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Paclitaxel, Ifosfamide & Cisplatin (TIP) as initial salvage chemotherapy for germ cell tumors (GCT): Long-term follow-up and outcomes for favorable- & unfavorable-risk disease

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Abstract

Background:

TIP is an established salvage regimen for GCT based on a Phase II trial but efficacy on a large patient cohort including patients with unfavorable risk features and long-term outcomes have not been reported. Herein, we report updated treatment efficacy and long-term follow-up with TIP.

Patients and Methods:

Patients with GCT who received TIP after cisplatin-based chemotherapy were eligible. Favorable response (complete response or partial response with negative tumor markers), overall survival (OS) and progression-free survival (PFS) rates, relapse, and toxicity were determined. Disease was reclassified according to the International Prognostic Factor Study Group (IPFSG) score.

Results:

Of 104 patients, 87 had favorable risk factors and 17 had at least one unfavorable factor by Memorial Sloan Kettering Cancer Center (MSKCC) criteria. Ten patients were treated for a second gonadal primary GCT. With a median follow-up of 8.9 years, 5-year PFS and OS rates were 66% (95% CI, 55-74%) and 69% (95% CI, 59-77%). Among 87 patients with favorable-risk disease, 69 (79%) achieved a favorable response and 5-year PFS and OS rates were 67% (95% CI, 56-76%) and 72% (95% CI, 61-80%). Among 17 patients with MSKCC unfavorable-risk disease, 13 (76%) achieved a favorable response with 5-year PFS and OS rates of 59% (95% CI, 33-78%) and 56% (95% CI, 28-76%). After IPFSG reclassification, 5-year PFS and OS rates for patients with ≤ intermediate-risk disease were 75% (95% CI, 50-89%) and 73% (95% CI, 55-85%).

Conclusion:

TIP is an effective second-line regimen for patients with GCT. Similar outcomes were observed in patients with favorable and unfavorable risk disease. The randomized TIGER trial (NCT02375204) comparing TIP with high-dose chemotherapy will determine the optimal second-line treatment approach.

Introduction:

While advanced germ cell tumors (GCT) are highly curable, approximately 20-30% of patients will experience disease progression after first-line chemotherapy. Initial salvage treatment options include both conventional-dose chemotherapy (CDCT) and high-dose chemotherapy (HDCT). We previously reported a phase II trial combining paclitaxel dosed at 250 mg/m^2 per cycle with ifosfamide and cisplatin (TIP) as initial salvage treatment in 46 patients with progressive GCT and favorable risk factors. Thirty-two (70%) patients achieved a favorable response (CR or PR-marker negative) with 29 (63%) remaining continuously disease-free at a median follow-up 69 months.[1] This study established TIP as a standard-of-care initial salvage CDCT option and led to its global adoption as treatment for patients both with and without favorable prognostic factors. Regimens with paclitaxel administered at lower doses to less well-selected patients were not as effective.[2, 3] Given the original Phase II study's sample size and restriction to favorable-risk disease, we reviewed our total experience with TIP combining patient cohorts from the trial and those who received initial salvage TIP as standard-of-care after trial completion. Long-term outcomes of all patients were assessed.

Patients and Methods:

The charts of all patients who received TIP for the diagnosis of GCT at Memorial Sloan Kettering Cancer Center (MSKCC) between 5/1/1994 and 10/1/2019 were reviewed. Patients who received TIP as their first regimen for metastatic GCT (generally as part of a clinical trial) [4, 5], as third- or later-line therapy, or in the adjuvant setting were ineligible. Among patients who received TIP as their second chemotherapy regimen for advanced GCT, those who participated in the international randomized trial comparing TIP with HDCT (N=17; NCT02375204) or who received

TIP for secondary somatic-type malignancy were excluded (**Supplemental Figure 1**). The resulting cohort included 46 patients from the original phase II study[1] and 58 additional patients identified from our prospectively maintained institutional database.

All patients had progressive GCT following first-line platinum-based therapy, which required either increasing elevated concentrations of serum alpha-fetoprotein (AFP) and/or human chorionic gonadotropin (HCG), and/or biopsy confirmation of viable non-teratomatous GCT. Patients were stratified into MSKCC favorable-risk and unfavorable-risk groups based on disease characteristics prior to TIP initiation. A patient's disease was considered favorable-risk if three MSKCC criteria were met: (1) prior chemotherapy limited to a single program of ≤6 cycles of cisplatin; (2) gonadal primary tumor site; and (3) either a complete response (CR) or partial response with normal tumor markers (PR-negative) lasting >6 months after first-line chemotherapy. Ten patients who received TIP for metastatic disease in the setting of a second gonadal primary GCT after having had EP-based chemotherapy to treat metastatic disease from the first (contralateral) gonadal primary GCT were included in the analysis. Late relapse was defined as relapse from CR or PR-negative status >2 years after completion of initial chemotherapy.[6] All disease was reclassified according to the International Prognostic Factor Study Group (IPFSG) prognostic model, which is based on six variables: primary site, first-line response, platinum-free interval, presence of bone, liver, or brain metastasis, and AFP and HCG levels prior to salvage chemotherapy.[11] The study was approved by the MSKCC Institutional Review Board.

Treatment:

There was a phase I component to the original trial, during which the paclitaxel dose was increased among cohorts until the maximum tolerated dose of 250 mg/m^2 was reached and a 6-day regimen

was modified to deliver the same doses of the drugs over 5 days.[2] The final standardized TIP regimen was administered as an inpatient: paclitaxel 250 mg/m^2 by 24-hour continuous infusion on day 1; ifosfamide 1,500 mg/m^2 daily on days 2 to 5; and cisplatin 25 mg/m^2 daily on days 2 to 5, for a total of four cycles every 21 days. Mesna 500 mg/m^2 was administered before the ifosfamide and at 4 and 8 hours after ifosfamide daily on days 2 to 5, for a total daily mesna dose of 1,500 mg/m^2 to match the daily ifosfamide dose. In more recent years, mesna 1500mg/m^2 was admixed 1:1 with ifosfamide as a single infusion. Granulocyte colony-stimulating factor (G-CSF) was administered for neutropenic fever prophylaxis. After 2008, most patients also received prophylactic levofloxacin 500 mg daily from day 7 to 13 of each cycle after the observation that prophylactic levofloxacin significantly decreased the incidence of neutropenic fever in patients treated with TIP in the first-line setting.[4] All 58 patients treated after completion of the original Phase II trial received the standard 5-day TIP regimen containing 250 mg/m^2 of paclitaxel.

Evaluation of Response and Toxicity

Computed tomography (CT) scans of the chest, abdomen, and pelvis were performed at baseline and post-treatment to assess tumor response. Imaging was not routinely performed between cycles unless dictated by patient symptoms. AFP, HCG, and lactate dehydrogenase (LDH) were obtained at baseline, throughout treatment (at least twice per cycle), and following chemotherapy. Residual masses present after chemotherapy were resected whenever feasible.

Response was categorized as CR, PR-negative, or incomplete response (IR). A CR to chemotherapy alone required maker normalization and either radiographic resolution of disease or surgical resection of residual disease revealing necrosis or teratoma but no viable non-teratomatous GCT. A CR to chemotherapy plus surgery required marker normalization and resection of all residual masses, with viable GCT identified in one or more sites. A PR-negative was defined as

normalization of tumor markers and stable or improved radiographic findings without development of new lesions. All CR and PR-negative outcomes had to last ≥4 weeks. The favorable response rate (FRR) was defined as the proportion of patients who achieved a CR or PR-negative. Any response other than CR or PR-negative was considered an IR.

Toxicity was recorded with specific focus on hematologic toxicity including nadir hemoglobin and platelet levels, numbers of units of red blood cells and platelets transfused, and episodes of neutropenic fever occurring any time after TIP initiation through 28 days after chemotherapy completion. Reasons for treatment discontinuation were recorded.

Progression and Relapse

Disease progression following TIP was defined as either an IR or relapse from favorable response confirmed by either: 1) biopsy-proven non-teratomatous GCT within a new or growing lesion; or 2) elevated and increasing serum levels of AFP or HCG with the date of the first abnormal rise considered the date of disease progression. The relapse rate was defined as the proportion of patients with disease progression following achievement of CR or PR-negative status.

Statistical Analysis:

Baseline characteristics and treatment received were summarized descriptively. Overall survival (OS) and progression-free survival (PFS) were calculated using Kaplan-Meier estimates from initiation of TIP until the date of death (OS) or date of disease progression or death (PFS). Patients not meeting these endpoints were censored at their last follow-up date. All patients who received at least one cycle of TIP at MSKCC were included in the analysis.

Analyses of outcomes were assessed for the entire patient cohort, and comparisons between MSKCC risk groups (favorable vs. unfavorable) as well as after IPFSG reclassification (very low,

low, intermediate, high and very high) were made. Twelve patients could not be assigned an IPFSG score including ten who received TIP for metastatic disease from a second gonadal primary GCT and therefore had no relapse-free interval, and two with insufficient documentation of response to first-line chemotherapy due to treatment at a different institution. To assess the efficacy of TIP in the initial salvage setting, PFS and OS were also calculated excluding patients who received TIP as first therapy for metastatic disease from a second primary GCT. Statistical analysis was performed using SAS v9.4 (Cary, NC).

Results:

Patient Characteristics:

Of 122 patients who received second-line TIP for advanced GCT between 5/1/1994 and 10/1/2019 (**Supplemental Figure 1)**, 18 were excluded for participation in an ongoing clinical trial (n=17), or for use of TIP to treat secondary somatic-type malignancy (n=1), leaving 104 male patients for analysis. Ten patients received TIP for metastatic disease from a second gonadal primary GCT following prior cisplatin-based chemotherapy to treat metastatic disease from the first (contralateral) gonadal primary GCT. Patient characteristics are detailed in **Table 1**.

Using MSKCC risk classification, of the 87 patients with favorable-risk disease, 68 (78%) had nonseminoma and 19 (22%) had seminoma. The median relapse-free interval prior to TIP was 1.2 years (range, 0.1-24.4 years). After IPFSG reclassification, 31 (36%) had very low- or low-risk, 36 (47%) had intermediate-risk, and 10 (13%) had high-risk scores.[7] In addition, 28 (32%) of 87 patients received TIP as initial salvage therapy for late-relapse.

Of 17 patients with ≥1 MSKCC unfavorable risk factor, 12 had a short disease-free interval (PR-negative lasting ≤6 months), including the one patient with a retroperitoneal primary site, and five

patients had previously received more than six cycles of platinum-based therapy.[5] Nine (53%) had seminoma and eight (47%) had nonseminoma. The median relapse-free interval in this cohort was 0.2 years (range, 0.1 – 9.2 years); two patients had experienced a late-relapse. Twelve (71%) patients had at least two metastatic sites and none had marker-only disease at initiation of TIP. Nine (53%) of these 17 patients had metastatic disease classified as either intermediate (n=5) or high-risk (n=4) after IPFSG reclassification **(Table 1)**.

Prior Chemotherapy:

Ninety patients (87%) had received a prior chemotherapy regimen containing etoposide plus cisplatin (EP), including 46 (44%) treated with EP alone and 44 (42%) with EP plus either bleomycin (BEP) or ifosfamide (VIP); 13 received other platinum-based regimens. All 17 patients with unfavorable-risk disease received prior chemotherapy with either EP (8 patients) or BEP or VIP (9 patients) (**Table 1**).

Efficacy and Survival:

Among all 104 patients, the FRR was 79%, including CR in 65 (63%) and PR-negative in 17 (16%). Favorable response was observed in 89% of patients with NSGCT, 75% with seminoma and 57% with late relapsed disease. Of 87 patients with elevated markers pre-TIP, 68 (78%) achieved marker normalization. Thirteen (16%) of 82 patients with a favorable response to TIP subsequently relapsed (**Table 2**); combined with the 22 patients with an IR, a total of 35 patients experienced disease progression. At a median follow-up for survivors of 8.9 years, there were 32 deaths, three without documented disease progression. The 5-year and 10-year PFS rates were 66% (95% CI, 55% to 74%) and 62% (95% CI, 52% to 71%), respectively, and the 5-year and 10-year OS rates 69% (95% CI, 59% to 77%) and 66% (95% CI, 55% to 75%), respectively (**Table 2**, **Figure 1 A&D**). Five-year OS rates were similar after IPFSG reclassification for the very low-

, low- and intermediate-risk groups (81%, 78% and 72%, respectively) and comparable to 5-year OS in patients with MSKCC favorable-risk disease. OS was worse for patients with IPFSG high-risk disease (21%). (**Figure 2 A&B**).

The 10 patients who received TIP for metastatic disease from a second gonadal primary GCT had a 5-year OS rate of 100%. Excluding these 10 patients from the overall cohort (n=94), PFS and OS rates were 62% and 66%, respectively at 5 years and 61% and 65% at 10 years.

Among patients with favorable-risk disease by MSKCC criteria, the FRR was 79% and at a median follow-up for survivors of 10.0 years, 27 patients had died. The resulting 5-year and 10-year PFS rates for patients with MSKCC favorable-risk disease were 67% (95% CI, 56% to 76%) and 63% (95% CI, 51% to 73%), respectively, and the 5-year and 10-year OS rates 72% (95% CI, 61% to 80%) and 68% (95% CI, 56% to 77%), respectively (**Figure 1 B&E**).

In the MSKCC unfavorable-risk cohort, the FRR was 76%, including CR in six (35%) and PR-negative in seven (41%). Three of seven with a PR-negative response had seminoma. Of 16 patients with elevated markers pre-TIP, 13 (81%) achieved marker normalization. Three (23%) of 13 patients relapsed after achieving a favorable response to TIP. With a median follow-up for survivors of 5.7 years, seven patients had died; the 5 and 10-year PFS rates were both 59% (95% CI, 33% to 78%) and 5 and 10-year OS rates were both 56% (95% CI, 28% to 76%), (**Figure 1 C&F**).

Treatment and Toxicity:

Eighty-three (80%) patients received all four planned TIP cycles; 63 (61%) had neither treatment deviation nor dose delay >7 days (**Table 3**). Of 21 patients with early TIP discontinuation, 12 completed three cycles, five completed two cycles, and four completed one cycle. The most

common reasons for omission of one or more cycles were progressive disease (n=9), infection (n=5) and renal insufficiency (n=5) (**Table 3**). Forty-one patients had a treatment delay >7 days, with a slightly higher rate in the unfavorable-risk (N=8, 47%) compared to the favorable-risk group (N=33, 38%). Delays >7 days were most commonly due to infection (n=15) and/or cytopenia (n=14). Neutropenic fever occurred in 27 (47%) patients. A red blood cell transfusion was required in 37 (64%) patients and a platelet transfusion in 24 (41%) (**Table 4**).

Discussion:

To our knowledge, this series describes outcomes on the largest cohort of GCT patients treated with initial salvage TIP using the doses established in our previous phase II trial, and is the first series to report outcomes with salvage TIP at these doses specifically among patients with unfavorable risk factors.[1] The FRR of 79%, 5-year PFS of 66%, and OS of 69% confirm the excellent efficacy of TIP for most patients with relapsed GCT and either MSKCC favorable-risk features or IPFSG very low-, low-, and intermediate-risk disease. Additionally, long-term follow-up of the original cohort (N=46) revealed durable benefit for those who achieved a favorable response, with only one relapse and death after the prior publication. A few observations warrant emphasis.

First, of 87 patients with MSKCC favorable-risk disease, nearly 50% had intermediate- or high-risk scores by IPFSG reclassification. Patients with IPFSG intermediate-risk scores fared well, achieving 5-year OS of 73.3%, which compares favorably to the 5-year OS of 46% with initial salvage CDCT and 3-year OS of 58.3% with any initial salvage chemotherapy (HDCT or CDCT) among the intermediate-risk cohort in the IPFSG publication.[7, 8] The higher proportions of

patients with seminoma histology (27%, vs 12.8% in IPFSG publication), and with brain metastases (12.9%) in this series as well as the multiple different salvage regimens used in the IPFSG publication may account for these differences. While patients in our series with IPFSG high-risk disease did not fare as well (21% 5-year OS), they had similar outcome as those treated with CDCT in the IPFSG publication (23% 3-year OS), although small numbers (n=10) in our cohort limit conclusions.

Second, patients with MSKCC unfavorable-risk disease, achieved excellent outcomes, including 76% FRR, 59% 5-year PFS, and 56% 5-year OS, outcomes similar to the favorable-risk cohort. While we cannot exclude selection bias and notably, 53% of this cohort had seminoma, patients with unfavorable-risk disease had shorter median relapse-free interval after initial chemotherapy (0.2 vs. 1.2 years, respectively) and more extensive metastatic disease (71% vs. 38% with ≥2 sites, respectively) than the favorable-risk group, factors expected to result in worse outcomes.

Of note, ten patients who received TIP for metastatic disease from a second gonadal primary GCT after prior EP-based chemotherapy for the first (contralateral) gonadal primary GCT were also included in the overall analysis. Despite the small sample size, the 5-year OS rate of 100% supports this strategy. Excluding these 10 patients to leave only those with true relapsed/refractory disease (n=94), PFS and OS rates were 62% and 66%, respectively at 5 years and 61% and 65% at 10 years, indicating that their inclusion did not impact overall study results.

The toxicity profile of TIP was also consistent with prior studies. Severe adverse events were primarily hematologic and infectious (**Table 4**) and only one treatment-related death was observed among the 104 patients. Despite the observed toxicity, 80% of patients completed all four cycles of full dose TIP chemotherapy (**Table 3**).

Vinblastine plus ifosfamide and cisplatin (VeIP) is another standard initial salvage CDCT option based on a reported CR rate of 50%. However, only half of those CRs remained durable and toxicity was worse (albeit before the routine use of G-CSF) than observed with TIP.[9, 10] The lower FRR with VeIP compared to TIP may be partially attributed to less favorable patient selection with inclusion of men with extragonadal primary sites and relapses one to six months after first-line chemotherapy. Unfortunately, a randomized trial comparing TIP with VeIP (NCT00072215) closed early due to poor accrual and no additional randomized studies comparing salvage CDCT regimens are planned. Therefore, given the favorable outcomes and safety profile of TIP in the current series and lack of comparable results with VeIP, we consider TIP the preferred regimen when initial salvage CDCT is used.

The broader question of optimal initial salvage chemotherapy approach (HDCT or CDCT) for advanced GCT remains controversial. Some experts prefer initial salvage HDCT based on durable remission rates of 47-63% in single-institution series despite inclusion of patients with adverse prognostic factors.[11, 12] In addition, among nearly 1600 patients in the IPFSG cohort, the 2-year PFS (50% vs. 28%) and 3-year OS (53% vs. 41%) were superior with initial salvage HDCT versus CDCT. However, the current series provides evidence that some patients with unfavorable-risk disease by either MSKCC criteria or IPFSG intermediate-risk score can achieve a durable response with initial salvage TIP and avoid HDCT. In addition, the IT-94 trial, in which 280 patients were randomly assigned to receive either four cycles of VIP (or VeIP), or three such cycles followed by one cycle of high-dose carboplatin, etoposide and cyclophosphamide (CarboPEC) with stem cell rescue reported similar complete and partial response rates in both treatment arms (56%; 95% CI 50% to 62%), and significantly higher rates of Grade ≥3 neutropenia, febrile neutropenia and thrombocytopenia, and toxic death (7% vs 3%) with the CarboPEC arm. [13]

Given greater toxicity without clear PFS or OS benefit over CDCT, many practitioners reserve HDCT for third-line treatment, despite reports of lower efficacy for HDCT in the third- or later line setting compared to second-line.[16] Risk-stratified approaches have also been proposed. This controversy between CDCT and HDCT as initial salvage therapy will remain unsettled until results of the international phase III TIGER trial (A031102, E1407, NCT02375204) comparing TIP to HDCT become available.

Limitations of the current study include its retrospective nature, small size of the MSKCC unfavorable-risk subgroup and some IPFSG risk groups after reclassification, and lack of data on long-term toxicity such as cardiovascular disease and secondary malignancies. Nevertheless, to our knowledge, this series represents the largest report of TIP with paclitaxel administered at full dose (250 mg/m^2) in a homogeneous fashion and provides useful important information to patients and oncologists.

In summary, most patients with relapsed GCT and MSKCC favorable-risk features will achieve a durable favorable response with initial salvage TIP. In addition, TIP demonstrated efficacy in patients with metastatic disease displaying adverse prognostic factors, including short relapse-free intervals. These data confirm TIP to be a standard initial salvage chemotherapy option for patients with advanced GCT.

References:

1. Kondagunta, G.V., et al., *Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors.* J Clin Oncol, 2005. **23**(27): p. 6549-55.
2. Motzer, R.J., et al., *Paclitaxel, ifosfamide, and cisplatin second-line therapy for patients with relapsed testicular germ cell cancer.* J Clin Oncol, 2000. **18**(12): p. 2413-8.
3. Mead, G.M., et al., *A phase II trial of TIP (paclitaxel, ifosfamide and cisplatin) given as second-line (post-BEP) salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial.* Br J Cancer, 2005. **93**(2): p. 178-84.
4. Feldman, D.R., et al., *Paclitaxel, Ifosfamide, and Cisplatin Efficacy for First-Line Treatment of Patients With Intermediate- or Poor-Risk Germ Cell Tumors.* J Clin Oncol, 2016. **34**(21): p. 2478-83.
5. Feldman, D.R., et al., *Multicenter randomized phase 2 trial of paclitaxel, ifosfamide, and cisplatin (TIP) versus bleomycin, etoposide, and cisplatin (BEP) for first-line treatment of patients (pts) with intermediate- or poor-risk germ cell tumors (GCT).* Journal of Clinical Oncology, 2018. **36**(15_suppl): p. 4508-4508.
6. Baniel, J., et al., *Late relapse of testicular cancer.* J Clin Oncol, 1995. **13**(5): p. 1170-6.
7. Lorch, A., et al., *Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy.* J Clin Oncol, 2010. **28**(33): p. 4906-11.
8. Lorch, A., et al., *Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database.* J Clin Oncol, 2011. **29**(16): p. 2178-84.
9. McCaffrey, J.A., et al., *Ifosfamide- and cisplatin-containing chemotherapy as first-line salvage therapy in germ cell tumors: response and survival.* J Clin Oncol, 1997. **15**(7): p. 2559-63.
10. Loehrer, P.J., Sr., et al., *Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor.* J Clin Oncol, 1998. **16**(7): p. 2500-4.
11. Feldman, D.R., et al., *TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis.* J Clin Oncol, 2010. **28**(10): p. 1706-13.
12. Adra, N., et al., *High-Dose Chemotherapy and Autologous Peripheral-Blood Stem-Cell Transplantation for Relapsed Metastatic Germ Cell Tumors: The Indiana University Experience.* J Clin Oncol, 2017. **35**(10): p. 1096-1102.
13. Pico, J.L., et al., *A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours.* Ann Oncol, 2005. **16**(7): p. 1152-9.

Table 1. Patient characteristics

	All patients (N=104)	Favorable[a] (N=87)	Unfavorable (N=17)
Age at TIP treatment, years – median (range)	36 (19, 71)	36 (20, 63)	36 (19, 71)
Histology[b]			
Seminoma	28 (27%)	19 (22%)	9 (53%)
Non-seminoma	76 (73%)	68 (78%)	8 (47%)
AFP, ng/mL			
Elevated (>15)	40 (38%)	36 (41%)	4 (24%)
Median elevated value (range)	233 (17.1, 149,000)	233 (17.1, 149,000)	197 (64.6, 615)
HCG[c], U/L			
Elevated (>2.2)	47 (47%)	36 (41%)	11 (65%)
Median elevated value (range)	37.8 (2.3, 79, 162)	40.1 (2.3, 79,162)	36.2 (3.9, 52,845)
Elevation of both AFP and HCG[c]	11 (11%)	10 (12%)	1 (6%)
LDH, U/L			
Elevated (>ULN)	53 (51%)	40 (46%)	13 (76%)
Median elevated value times ULN (range)	1.58 (1.06, 27.5)	1.50 (1.06, 5.52)	1.64 (1.17, 27.5)
Relapse-free interval[d], years – median (range)	0.9 (0.1, 24.4)	1.2 (0.1, 24.4)	0.2 (0.1, 9.2)
Late relapse[d]	30 (32%)	28 (36%)	2 (12%)
IPFSG score prior to TIP[e]			
Very low (-1)	14 (15%)	11 (14%)	3 (20%)
Low (0)	23 (25%)	20 (26%)	3 (20%)
Intermediate (1)	41 (45%)	36 (47%)	5 (33%)
High (2)	14 (15%)	10 (13%)	4 (47%)
Number of metastatic sites – median (range)	1 (0, 6)	1 (0, 6)	2 (1, 4)
0 (elevated markers only)	3 (3%)	3 (4%)	0 (0%)
1	56 (54%)	51 (59%)	5 (29%)
≥2	45 (43%)	33 (38%)	12 (71%)
Prior chemotherapy[f,g]			
EP[h]	46 (44%)	38 (44%)	8 (47%)
BEP or VIP	44 (42%)	35 (41%)	9 (53%)
VAB-6 or other similar	10 (10%)	10 (11%)	0 (0%)
Etoposide + carboplatin +/- bleomycin	3 (3%)	3 (3%)	0 (0%)

Abbreviations: TIP, paclitaxel, ifosfamide, and cisplatin; ULN, upper limit of normal; HCG, human chorionic gonadotrophin; AFP, alpha-fetoprotein; LDH, lactate dehydrogenase; BEP, bleomycin, etoposide, cisplatin; VIP, etoposide, ifosfamide, cisplatin; VAB-6, cisplatin, vinblastine, dactinomycin, bleomycin, and cyclophosphamide; IPFSG, international prognostic factor study group.

[a]Includes previously reported (n=46) and newly reported (n=41) patients.

[b]One seminoma patient from the previously reported favorable cohort had elevated AFP and is classified as seminoma to match previous reporting.

[c]HCG missing for 3 patients from the previously reported favorable cohort.

[d]Relapse-free interval not reported for 10 contralateral patients.

[e]Ten and 2 patients were not able to have an IPFSG score assigned in the favorable- and unfavorable-risk cohorts, respectively. No patients were classified as very high.

[f]One prior cisplatin-based regimen in the favorable cohort could not be classified due to lack of confirmatory chemotherapy records.

[g]Ten patients in the favorable-risk cohort received TIP as first-line chemotherapy for a new GCT primary after prior chemotherapy for a contralateral testicular GCT

[h]One patient in the unfavorable cohort underwent primary retroperitoneal lymph node dissection with two cycles of adjuvant EP, not four cycles, but had progression 4 months after adjuvant chemotherapy.

Table 2. Treatment efficacy

	All patients (N=104)	**Favorable (N=87)**	**Unfavorable (N=17)**
Favorable Response Rate (FRR)	82 (79%)	69 (79%)	13 (76%)
Complete response (CR)	65 (63%)	59 (68%)	6 (35%)
Chemotherapy alone	59 (57%)	53 (61%)	6 (35%)
Chemotherapy + surgery[a]	6 (6%)	6 (7%)	0 (0%)
Partial response with negative markers (PR-)	17 (16%)	10 (11%)	7 (41%)
Incomplete response (IR)	22 (21%)	18 (21%)	4 (24%)
Favorable Response Rate by Subtype			
Seminoma	25 (89%)	18 (95%)	7 (78%)
Non-Seminoma	57 (75%)	51 (75%)	6 (75%)
Favorable Response in late relapse patients	17 (57%)	16 (57%)	1 (50%)
Favorable Response by IPFSG score			
Very low (-1)	13 (93%)	11 (100%)	2 (67%)
Low (0)	21 (91%)	18 (90%)	3 (100%)
Intermediate (1)	32 (78%)	28 (78%)	4 (80%)
High (2)	4 (29%)	2 (20%)	2 (50%)
Marker normalization with TIP[b]	68 (78%)	55 (77%)	13 (81%)
Relapse[c]	13 (16%)	10 (14%)	3 (23%)
Progression-free survival, %			
5-year (95% CI)	66 (55, 74)	67 (56, 76)	59 (33, 78)
10-year (95% CI)	62 (52, 71)	63 (52, 73)	59 (33, 78)
Overall survival, %			
5-year (95% CI)	69 (59, 77)	72 (61, 80)	56 (28, 76)
10-year (95% CI)	66 (55, 75)	68 (56, 77)	56 (28, 76)

[a]Complete resection of residual masses following chemotherapy with pathology at resection demonstrating viable GCT.

[b]Of 71 patients with elevated pre-treatment markers in the favorable and 16 in the unfavorable cohorts.

[c]In patients with favorable response

Table 3. Chemotherapy treatment

	All patients (N=104)	Favorable (N=87)	Unfavorable (N=17)
Completed full dose TIPx4	83 (80%)	72 (83%)	11 (65%)
Completed full dose TIPx4 without delay >7 days	63 (61%)	54 (62%)	9 (53%)
Any deviation from planned TIPx4[a]	41 (39%)	33 (38%)	8 (47%)
Dose delay >7 days	28 (27%)	23 (26%)	5 (29%)
Dose reduction	6 (6%)	4 (5%)	2 (12%)
<4 cycles of TIP	21 (20%)	15 (17%)	6 (35%)
Cisplatin switched to carboplatin	2 (2%)	0 (0%)	2 (12%)
Reason for dose delay >7 days (n=28)			
Cytopenia	14 (50%)	12 (52%)	2 (40%)
Infection	15 (54%)	12 (52%)	3 (60%)
Renal insufficiency	5 (18%)	3 (13%)	2 (40%)
Other	9 (32%)	7 (30%)	2 (40%)
Reason for <4 cycles of TIP (n=21)[b]			
Progressive disease	9 (43%)	8 (53%)	1 (17%)
Renal insufficiency	5 (24%)	2 (13%)	3 (50%)
Infection	5 (24%)	3 (20%)	2 (33%)
Neuropathy	3 (14%)	2 (13%)	1 (17%)
Other[c]	6 (29%)	4 (27%)	2 (33%)

[a]Ten patients in the favorable cohort had two deviations (dose delay and <4 cycles TIP, n=7; dose delay and dose reduction, n=2; dose reduction and <4 cycles TIP, n=1). Three patients in the unfavorable cohort had two deviations (dose delay and carboplatin switch; dose delay and dose reduction; dose delay and <4 cycles TIP) and 1 patient had three deviations (dose delay, dose reduction and carboplatin switch).

[b]Some patients had more than one reason for receipt of <4 cycles of TIP so numbers do not add up to 21;

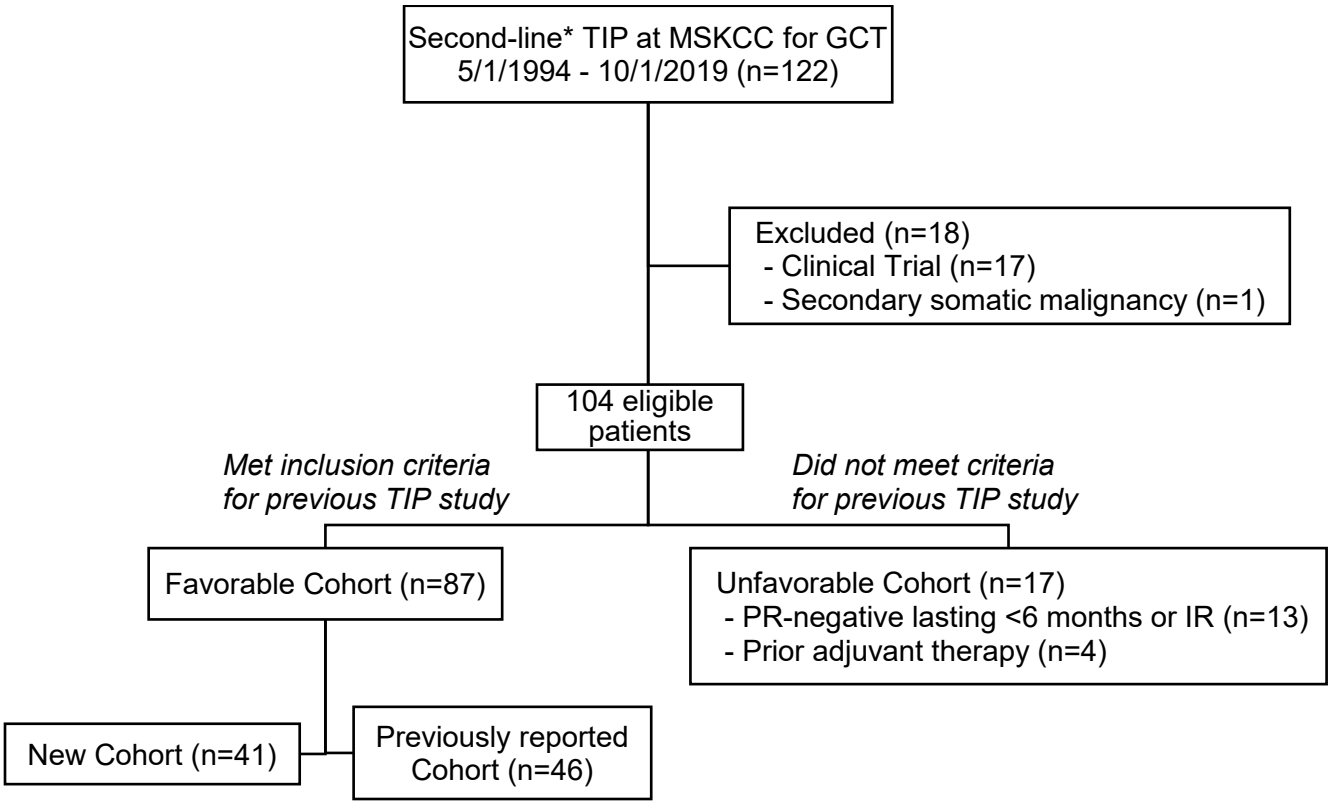
[c]Other reasons for not completing 4 cycles of TIP included: hypersensitivity reaction to paclitaxel in 1 patient, receipt of 1 cycle of BEP at an outside hospital prior to 3 cycles of TIP for a total of 4 cycles in 1 patient, thrombocytopenia in 1 patient, pulmonary toxicity in 1 patient, and multisystem complications in 2 patients including the one treatment-related death[5],

Table 4. Hematologic toxicity

	All patients (N=58[a])	Favorable (N=41[a])	Unfavorable (N=17)
Nadir hemoglobin, g/dL			
Median (range)	7.2 (5.3, 11.0)	7.4 (5.3, 11.0)	6.8 (5.7, 9.3)
<7	26 (45%)	17 (41%)	9 (53%)
RBC transfusions			
No. of patients	37 (64%)	25 (61%)	12 (71%)
No. of units – median (range)	5 (1, 19)	5 (1, 19)	7 (3, 14)
Nadir platelet count, $x10^9$/L			
Median (range)	33.5 (4, 204)	34 (4, 204)	33 (7, 77)
<20	21 (36%)	15 (37%)	6 (35%)
Platelet transfusions			
No. of patients, n (%)	24 (41%)	16 (39%)	8 (47%)
No. of units – median (range)	4 (1, 25)	3 (1, 25)	8 (1, 21)
Neutropenic Fever	27 (47%)	20 (49%)	7 (41%)

[a]Reported for 58 patients not treated as part of the phase II clinical trial. Data for the original 46 patient cohort has previously been published (Kondagunta et al, JCO 2005)

Supplemental Figure 1: Flowchart of patient inclusion



*Ten patients in the favorable-risk cohort received TIP as first-line chemotherapy for a new GCT primary after prior chemotherapy for a contralateral testicular GCT

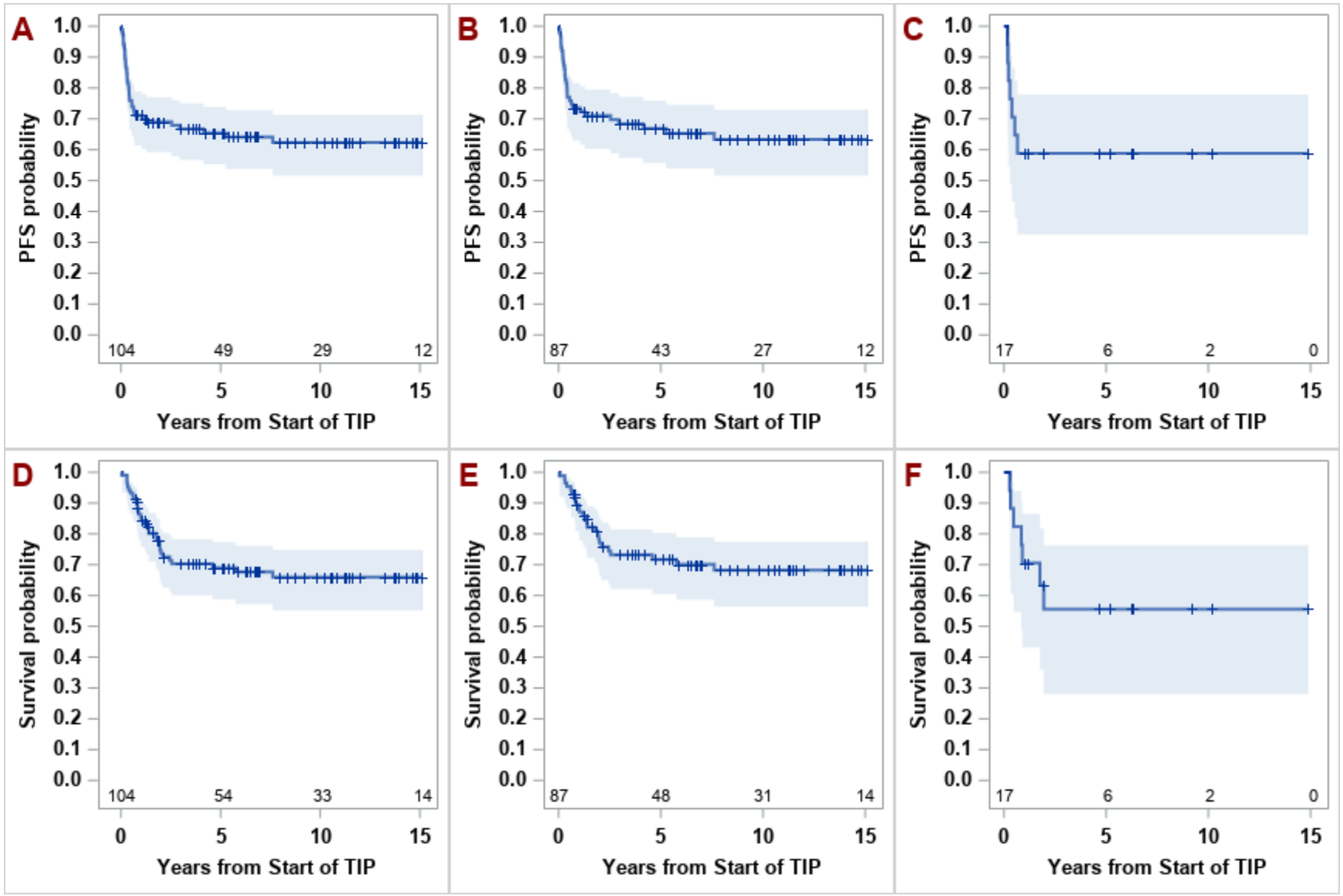


Figure 1 A-F. Progression-free survival (PFS) in all patients (panel A, 37 events), MSKCC favorable-risk cohort (panel B, 30 events) and MSKCC unfavorable-risk cohort (panel C, 7 events) and overall survival (OS) for all patients (panel D, 32 events), MSKCC favorable-risk cohort (panel E, 25 events) and MSKCC unfavorable-risk cohort (panel F, 7 events).

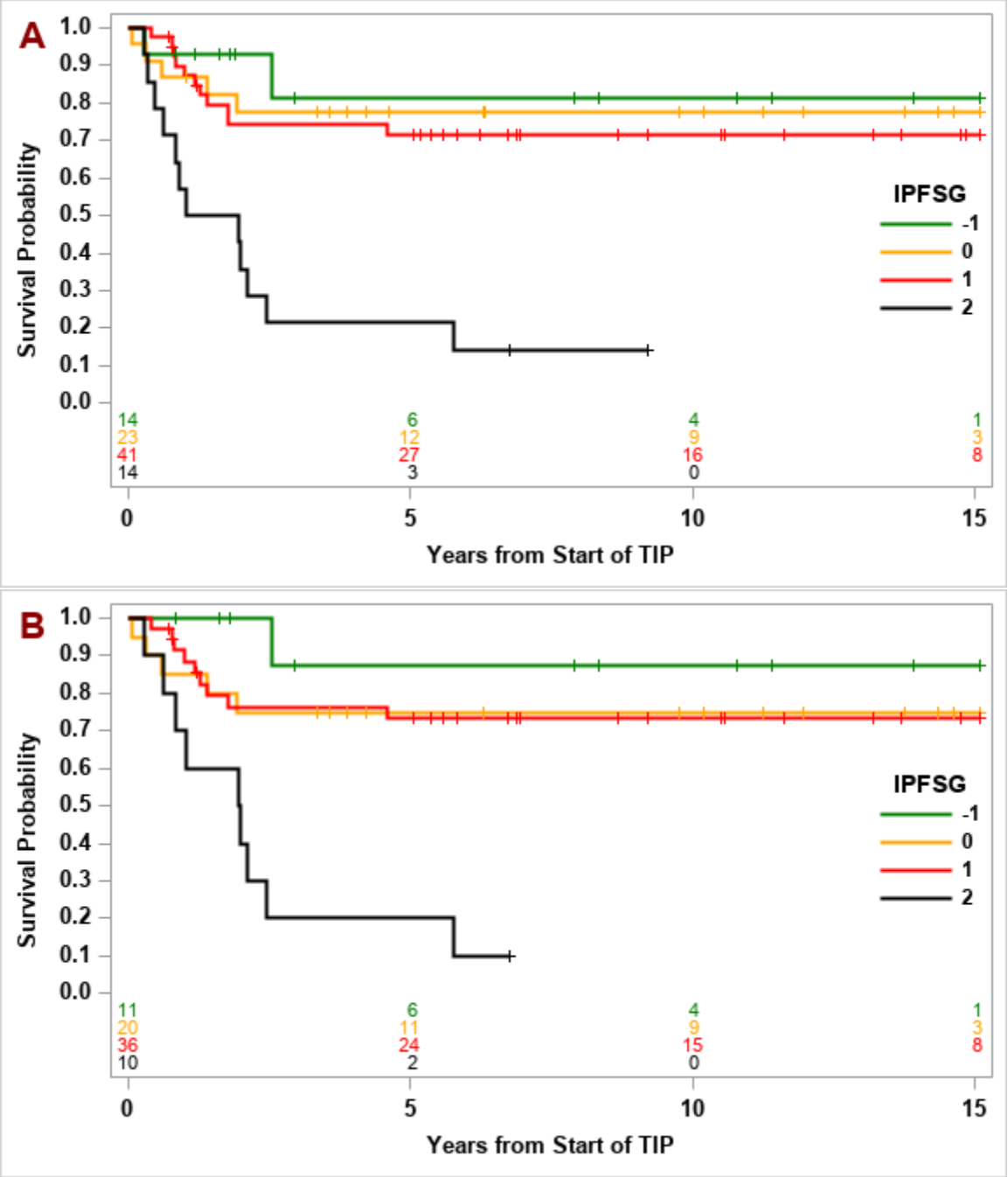


Figure 2A-B: OS by IPFSG group in all patients (panel A) and favorable cohort (panel B).

Among all patients, 5-year OS in very low, low, intermediate, and high risk IPFSG groups is 81% (42%, 95%), 78% (55%, 90%), 72% (55%, 83%) and 21% (5%, 45%), respectively.

In the favorable cohort, 5-year OS in very low, low, intermediate, and high risk IPFSG groups is 88% (95% CI: 39, 98), 75% (95% CI: 50, 89), 73% (95% CI: 55, 85) and 20% (95% CI: 3, 48), respectively.