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A Randomized, Open-label, Phase II, Multi-center Trial of Gemcitabine with Pazopanib or Gemcitabine with Docetaxel in Advanced Soft Tissue Sarcoma

Running title: Combination Drug Therapy for Sarcoma

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PRECIS

The results of this trial suggest the similarity of the G+P regimen to the G+T treatment in efficacy and tolerability. In patients who are not suitable for G+T, G+P is a reasonable alternate regimen for second-line treatment of metastatic non-adipocytic sarcomas.

BACKGROUND

Therapeutic options for advanced soft tissue sarcoma (STS) are limited. The goal of this phase II study was to examine the clinical activity and safety of the combination of gemcitabine plus pazopanib, a multityrosine kinase inhibitor with activity in STS.

METHODS

This randomized phase II trial enrolled advanced non-adipocytic STS patients who had received prior anthracycline based therapy. Patients were assigned (1:1) to receive gemcitabine 1000 mg/m2 on days 1 and 8 with pazopanib 800 mg daily (G+P) or gemcitabine 900 mg/m2 on days 1 and 8 and docetaxel 100 mg/m2 on day 8 (G+T) every 3 weeks. Cross-over was allowed upon progression. This was a non-comparative statistical design based on the precision of 95% confidence intervals for reporting the primary endpoints of median progression-free survival (PFS), and rate of grade ≥ 3 adverse events (AEs), for these two regimens, based on the intent-to-treat patient population.

RESULTS

90 patients were enrolled; 45 on each arm. Median PFS was 4.1 months for each arm (p=0.3, log-rank test). Best overall response of SD or better (CR+PR+SD) was the same for both arms (64% for G+T and G+P). Rate of related grade ≥3 AEs was 82% with G+T and 78% with G+P. Related grade ≥3 AEs (%) occurring in ≥10% of patients (G+T; G+P) were anemia (36, 20), fatigue (29; 13), thrombocytopenia (53; 49), neutropenia (20; 49), lymphopenia (13;11) and hypertension (2; 20).

CONCLUSION

This data demonstrates the safety and efficacy of G+P as an alternative to G+T for non-adipocytic STS.

KEYWORDS – soft tissue sarcoma, Gemcitabine and Pazopanib, best overall response, adverse events

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INTRODUCTION

Chemotherapy is widely used in the treatment of non-resectable or metastatic soft tissue sarcoma (STS)[1,2]. Initial standard chemotherapy for these tumors consists of an anthracycline given as a single agent or in combination with ifosfamide[3, 4] though the cardiotoxicity of cumulative anthracycline use is often dose limiting.[5-7] The combination of gemcitabine and docetaxel (G+T) is another frequently used regimen to treat metastatic STS based on a phase II study reported by Maki et al. that demonstrated a survival benefit for this combination versus single agent gemcitabine.[8,9] The median progression-free survival (mPFS) of gemcitabine therapy alone was 3 months; when combined with docetaxel, the mPFS increased to 6.2 months, with leiomyosarcoma (LMS) and undifferentiated pleomorphic sarcoma subtypes having the most benefit. However, the combination of G+T was a relatively poorly tolerated regimen with 46% of patients requiring at least one dose reduction, and many patients discontinuing therapy within 6 months due to toxicity [8,9]. The TAXOGEM study[10] carried out by the French Sarcoma Group focusing only on relapsed LMS found the PFS in uterine and nonuterine LMS of 5.5/6.3 months respectively for gemcitabine and 4.7/3.8 months for the combination of gemcitabine and docetaxel. The GeDDiS trial[11] compared G+T at a lower starting dose than previous studies to doxorubicin in front-line treatment for advanced sarcoma demonstrating a similar mPFS of around 5.5 months. In these studies, unlike pancreatic cancer, gemcitabine is given as a fixed dose regimen at 10 mg/m2/min.

An alternative to G +T might involve the use of pazopanib which is an oral targeted tyrosine kinase inhibitor (TKI) that blocks multiple growth factor receptors including vascular endothelial, platelet-derived, and fibroblast growth factor receptors amongst many others[12]. Pazopanib was approved for treatment of sarcoma based on a double-blind, placebo-controlled
randomized phase III trial (PALETTE) which demonstrated significant prolongation of progression-free survival (PFS) in patients with pretreated non-adipocytic sarcoma[13]. However, despite the overall increase in PFS that was seen in this study, there was no overall survival (OS) benefit. Multivariant analysis of long-term survivors showed that both performance status and tumor grade had significance for PFS and OS from pazopanib[14]. This

study excluded adipocytic sarcomas, as this subtype cohort was halted early in the preceding phase II trial as it did not meet the prespecified efficacy cut-off. Though subsequent studies in liposarcomas[15], demonstrated similar results to PALETTE with a mPFS and OS of 4.4 and 12.6 months, respectively, these were resulted after our current study was enrolling, and have not led a change in the label indication for pazopanib.

To build upon the activity of pazopanib and develop a new combined therapy for sarcoma, this agent has been combined with a MEK inhibitor trametinib in 25 patients[16]. In this trial, the mPFS was 2.27 months, and the 4-month PFS rate was 21.1%, suggesting that the combination did not improve efficacy. Antiangiogenic therapies such as pazopanib work by inducing vascular normalization, thereby alleviating hypoxia and increasing the delivery of cytotoxic chemotherapies to cancer cells[17]. Increased penetration of drugs throughout the tumor could enhance the antitumor benefit of chemotherapy, hence we explored combination of pazopanib with chemotherapy. To examine further whether a potential combination of pazopanib and gemcitabine (G+P) might be developed as a sarcoma therapy, our team has randomized 90 patients with non-adipocytic sarcomas to receive either pazopanib plus gemcitabine or the currently used regimen of gemcitabine plus docetaxel. This trial excluded adipocytic sarcomas based on the initial PALETTE results. Cross-over was allowed after progression; patients on each arm were evaluated for PFS and toxicity, and secondarily for overall survival and quality of life (QOL).

PATIENTS AND METHODS

Patient Eligibility

Eligible patients had to have metastatic or locally advanced/recurrent histologically or cytologically confirmed diagnosis of non-adipocytic sarcoma of soft tissue, be 18 years or older. All patients signed written informed consent prior to any study interventions. Human investigations were performed after approval by the local Human Investigations Committee/ Institutional Review Board at each Institution and in accordance with an assurance filed with and approved by the Department of Health and Human Services. Patients should have received a prior anthracycline based regimen unless otherwise contraindicated. Additional criteria included: an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, disease that was not amenable to curative surgical resection, ≤3 prior chemotherapy regimens for

recurrent/metastatic disease, measurable disease by RECIST or cutaneous disease amenable to serial measurements if present, able to swallow and retain oral medication, and have adequate organ system function including an alanine amino transferase (ALT) and aspartate aminotransferase (AST) ≤2.5 the upper limit of normal, and a serum creatinine <1.5 mg/dl.

Patients were excluded if they had a history of untreated central nervous system metastases, active peptic ulcer disease, intraluminal metastatic lesions with a risk of bleeding, corrected QT interval (QTc) >480 msecs, poorly controlled hypertension, history of a pulmonary embolism or transient ischemic attack, or major surgery within 28 days of registration.

Study Design and Treatments

Patients were randomized 1:1 to either G+P or G+T. Randomization was stratified by both leiomyosarcoma histology (yes/no) and by prior pelvic radiation (yes/no) using blocks of size 4.

The trial was designed to enroll 90 patients who were randomized 1:1 to receive G 1000mg/m2
intravenously (i.v.) over 100 minutes (min) on days 1 and 8 cycled every 21 days along with P 800 mg PO once daily days 1 through 21 (G+P), or G 900 mg/m2 i.v. over 90 min on days 1 and 8 along with T 100 mg/m2 i.v. over 60 min on day 8 every 21 days (G+T). The starting dose of G+P was the recommended phase 2 dosing set by the sponsor based on the phase 1 study[18], and the starting dose for G+T was the established maximum dosing used in prior phase II studies[9,10]. Gemcitabine was given at a fixed-dose rate of 10mg/m2/hour based on higher efficacy compared to 30-minute infusion in sarcoma[19-22,] . Pegfilgrastim or filgrastim could be used on either arm at the discretion of the investigator. Patients discontinued treatment for disease progression, intolerable toxicity, or if treatment was interrupted for greater than 21 days. Since G+T may be more active in leiomyosarcoma compared to other soft tissue sarcoma sub-types, patients were stratified by sarcoma subtype (leiomyosarcoma vs. other) prior to randomization. Randomization was also stratified based on prior pelvic radiation because of the potential for differential response by prior pelvic radiation. Each patient was followed for a minimum of 18 months for progression and death events.

Disease progression was assessed every 2 cycles (6 weeks) for the first 24 weeks and then every 3 cycles. Optional blood draws for biomarkers and pharmacokinetics (G+P arm) and specimen banking (both arms) occurred at baseline, 6 weeks, and progression was carried out. Predefined early stopping rules allowed for early stopping in each arm for excessive toxicity. Upon progression, patients were allowed to cross-over to the other treatment arm (Fig 1), allowing for the evaluation of PFS of G+P after exposure to G+T and vice versa. To crossover, patients must have maintained ECOG performance status of 0-2, measurable disease by RECIST 1.1, toxicities resolved to ≤ grade 1, and adequate organ function. If the patient had been dose reduced during therapy, then this dose reduction would carry over to the cross-over.

Dose delays and modifications for ≥ grade 3 non-hematologic toxicities with G, P and T were permanent. Dose reescalation to one level higher if the counts permitted was allowed if reductions occurred for treatment related hematologic toxicities. For P specific side effects, isolated dose reduction of P was allowed. If a second reduction was required, reescalation was not permitted. The dose levels (DL) were as follows: G+P -- DL-1 G 800 mg/m^2, P 600 mg; DL-2 G- 675 mg/m^2, P 400 mg; G+T – DL-1 G- 700 mg/m^2, T-75 mg/m^2; DL-2 G 600 mg/m^2, T-60 mg/m^2.

Study Objectives and Assessments

The primary objective was to estimate mPFS and the rate of grade ≥ 3 toxicity for the G+P arm and G+T arms. Key secondary objectives included estimating the hazard ratio (HR) for PFS, and best overall response rates, QOL, and median overall survival (OS) in each arm.

The EORTC core quality of life questionnaire QLQ-C30 was administered to patients at four time points (registration, cycle 2, cycle 6, and end of treatment). Tumor response (complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) was assessed by the treating or site investigator and was based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The best overall response was defined as the best recorded response

from the start of study treatment until disease progression or end of treatment. For a best overall response of SD, the criteria for SD was met at least once no less than for 6 weeks from the pre-treatment assessment. Adverse Events were graded according to the NCI Common Terminology Criteria for Adverse Events v4.0, and their attribution was determined by the local principal investigator.

Statistical Analysis

Co-primary endpoints are PFS and the toxicity of grade 3 or higher, with estimation of median PFS and rate of grade 3 or higher toxicity as co-primary objectives. Sample size was derived based on the precision of 95% confidence intervals for reporting toxicity rates and mPFS in each arm. With 45 patients per arm and assuming an observed toxicity rate of less than 30%, the maximum half-width of the 95% confidence interval is <14%. For PFS, the precision of the 95% confidence interval will depend heavily on the observed median PFS. With observed median PFS of 3, 6 or 8 months, the estimated half-widths of 95% confidence interval would be expected to be 1.4, 2.9, or 3.9 months, respectively, based on results from Kaplan-Meier curves and using Greenwood's formula for variance. Hypothesis testing was not implemented due to the uncertainty in choosing a historical control PFS rate. With 45 patients per arm and assuming an observed toxicity rate of less than 30%, the maximum half-width of the 95% confidence interval would be <14%. For PFS, the precision of the 95% confidence interval would depend heavily on the observed mPFS. With observed mPFS of 3, 6 or 8 months, the estimated half-widths of 95% confidence interval would be expected to be 1.4, 2.9, or 3.9 months, respectively, based on results from Kaplan-Meier curves and using Greenwood's formula for variance. These estimates would be considered sufficiently precise for determining if the efficacy and safety profile warrant further exploration of G+P as combined therapy. Hazard ratios (HR) were estimated between the two groups using Cox proportional hazards regression models adjusting for stratification variables. Data was compared between arms via Fisher's exact and Chi square tests for binary and categorical data, as appropriate, and via two-sample t-tests and Wilcoxon rank sum tests for continuous data, as appropriate. All randomized patients (intention-to-treat population) were assessed for response to treatment. PFS and OS were described using Kaplan-Meier curves, and curves compared using stratified log rank tests. For the crossover portion of the study, comparison of best overall response of SD or

better (CR+PR+SD) was performed using exact logistic regression adjusting for stratification variables, and corresponding exact binomial 95% confidence intervals (CIs) were constructed. The proportion of patients in each arm with grade 3 or higher at least possibly related toxicities were reported with their 95% CIs. Toxicity profiles were described by estimating the serious adverse event (SAE) rate per arm and tabulating toxicities per arm by type and grade. Quality of life measurements were evaluated via general linear mixed models to examine the relationship with time, treatment arm, and the interaction between the two. Non-significant interaction terms were removed from the model in order to evaluate the main effects of treatment arm and time

RESULTS

Ninety patients with non-adipocytic sarcoma were accrued to this study across 10 sites (with a range of 1 to 21 patients per site) with 45 randomized to each arm over the years 2011-2018 (Table 1). The mean age of these patient was 56 years (range 21.7 to 82.2) with approximately 50% male patients evenly distributed in the two arms. Eighty-one (90%) of the patients had prior surgery and these patients were equally balanced between both arms as well. The majority (82%) of the patients received at least one line of prior therapy before being enrolled on this protocol. Overall, 10 had received prior pelvic radiation (11%). Amongst the 28 with LMS, 3 had had prior pelvic radiation. There were no statistical differences in these characteristics between treatment arms.

Treatment Administered

Patients in the G+T arm received a median number of 4 cycles (range 2-8) while those on the G+P arm received a median number of 3 cycles (range 2-10). The median (interquartile range (IQR)) time to best response for both the G+P and G+T arm was similar for both arms with 42 days (IQR=38 to 49) for G+T and 43 days (IQR=37 to 49) for G+P. The median duration of therapy for the two arms was not statistically different (p=0.90): G+P 62 days (range 28 to 203 days) and G+T 70 days (range 28 to 161 days) (Table 2). The most common reason for study discontinuation was disease progression on both arms (Table 3). A total of 13 patients (29%) in the G+T arm crossed over to G+P, while a total of 9 patients (20%) in the G+P arm were treated with G+T after progression (Table 2).

Efficacy End Points

The mPFS) was 4.1 months (95% CI: 2.7-11.4 months) in the G+T arm, and 4.1 months (95% CI: 2.4-8.6 months) in the G+P arm (p = 0.29, Fig 2a). The median OS was 15.9 months (95% CI: 9.2-24.2 months) in the G+T arm, and 12.4 months (95% CI: 8.8-21.8 months) in the G+P arm (Fig 2b). The distribution of response by RECIST 1.1 in the G+P arm was: partial response (PR) 11% (5/45), stable disease (SD) 53% (24/45), and progressive disease (PD) 31% (14/45). Two patients in the G+P arm were withdrawn prior to the first radiographic assessment and not evaluable for response, one due to toxicity and one due to investigator decision. The best overall response rate of SD or better (CR+PR+SD) in the G+P arm was 64%. In comparison, for G+T, PR was 18% (8/45), SD 47% (21/45), and PD 36% (16/45) for a best overall response rate of SD or better of 64% (Table 4). The hazard ratio for PFS comparing the G +P treated patients to the G +T treated patients was 1.23 (95% CI = 0.77 to 1.94; p=0.38); the hazard ratio for OS was also 1.23 (95% CI = 0.74 to 2.04, p=0.42).

Crossover Patients

Twenty-three patients agreed to participate in the cross-over study following progression on the initial treatment. However, one patient was taken off study prior to treatment due to declining performance status. Twenty-two patients were included in the cross over study: 13 crossed-over from G+T to G+P, and 9 crossed-over from G+P to G+T. The responses were as follows: for those crossing over to G+P, PR was 15% (2/13) with 62% demonstrating SD (8/13) and 23% (3/13) having PD. For patients who crossed over to G+T, none had responses, 1 patient (11%) demonstrated SD, and the remaining 89% (8/9) had PD (Table 4). Although the numbers are small, the best overall response rate of SD or better in the crossover portion of the study favored G+P (rate = 0.77, 95% CI = 0.46 to 0.95) over G+T (rate = 0.11, 95% CI = 0.003 to 0.48); p=0.0093). The mPFS for patients who crossed over from G+P to G+T was 1.3 months (95% CI = 1.2 months to not estimable). The mPFS for patients who crossed over from G+T to G+P was 6.4 months (95% CI = 2.9 months to not estimable). The Kaplan-Meier curve detailing these results is shown in Figure 2C. The HR for PFS G+P relative to G+T for the cross-over was 0.43 (95% CI = 0.17 to 1.10; p=0.077).

Quality of Life Measurements

The QLQ-C30 symptom scale was measured at baseline upon registration, after cycle 2, after cycle 6 and at the end of treatment. In comparing these two treatment groups there was no difference in fatigue, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea or financial stress. Regarding nausea and vomiting after adjusting for baseline values, the G+T group was found to remain largely stable over time, while the G+P group had lower scores over time, demonstrating an improvement in this symptom (p=0.0001).

Safety and Tolerability

At least possibly related grade ≥3 adverse events suspected to be related to study treatment occurred in 78% of patients in the G+P arm and in 82% in the G+T arm (Table 5). Table 2 summarizes modifications that occur during the cycles. In the G+P arm 42 (93%) had doses held or skipped compared to 26 (58%) in the G +T arm (p=0.0001), potentially because P was dosed daily and patients could independently hold P for side effects, which counted toward doses skipped. In the G+P arm 36 (80%) had dose reductions compared to 26 (58%) of patients in the G+T arm had dose reductions and 26 (58%) had doses held. Conversely, patients were more likely to delay dosing on G+T, which did not count toward held/skipped doses. The number of dose reductions for each arm was also significantly different [G+P 36 (80%), G+T 26 (58%); p = 0.04, Table 2].

Table 6 examines the day 1 doses and demonstrates changes in dosing over all cycles. In the G +T arm this includes both the Day 1 and the Day 8 docetaxel dose. The pattern shown in Table 2 is also evident here with the G +P arm having a greater number of overall dose reductions (Table 5).

In the G+P arm, the most common related grade ≥ 3 toxicity events were neutropenia (49%), thrombocytopenia (49%), anemia (20%), hypertension (20%), fatigue (13%), lymphopenia (11%), ALT increase (9%), and thromboembolic events (4%). While in the G+T arm, the most common grade ≥ 3 related toxicity events included thrombocytopenia (53.3%), anemia (35.6%), fatigue (28.9%), neutropenia (20%), lymphopenia (13.3%), and edema (8.9%) (Table 5). The total number of at least possibly related grade 3 and 4 events was similar in the two arms; there

were 160 events in the G+P arm and 156 in G +T. In the pazopanib treated patients either previously treated or not with an anthracycline there were no cardiac events.

DISCUSSION

This randomized phase II study in non-adipocytic sarcoma demonstrates the efficacy and toxicity of G+P in advanced STS and its similarity to the standard G+T regimen. In this study, 45 patients were randomized to each arm and patient characteristics were well balanced. The estimated median time to best response and the rate of best overall response of SD or better for each arm was the same. The mPFS and the grade 3 and 4 toxicity rates for each regimen were very similar. The QOL estimates showed that these regimens were comparable except for lower cumulative nausea in the G+P arm. Of note, this study allowed the crossover of patients from the initial therapy. In those who did crossover, the best overall response of SD or better favored moving to the G+P arm (p=0.0093), which contained partial responses to second line therapy. In the absence of a larger comparative study, these data demonstrate that G+P could be considered in select sarcoma patients who would benefit from combination therapy in the second line and are not candidates for G+T.

Interestingly, our study noted a mPFS of 4.1 months for each arm, including G+T, which is lower than the mPFS of 6.2 months in the initially reported studies of this regimen[9]. One contributing factor could have been the prior study's inclusion of liposarcoma, which was excluded in this trial, and variability in the distribution of other subtypes. Most of the liposarcomas included were well-differentiated or dedifferentiated liposarcomas (n=5), which tend to have a longer PFS, and were reported on the Maki et al study[9] to have SD as the best response on the G+T arm. The remaining were pleomorphic liposarcomas, 2 with PR, 1 with SD as best response. However, the percentage of total patients with leiomyosarcoma was almost identical (approximately 30%) in this study and the prior one. There could also have been a difference in dose intensity, as well. In this study's G+T arm, 56% of patients required a dose reduction in docetaxel and 34% required a decrease in the gemcitabine dose. The Maki et al. study reported a dose intensity of 90% for G+T. Strict dose reduction guidelines in this study

may have contributed to higher number of dose reductions. A French Sarcoma Group Study (LMSO3)[23] examined the combination of G+P (gemcitabine 1000 mg/m2 on day 1 and 8 with 800 mg daily of pazopanib for a maximum of 8 cycles, followed by maintenance pazopanib) for the treatment of leiomyosarcoma after first-line doxorubicin chemotherapy failure. The 9-month PFS was 32% in this single-arm study, which was lower than the prespecified target PFS of 44%, making it a negative study. Patients treated with the same starting doses of G+P as in this study, demonstrated a PFS of 6.5 months (95% CI: 5.6-8.2) which was similar to that obtained for G+T in the TAXOGEM study[10] for leiomyosarcoma patients again suggesting the similarity of these regimens. The higher sensitivity of leiomyosarcomas to these chemotherapy agents, might account for the higher PFS seen in LMS03 and TAXOGEM compared to the current study that included subtypes other than leiomyosarcoma.

Although cross trial comparisons are not statistically valid, the PFS result of 4.1 months for the G+P combination compares well with other gemcitabine combinatorial regimens. Gemcitabine plus dacarbazine study from the Spanish Sarcoma group reported a PFS of 4.2 months[24] while the same group also tested gemcitabine plus sirolimus resulting in a PFS of 1.8 months[25]. A single institution study of gemcitabine and vinorelbine[26] produced a PFS of 3.4 months. These studies all focused on STS albeit with different eligibility criteria. Nonetheless, G+P activity sits favorably amongst these other phase II studies.

Our cross-over data is limited by the small number of patients that crossed-over. The reasons for low rate of cross-over were multi- factorial; toxicity was not an allowable reason for cross-over, RECIST progression was required, and these regimens, especially G+T, were available off-study and could be administered at local centers. In our small data set, patients who switch from G + T to G + P (n=13) appear to benefit more (PR 15%, mPFS 6.4 months) than switching from G + P to G + T (n=9, PR 0%, mPFS 1.3 months). However, following G + T it is difficult to ascertain if combining gemcitabine with pazopanib adds to pazopanib alone. Results from the PALETTE study of pazopanib vs placebo, revealed a response rate of 6% for pazopanib alone, with a mPFS of 4.6 months[13]. For patients who progress on G + T, the current standard recommendation would be for single agent pazopanib.

The side effects of the G+P therapy were consistent with the expected side effects of pazopanib and gemcitabine. The major grade 3 or higher toxicities included neutropenia (49%), thrombocytopenia (49%), anemia (20%), hypertension (20%), fatigue (13%), lymphopenia (11%), ALT increase (9%), and thromboembolic events (4%), all of which have been detailed previously. Although the side effects of the G+T therapy were different with a higher incidence of leg edema, the overall number of grade 3 and 4 toxicities was not different between the two regimens. These toxicities associated with docetaxel sometimes make it challenging to continue G+T as a long-term regimen.

When G+P is administered at a starting dose of 1000 mg/m2 on day 1 and 8 for gemcitabine and 800 mg daily for pazopanib (Table 6), the results of this study suggest that approximately 70% of patients may require one or multiple dose reductions for gemcitabine and a similar percentage for pazopanib. Lack of or infrequent use of G-CSF in this arm likely contributed to higher rates of neutropenia. A similar rate of grade 3 or higher toxicity (87%) was reported on the recent LMS03 study that used similar starting doses for G+P, with 53% requiring dose reductions and 27% discontinuing due to toxicity[23]. Based on these findings, patients should probably be started at lower starting doses, with doses being escalated or deescalated based on patient tolerance. Majority patients were able to maintain dosing of gemcitabine at or above 800 mg/m2, while around 50% of patients ultimately reduced pazopanib dose to 400 mg daily in the G+P arm. This suggests the combination of G+P would be better tolerated with gemcitabine at 900 mg/m2 on day 1 and 8, with pazopanib at 400 mg of daily, allowing, if well tolerated, for dose escalation by 200 mg each cycle, to a maximum dose of 800 mg daily. For G+T, we would recommend the starting dose of gemcitabine to be 900 mg/m2 on day 1 and 8, with docetaxel 75 mg/m2 on day 8, as is often used in standard practice.

The results of this trial suggest the similarity of the G+P regimen to the G+T treatment in efficacy and tolerability. In patients who are not suitable for G+T (due to contraindication or intolerance to docetaxel), G+P would be a reasonable alternate regimen for second-line treatment of metastatic non-adipocytic sarcomas.

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FIGURE LEGENDS

Figure 1 – Consort diagram

Figure 2 – (a**)** Kaplan-Meier curves demonstrating progression free survival (PFS) for both arms of the study as well as patients at risk over time. (b) Kaplan-Meier curves showing overall survival (OS). (c) Kaplan-Meier curve demonstrating progression free survival (PFS) of patients that crossed over after initial treatment. Number of patients at risk after crossover treatment are shown.

Table 1 Patient Characteristics

	Overall N (%)	Gemcitabine + Docetaxel N (%)	Gemcitabine + Pazopanib N (%)
No. of Patients	90	45	45
Age (mean±SD, years)	56.27±13.95	54.60±14.10	57.93±13.76
Sex			
Female	46 (51)	22 (49)	24 (53)
Male	44 (49)	23 (51)	21 (47)
Leiomyosarcoma	28 (31)	13 (29)	15 (33)
Prior therapies received			
Pelvic RT	10 (11)	5 (11)	5 (11)
Surgery	81 (90)	42 (93)	39 (87)
Radiation	51 (57)	23 (51)	28 (62)
Chemotherapy	74 (82)	37 (82)	37 (82)
Other prior therapy	6 (7)	4 (9)	2 (4)
Received prior doxorubicin based therapy	70 (78)	35 (78)	35 (78)
Number of lines of prior chemotherapy*			
Median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)
0	16 (18)	8 (18)	8 (18)
1	45 (50)	21 (47)	24 (53)
2	21 (23)	12 (27)	9 (20)
3	8 (9)	4 (9)	4 (9)

*Max of 3 prior therapies were allowed

Table 2 Chemotherapy cycles, duration of therapy received, and dose held/skipped

		Gemcitabine + Docetaxel	**Gemcitabine + Pazopanib**

No. of cycles	Median (IQR)	4 (2, 8)	3 (2, 10)
Duration of therapy (days)	Median (IQR)	70 (28, 161)	62 (28, 203)
Dose reduction	N (%)	26 (58)	36 (80)
Dose held/skipped	N (%)	26 (58)	42 (93)
No. of patients crossed over	N (%)	13 (29)	9 (20)

Table 3 Reason for patient being taken off study, main study only.

Reason for treatment termination	**Overall** **N (%)**	**Gemcitabine + Docetaxel** **N (%)**	**Gemcitabine + Pazopanib** **N (%)**
No. of Patients	90	45	45
Progression per RECIST 1.1	44 (24)	21 (23)	23 (26)
Clinical progression	11 (6)	4 (4)	7 (8)
Toxicity, treatment termination medically required	20 (11)	11 (12)	9 (10)
Investigator decision for reasons other than toxicity	5 (3)	2 (2)	3 (3)
Patient refusal due to toxicity	2 (1)	1 (1)	1 (1)
Patient refusal for reasons other than toxicity	1 (1)	0 (0)	1 (1)
Death	2 (1)	1 (1)	1 (1)

Other	5 (3)	5 (6)	0 (0)

Table 4 Efficacy endpoints

	Gemcitabine + Docetaxel N (%)	**Gemcitabine + Pazopanib N (%)**
No. of Patients	45	45
Median PFS (95% CI), months	4.1 (2.7, 11.4)	4.1 (2.4, 8.6)
Median OS (95% CI), months	15.9 (9.2, 24.2)	12.4 (8.8, 21.8)
Best response, N (%)		
CR	0 (0)	0 (0)
PR	8 (18)	5 (11)
SD	21 (47)	24 (53)
PD	16 (36)	14 (31)
Non-evaluable*	0	2 (4)
Best overall response (CR+PR+SD)**	29 (64)	29 (64)
Cross-over Portion	**From G+P to G+T**	**From G+T to G+P**
No. of Patients	9	13
Median PFS (95% CI), months	1.3 (1.2, NA)	6.4 (2.9, NA)
Best response, N (%)		
CR	0 (0)	0 (0)
PR	0 (0)	2 (15)
SD	1 (11)	8 (62)
PD	8 (89)	3 (23)
Best overall response (CR+PR+SD)**	1 (11)	10 (78)

*Two patients in G+P were not evaluable for response and removed prior to the first post-baseline scan. One was removed due to toxicity, and a second was removed due to investigator decision.

**Including CR, PR and SD at 6 weeks.

Table 5 Summary of Adverse Events at least possibly related to study treatment.

AE*	**Gemcitabine + Docetaxel (N=45)**					**Gemcitabine + Pazopanib (N=45)**				
Grade	Grade 1	Grade 2	Grade 3	Grade 4	% Patients Grade ≥3 (95% CI)**	Grade 1	Grade 2	Grade 3	Grade 4	% Patients Grade ≥3 (95% CI)*
Neutropenia	0	2	3	6	20 (10, 35)	1	6	16	6	49 (34, 64)
Thrombocytopenia	7	7	13	11	53 (38, 68)	10	9	11	11	49 (34, 64)
Anemia	2	18	16	0	36 (22, 51)	3	22	9	0	20 (10, 35)
Hypertension	0	0	1	0	2 (0, 12)	2	7	9	0	20 (10, 35)
Fatigue	8	7	13	0	29 (16, 44)	21	10	6	0	13 (5, 27)
Lymphopenia	3	1	5	1	13 (5, 27)	1	5	2	3	11 (4, 24)
ALT increase	10	1	1	0	2 (0, 12)	12	7	3	1	9 (3, 21)
Edema	4	7	4	0	9 (3, 21)	6	1	0	0	0 (0, 0)
Thromboembolic event	0	0	0	0	0 (0, 0)	0	3	2	0	4 (1, 15)

* Only Adverse Events reported here are those that affected ≥10% of patients

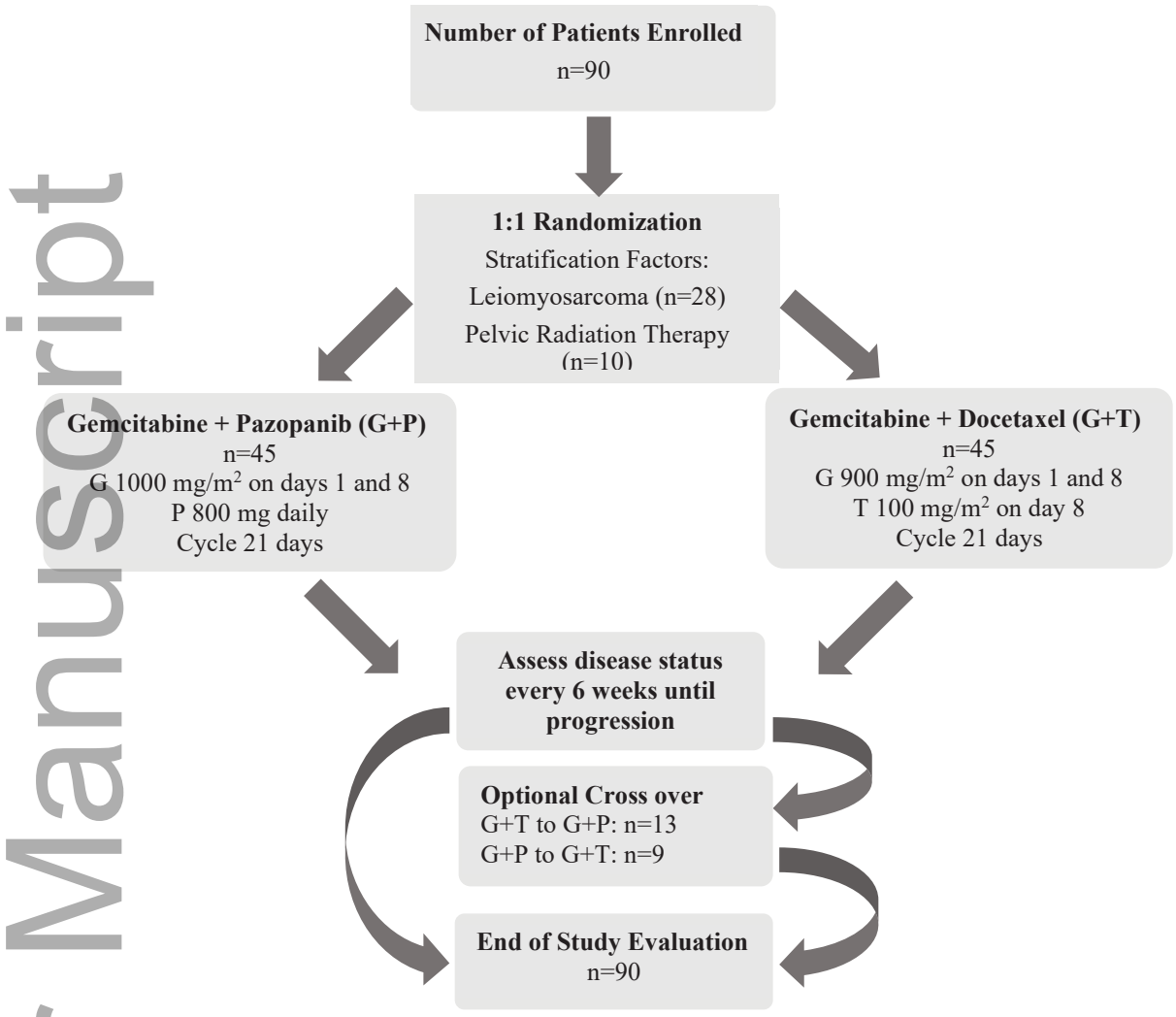
**Binomial 95% confidence interval

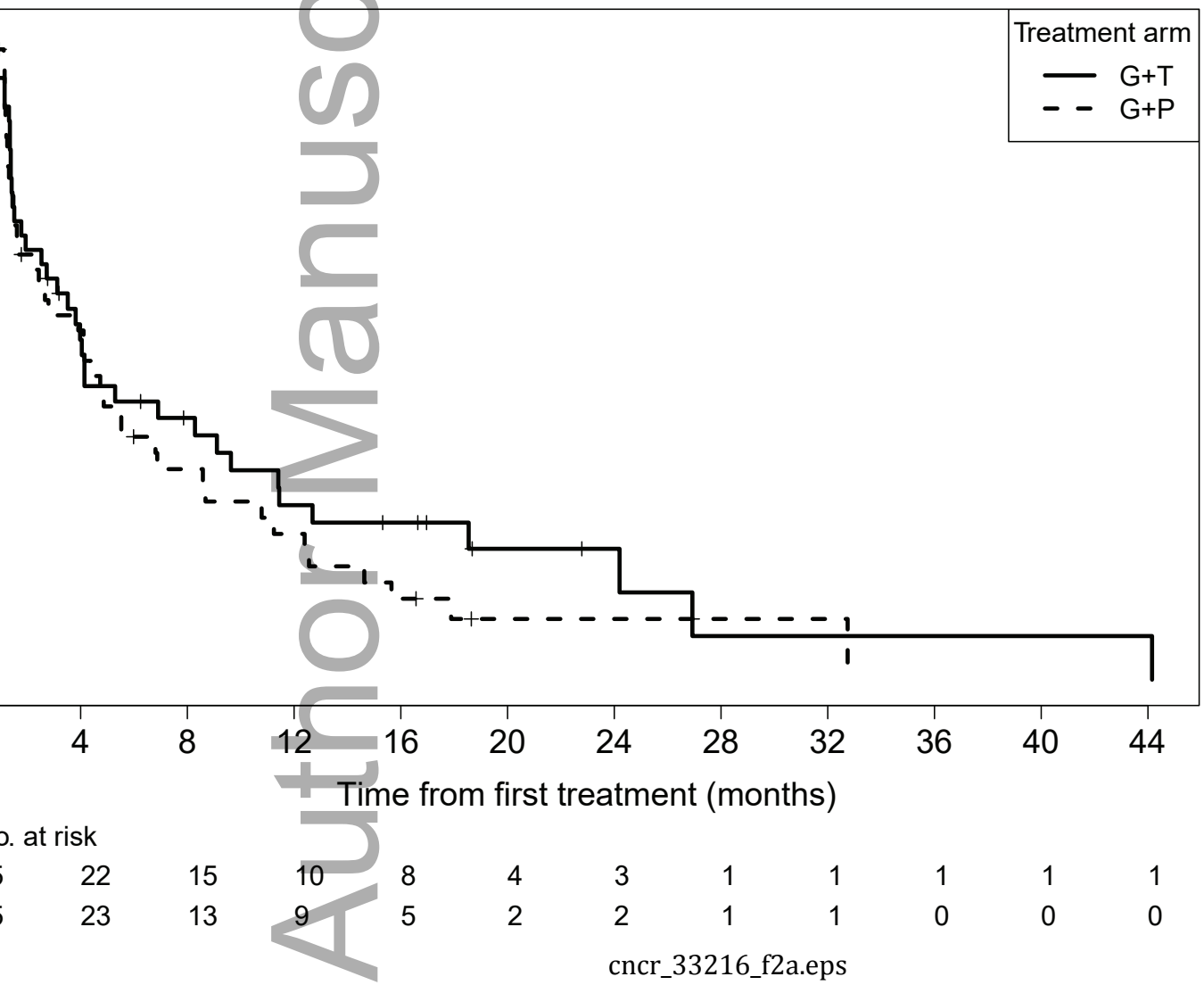
Table 6. Dose Summary

Gemcitabine + Docetaxel N (%)		Gemcitabine + Pazopanib N (%)	
GEMCITABINE		**GEMCITABINE**	
No. of cycles (Day 1 dose)	234 (100)	No. of cycles (Day 1 dose)	294 (100)
900 mg/m^2	155 (66)	1000 mg/m^2	86 (29)
700 mg/m^2	54 (23)	800 mg/m^2	107 (36)
600 mg/m^2	23 (10)	675 mg/m^2	101 (34)
525 mg/m^2	2 (1)		
Any dose reduction	18 (40)	Any dose reduction	30 (67)
Lowest Dose Administered		Lowest Dose Administered	
900 mg/m^2	27 (60)	1000 mg/m^2	15 (33)
700 mg/m^2	12 (27)	800 mg/m^2	15 (33)
600 mg/m^2	5 (11)	675 mg/m^2	15 (33)
525 mg/m^2	1 (2)		
DOCETAXEL		**PAZOPANIB**	
No. of cycles (Day 8 dose)	220 (100)	No. of cycles (Day 1 dose)	289 (100)
100 mg/m^2	92 (42)	800 mg	75 (26)
75 mg/m^2	80 (36)	600 mg	78 (27)
60 mg/m^2	44 (20)	400 mg	136 (47)

56.25 mg/m^2	4 (2)		
Any dose reduction	25 (56)	Any dose reduction	35 (78)
Lowest Dose Administered		Lowest Dose Administered	
100 mg/m^2	16 (36)	800 mg	10 (22)
75 mg/m^2	17 (38)	600 mg	13 (29)
60 mg/m^2	10 (22)	400 mg	22 (49)
56.25 mg/m^2	2 (4)		

Figure 1





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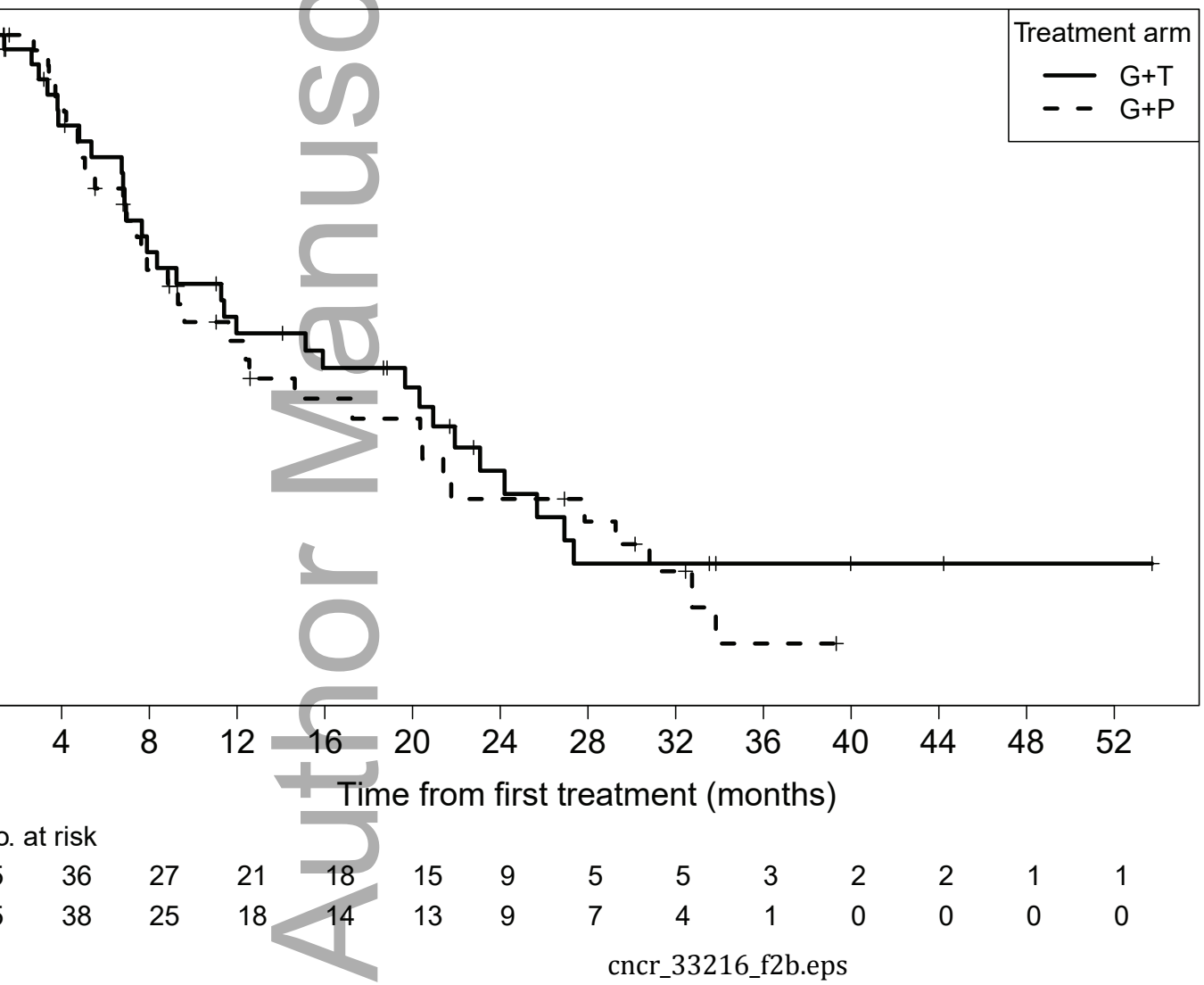

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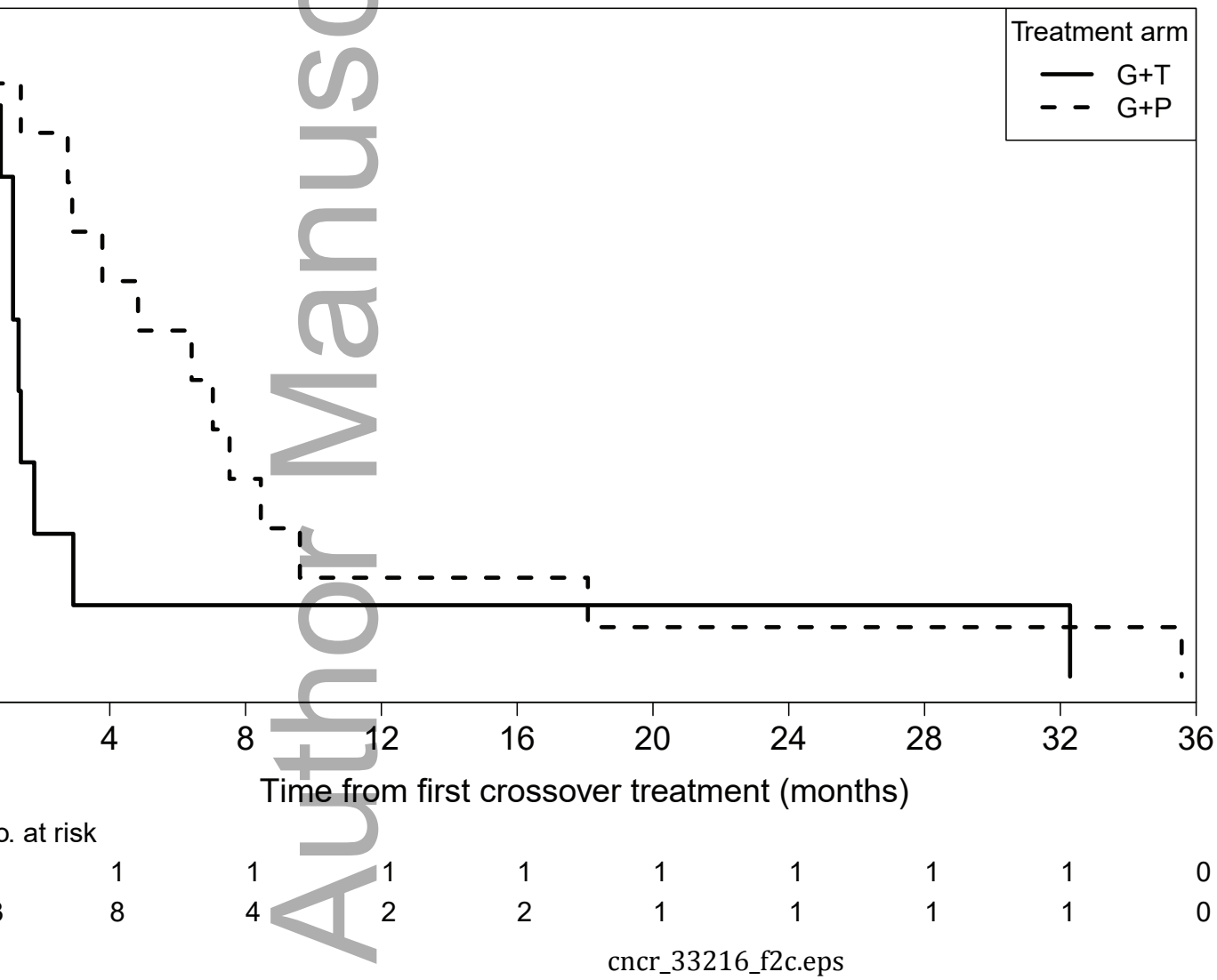

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