for Future Research

Biospecimens will remain in the NRG BB-Columbus and made available for approved research projects if the patient has provided permission for the use of her biospecimens for future health research.

Note: Testing of banked biospecimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The patient's biospecimen consent choices will be recorded on the signed informed consent document and electronically via the Specimen Consent form. At the time of biospecimen selection for project distribution, the most recent consent information will be used.

Sites can amend a patient's choices regarding the future use of her biospecimens at any time if the patient changes her mind.

If the patient revokes permission to use her biospecimens, the NRG BB-Columbus will destroy or return any remaining biospecimens. The patient's biospecimens will not be used for any further research; however, any biospecimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her biospecimens distributed prior to revoking consent.

Note: If return of biospecimens is requested, shipping will be at the site's expense.

APPENDIX X - PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD (10/10/2016)

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **Ruxolitinib**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

The following concomitant medications, treatments or supplements are prohibited:

- Amifostine
- Inducers of CYP3A4 may be used with caution, and physicians should seek other options if available. Any intended use of a CYP3A4 inducer should be discussed with the study investigator in advance.
- Use of potent inhibitors of CYP3A4 (ketoconazole, clarithromycin, itraconazole, nefazodone or telithromycin, voriconazole or posaconazole, and use of fluconazole should be avoided; any intended use should be discussed with the study investigator prior to co-administration. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole in the study.
- Moderate CYP3A4 inhibitors may be used with caution. Differences in individual sensitivity and variation in potency of inhibition of various CYP enzymes may result in the need for a reduced dose of ruxolitinib during a period of concomitant medication use. Any intended use should be discussed with the study investigator prior to co-administration.
- Use of any concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, or tumor embolization) other than those specified in the research protocol.
- Concomitant use of a JAK inhibitor.
- Use of any investigational medication within 30 days or 5 half-lives, whichever is longer, prior to Cycle 1, Day 1 of study treatment is prohibited.
- St John's wort and rifampin are not permitted at any time during participation in the study.

Please refer to a frequently-updated drug information reference for strong CYP3A4 inducers and inhibitors:

http://www.upToDate.com/contents/image?imageKey=CARD/76992&topicKey=HEME%2F1370&source=outline_link&utdPopup=true

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Ruxolitinib may interact with other drugs which can cause side effects. Certain medications, supplements and food products are **prohibited** while on this study, including **grapefruit juice and St. John's Wort are not allowed on this study.**

For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Ruxolitinib must be used very carefully with other medicines that use certain liver enzymes to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered inducers/inhibitors of CYP isoenzymes.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **Ruxolitinib** _____.

This clinical trial is sponsored by the NCI. **Ruxolitinib** _____ may interact with drugs that are **processed by your liver**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Ruxolitinib _____ interacts with a **specific liver enzyme called CYP3A4** and must be used very carefully with other medicines that interact with **this enzyme**.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **inducers/inhibitors of CYP3A4**.
- Before prescribing new medicines, your regular health care providers should go to [a frequently-updated medical reference](#) for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

APPENDIX XI - CANCER THERAPY EVALUATION PROGRAM INTELLECTUAL PROPERTY OPTION TO COLLABORATORS

A. The IP Option described in this Section A would apply to inventions that would be described in patent disclosures that claim the use and/or the composition of the Agent(s) and that are conceived or first actually reduced to practice pursuant to clinical or non-clinical studies utilizing the NCI CTEP provided Agent(s) ("Section A Inventions"):

Institution agrees to grant to Collaborator(s): (i) a royalty-free, worldwide, non-exclusive license for commercial purposes with the right to sub license to affiliates or collaborators working on behalf of Collaborator for Collaborator's development purposes; and (ii) a time limited first option to negotiate an exclusive, or co-exclusive, if applicable, world-wide, royalty bearing license for commercial purposes, including the right to grant sub licenses, subject to any rights of the Government of the United States of America, on terms to be negotiated in good faith by the Collaborator(s) and Institution. If Collaborator accepts the non-exclusive commercial license, the Collaborator agrees to pay all out of pocket patent prosecution and maintenance costs which will be pro-rated and divided equally among all licensees. If Collaborator obtains an exclusive commercial license, in addition to any other agreed upon licensing arrangements such as royalties and due diligence requirements, the Collaborator agrees to pay all out of pocket patent prosecution and maintenance costs. Collaborator(s) will notify Institution, in writing, if it is interested in obtaining a commercial license to any Section A Invention within three (3) months of Collaborator's receipt of a patent application or six (6) months of receipt of an invention report notification of such a section A invention. In the event that Collaborator fails to so notify Institution, or elects not to obtain an exclusive license, then Collaborator's option expires with respect to that Section A Invention, and Institution will be free to dispose of its interests in accordance with its policies. If Institution and Collaborator fail to reach agreement within ninety (90) days, (or such additional period as Collaborator and Institution may agree) on the terms for an exclusive license for a particular Section A Invention, then for a period of three (3) months thereafter Institution agrees not to offer to license the Section A Invention to any third party on materially better terms than those last offered to Collaborator without first offering such terms to Collaborator, in which case Collaborator will have a period of thirty (30) days in which to accept or reject the offer. If Collaborator elects to negotiate an exclusive commercial license to a Section A Invention, then Institution agrees to file and prosecute patent application(s) diligently and in a timely manner and to

give Collaborator an opportunity to comment on the preparation and filing of any such patent application(s). Notwithstanding the above, Institution is under no obligation to file or maintain patent prosecution for any Section A Invention.

For all Section A Inventions, regardless of Collaborator's decision to seek a commercial license, Institution agrees to grant Collaborator a paid-up, nonexclusive, royalty-free, world-wide license for research purposes only. Institution retains the right to make and use any Section A Invention for all non-profit research, including for educational purposes and to permit other educational and non-profit institutions to do so.

B. The IP Option described in this Section B would apply to inventions not covered by Section A, but are nevertheless conceived or first actually reduced to practice pursuant to clinical or non-clinical studies utilizing the CTEP-provided Agent(s). It also applies to inventions that are conceived or first actually reduced to practice pursuant to NCI CTEP-approved studies that use non-publicly available clinical data or specimens from patients treated with the CTEP-provided Agent (including specimens obtained from NCI CTEP-funded tissue banks) (“Section B Inventions”):

Institution agrees to grant to Collaborator(s): (i) a paid-up nonexclusive, nontransferable, royalty-free, world-wide license to all Section B Inventions for research purposes only; and (ii) a nonexclusive, royalty-free, world-wide license to (a.) disclose Section B Inventions to a regulatory authority when seeking marketing authorization of the Agent, and (b.) disclose Section B Inventions on a product insert or other promotional material regarding the Agent after having obtained marketing authorization from a regulatory authority. Notwithstanding the above, Institution is under no obligation to file or maintain patent prosecution for any Section B Invention.

C. The IP Option described in this Section C would apply to inventions made by Institution's investigator(s) or any other employees or agents of Institution, which are or may be patentable or otherwise protectable, as a result of research utilizing the CTEP-provided Agent(s), unreleased or non-publicly available clinical data or Agent treated specimens outside the scope of approval granted by the NCI CTEP (Unauthorized Inventions):

Institution agrees, at Collaborator's request and expense, to grant to Collaborator a royalty-free exclusive or co-exclusive license to Unauthorized Inventions. Institution will retain a non-exclusive, non-sub-licensable royalty free license to practice the invention for research use purposes.

D. Institution Notification

Institution agrees to promptly and confidentially notify NCI CTEP (NCICTEPpubs@mail.nih.gov) and Collaborator(s) in writing of any Section A Inventions, Section B Inventions, and Unauthorized Inventions upon the earlier of: (i) any submission of any invention disclosure to Institution of a Section A, Section B, or Unauthorized Invention, or (ii) the filing of any patent applications of a Section A, Section B, or Unauthorized Invention. Institution agrees to provide a copy of either the invention disclosure or the patent application to the Collaborator and to NCI CTEP which will treat it in accordance with 37 CFR Part 401. These requirements do not replace any applicable reporting requirements under the Bayh-Dole Act, 35 USC 200-212, and implementing regulations at 37 CFR Part 401.

APPENDIX XII – PATHOLOGY VERIFICATION FORM (04/06/2018) (04/05/2019)

A copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the NRG BB-Columbus.

If a pathology report is not available for frozen tissue biospecimens (i.e., snap frozen, cryopreserved, and/or OCT frozen), a copy of the radiology report or operative report from the tissue collection procedure must be sent to the NRG BB-Columbus. A completed copy of this appendix (i.e., Pathology Verification Form) must also be submitted to the NRG BB-Columbus.

Note: If this information is not provided with a frozen tissue biospecimen, it will not be accepted by the NRG BB-Columbus.

Please have the Pathologist responsible for signing out this patient’s case complete the following:

Bank ID: _____ - ____ - G _____

Study ID: _____ - G Y 0 0 7 - _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one):

Primary	Metastatic
Interval Primary	Interval Metastatic
Adjacent Normal	

Site Tissue Taken From: _____

Diagnosis: _____

Recurrent disease documented by: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient’s care.

Pathologist’s Signature

Date

Pathologist’s Printed Name

**APPENDIX XIII – PARTICIPATING INSTITUTIONS FOR PHASE I SAFETY LEAD-IN
(04/06/2018)**

Participating Institutions for Phase I Safety Lead-In	
PA075	Abramson Cancer Center at the University of Pennsylvania
AZ151	Arizona Cancer Center
OH027	Cleveland Clinic Foundation
PA086	Fox Chase Cancer Center
MD017	Johns Hopkins University/Sidney Kimmel Cancer Center
GA020	Georgia Regents University
CT009	Hartford Hospital
TX035	M.D. Anderson Cancer Center
NY016	Memorial Sloan-Kettering
WI013	Froedtert and the Medical College of Wisconsin
OH007	Ohio State University
OK003	Oklahoma University
NY158	Roswell Park Cancer Institute
PA121	Thomas Jefferson University
CA189	UC Davis Medical Center
CA088	University of California Medical Center at Irvine-Orange Campus
OH274	UHHS – Chagrin Highlands Medical Center
IL057	University of Chicago
CO070	University of Colorado Cancer Center
OH029	Case Western Reserve University
IA018	University of Iowa Hospitals and Clinics
PA015	University of Pittsburgh Cancer Center
VA009	University of Virginia Health Systems
VA010	Virginia Commonwealth University
MO011	Washington University School of Medicine
RI012	Women’s and Infants Hospital