

## RESEARCH ARTICLE

# Extracranial germ cell tumours in children and adolescents: Results from the French TGM13 protocol

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[Correction added on 14 January 2023 after first online publication: In this version, the order of the corresponding author's first and last names has been corrected.]

## Abstract

**Background:** Chemotherapy for non-seminomatous germ cell tumours (NSGCT) exposes to dose-dependent toxicities. The TGM13-NS protocol (EudraCT 2013-004039-60) aimed to decrease the chemotherapy burden compared to the previous TGM95 protocol while maintaining the 5-year event-free survival (EFS) at 80% or more.

**Abbreviations:** AFP, alpha-fetoprotein; AUC, area under the curve; EFS, event-free survival; ENT, ear-nose-throat; FFS, failure-free survival; GCT, germ cell tumour; GFR, glomerular filtration rate; HCG, human chorionic gonadotropin; HR, high risk; IR, intermediate risk; LDH, lactate dehydrogenase; LR, low risk; NSGCT, non-seminomatous germ cell tumours; OS, overall survival; TGM, tumeur germinale maligne; TM, tumour marker; TNM, tumour-nodes-metastases; TTN, time to normalisation; VBP, vinblastine-bleomycin-cisplatin; VIP, etoposide-ifosfamide-cisplatin.

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**Procedure:** Patients less than 19 years of age with disseminated NSGCT were enrolled (May 2014 to May 2019) and stratified into four groups: two intermediate-risk (IR: localised tumour with low tumour markers [TM]) groups treated with VBP (vinblastine–bleomycin–cisplatin): three courses for IR1 (ovarian tumour any age/testis tumour less than or equal to 10 years) and four courses for IR2 (extragonadal tumour 10 years or less) groups, and two high-risk (HR: metastatic and/or high TM) groups treated with etoposide–cisplatin and either ifosfamide (VIP) or bleomycin (BEP): three courses for HR1 (ovarian tumour any age/testis tumour less than or equal to 10 years and low TM/testis tumour more than 10 years and very low TM) groups and four courses for HR2 (remainder) groups.

**Results:** One hundred fifteen patients were included: median age of 12.8 years (0.4–18.9); tumour sites: 44 ovaries, 37 testes and 34 extragonadal. The 5-year EFS and overall survival (OS) were 87% (95% CI: 80–92) and 95% (89–98), respectively (median follow-up: 3.5 years, range: 0.2–5.9), similar to those of the TGM95 protocol (5-year EFS 89% (84–93), 5-year OS 93% (89–95),  $p = .561$ ). The 5-year EFS were 93% (95% CI: 80–98), 88% (71–95) and 79% (62–90) for ovarian, testicular and extragonadal tumours, respectively. The 5-year EFS varied ( $p = .02$ ) according to the risk groups: 90% (66–97), 64% (30–85), 95% (72–99) and 87% (74–94) for IR1, IR2, HR1 and HR2, respectively. TM decline adjusted to tumour site, and alpha-fetoprotein (AFP) level revealed a prognostic impact of time to normalisation on EFS: HR = 1.03 (1.003–1.007).

**Conclusion:** Risk-adapted and globally decreased chemotherapy burden maintains excellent outcomes, exclusive of the IR2 group, which warrants more intensive chemotherapy.

**KEYWORDS**

chemotherapy, children, germ cell tumours, tumour marker decline

## 1 | INTRODUCTION

The prognosis for disseminated (i.e., tumour-nodes-metastases [TNM] stage 2, 3 or 4) non-seminomatous germ cell tumours (NSGCT) is generally excellent because of cisplatin-based chemotherapy, although the latter exposes to significant dose-dependent toxicities. Long-term studies in germ cell tumour (GCT) survivors have reported kidney and auditive toxicities (the latter impairing speech development in young children), as well as secondary malignancies, cardiovascular, neurologic and pulmonary toxicities, and infertility.<sup>1–3</sup> A general cisplatin cumulative dose threshold of 400 mg/m<sup>2</sup> has been reported, above which the toxicity increases dramatically.<sup>4</sup> The French paediatric tumeur germinale maligne (TGM)95 protocol was based on an 'n + 2 strategy', where 'n' was the number of chemotherapy courses to tumour marker (TM) normalisation implemented by two additional courses. The outcomes were excellent, with a 5-year event-free survival (EFS) above 85% and a 5-year overall survival (OS) above 90%.<sup>5</sup> Nevertheless, the cumulative doses of cisplatin were high: the median number of cisplatin courses was four (equivalent to a 400 mg/m<sup>2</sup> cumulative dose

of cisplatin) and up to seven in the intermediate-risk (IR) group and five (equivalent to a 500 mg/m<sup>2</sup> cumulative dose of cisplatin) and up to nine in the high-risk (HR) group, raising concerns regarding potential long-term sequelae. This was the rationale of the subsequent therapy-decreasing TGM13-NS protocol presented here, for which the main objective was to maintain a high cure rate while also decreasing the cumulative dose of chemotherapy and especially the cumulative dose of cisplatin delivered.

## 2 | MATERIALS AND METHODS

TGM13-NS (Eudract 2013-004039-60) was open to enrolment from May 2014 through May 2019 in 29 French and seven Belgian centres. Patients were younger than 19 years of age and exhibited an extracranial IR or HR NSGCT based on either histological confirmation or clinical evidence and elevated serum human chorionic gonadotropin (HCG) or alpha-fetoprotein (AFP) concentrations. Patients with a low-risk (LR) NSGCT (defined as a post-surgical TNM stage I gonadal

**TABLE 1** Risk group stratification

Site/stage	Age	Tumour markers	Risk group
TNM stage 2 or 3 <sup>a</sup> ovarian tumour	Any	AFP < 10,000 ng/ml + HCG < 5000 IU/L	IR1: 3 courses of VBP
		AFP ≥ 10,000 ng/ml or HCG ≥ 5000 IU/L	HR1: 3 courses of VIP
TNM stage 2 or 3 <sup>a</sup> testis tumour	≤10 years	AFP < 10,000 ng/ml + HCG < 5000 IU/L	IR1: 3 courses of VBP
		AFP ≥ 10,000 ng/ml or HCG ≥ 5000 IU/L	HR1: 3 courses of VIP
	>10 years	AFP < 1000 ng/ml + HCG < 5000 IU/L + LDH < 1.5 ULN	HR1: 3 courses of VIP
		AFP ≥ 1000 ng/ml or HCG ≥ 5000 IU/L or LDH ≥ 1.5 ULN	HR2: 4 courses of VIP
TNM stage 2 or 3 <sup>a</sup> extragonadal tumour	≤10 years	AFP < 10,000 ng/ml + HCG < 5000 IU/L	IR2: 4 courses of VBP
		AFP ≥ 10,000 ng/ml or HCG ≥ 5000 IU/L	HR2: 4 courses of VIP
	>10 years	All	HR2: 4 courses of VIP
		All	HR2: 4 courses of VIP
TNM stage 4 <sup>b</sup> tumour	Any	All	HR2: 4 courses of VIP

Note: BEP alternative to VIP for post-pubertal patients.

Abbreviations: BEP, bleomycin-etoposide-cisplatin; TNM, tumour-nodes-metastases; ULN, upper limit of normal; VBP, velbe-bleomycin-cisplatin; VIP, etoposide-ifosfamide-cisplatin.

<sup>a</sup>Equivalent to a COG stage 2 or 3.

<sup>b</sup>Equivalent to a COG stage 4.

tumour) were included in a surveillance programme and became eligible for this trial if they experienced a relapse.

The standard requirements at study entry were a documented medical history, physical examination and AFP and HCG TMs assessment. Lactate dehydrogenase (LDH) was also assessed in case of testicular tumours. The imaging workup was adapted to the tumour site and aimed to assess the TNM staging.

The initial surgery was performed when a complete tumour resection was possible with non-mutilating surgery (mostly in case of gonadal tumours). In case of bulky or metastatic tumours, a delayed post-chemotherapy tumour resection was recommended. Complete resection was defined as follows: 'en bloc' tumour resection including the organ of origin (gonadal, coccyx), without tumour rupture and with histologically free resection margins.

Two IR groups and two HR groups were defined (Table 1) according to previously reported prognostic factors<sup>6–8</sup>: stage (locally advanced vs. metastatic), tumour site (ovary/testis/extragonadal), age (≤10 years or >10 years) and TM level (AFP <10,000 or ≥10,000 ng/ml, HCG <5000 or ≥5000 IU/L, LDH <1.5 times or ≥1.5 times the upper limit of normal).

Patients in the IR group received vinblastine-bleomycin-cisplatin (VBP) chemotherapy: vinblastine 3 mg/m<sup>2</sup>/day, days 1–2; bleomycin 15 mg/m<sup>2</sup>/day, days 1–2; and cisplatin 33 mg/m<sup>2</sup>/day, days 3–5. Patients received either three courses in the IR1 group or four courses in the IR2 group. Patients in the HR group received VIP chemotherapy (etoposide 75 mg/m<sup>2</sup>/day, days 1–5; ifosfamide 3 g/m<sup>2</sup>/day, days 1–2; and cisplatin 20 mg/m<sup>2</sup>/day, days 1–5). Patients received three courses in the HR1 group and four courses in the HR2 group. At the physician's discretion, post-pubertal patients in the HR groups could receive BEP chemotherapy (etoposide 100 mg/m<sup>2</sup>/day, days 1–5; bleomycin 30 mg on days 1, 8, and 15; cisplatin 20 mg/m<sup>2</sup>/day, days 1–5) instead of VIP, provided pulmonary function assessment allowed for it.

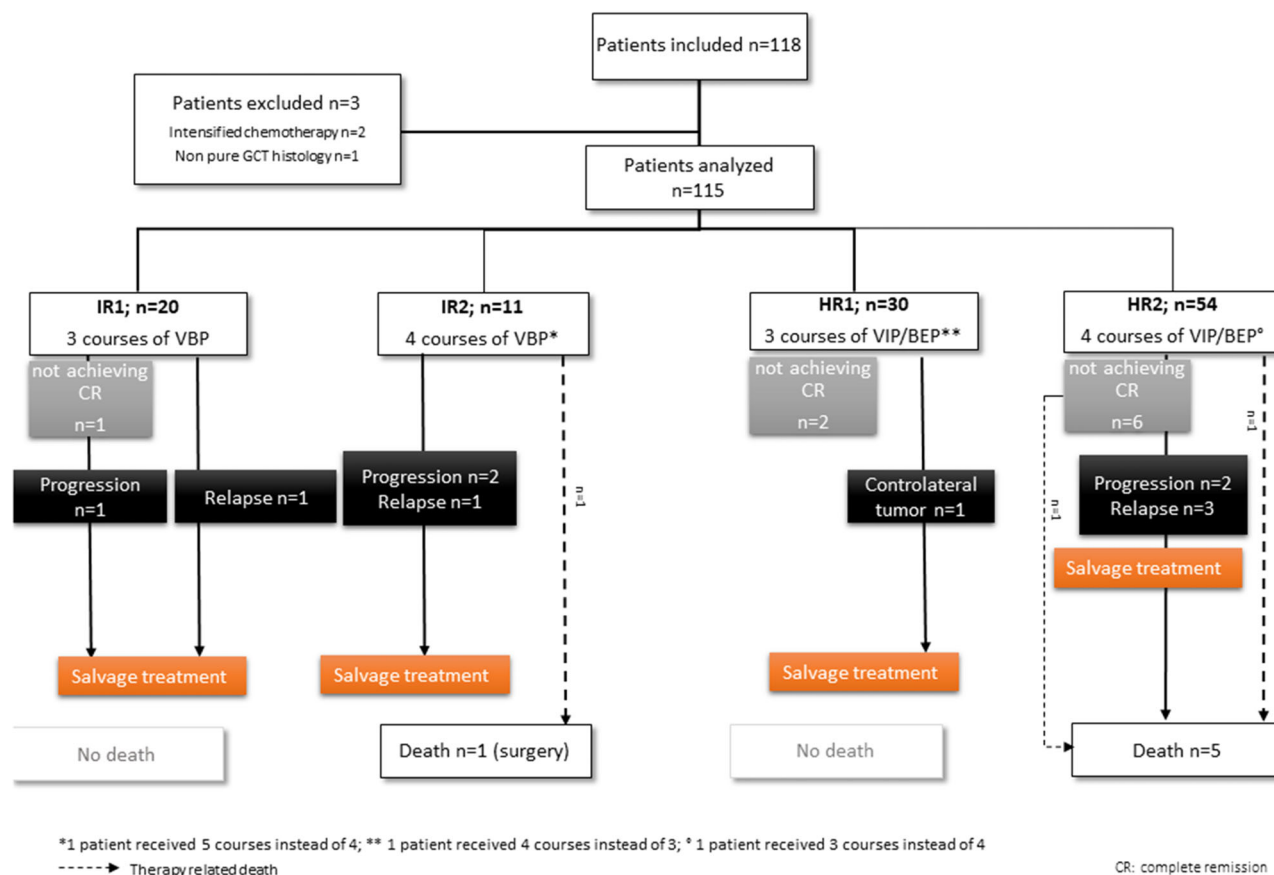
After three or four cycles of chemotherapy (depending on the risk group), an evaluation of the response was conducted based on serum TM levels and radiologic imaging. Second-look surgery was recommended for patients with a residual mass. A complete response was defined as normalisation of TMs with either no radiologic evidence of disease or a residual mass with no viable malignant tumour. Patients who achieved a complete response did not receive any further chemotherapy. Patients in incomplete remission (TMs above the upper limit of normal for age or incompletely resected viable residue) after a first-line treatment, including chemotherapy and surgery, received a second-line treatment: VIP for patients treated with VBP or BEP, and VBPA (vinblastine, bleomycin, cisplatin and adriamycin) for patients treated with VIP. Patients experiencing tumour progression or relapse (increasing TM and size of the tumour or appearance of new lesions) received a salvage treatment.

Renal toxicity was monitored by measurement of the glomerular filtration rate (GFR) according to the Schwartz formula before each chemotherapy course and during follow-up. A Schwartz-estimated GFR above 90 ml/min/1.73 m<sup>2</sup> was considered to be normal.<sup>9</sup> Nephrotoxicity was graded according to the CTCAE v4.0 scale. Audiograms were graded according to the Brock scale.<sup>10</sup>

Written informed consent was obtained from all patients/guardians at diagnosis, and the national ethics review boards approved the trial.

### 3 | STATISTICAL ANALYSIS

A Fleming single-arm, single-stage, phase 2 trial was used to calibrate the sample size. The study was designed to reject the null hypothesis of a 2-year progression-free survival (PFS) rate of less than or equal to 80% with a type I error of 0.05 and a statistical power of 85% at the alternative hypothesis of a 2-year PFS rate of 90% or more. With this hypothesis, 94 patients evaluable at 2 years were needed.



**FIGURE 1** CONSORT diagram

Survival curves for EFS (time from enrolment until disease progression, second malignant neoplasm, death or last patient contact, whichever occurred first) and OS (time from enrolment until death or last patient) were analysed using the Kaplan–Meier method. Patients who were not in complete remission at the end of the first-line treatment and thus received a second-line treatment (i.e., they received more than the initially scheduled therapy) were assessed based on failure-free survival (FFS, time from diagnosis to event or second-line treatment). Growing teratomas were not considered to represent an event. Comparisons of the TGM13 and TGM95 survival distributions were assessed using the log-rank test.

TM decline was assessed after the first course (C1) of chemotherapy. It was calculated using two values: the AFP baseline value ( $M_0$ , assessed 10 days before to 2 days after C1) and the AFP value obtained after one course of chemotherapy ( $M_1$ , assessed 18 days after C1 to 2 days after the second course).  $M_N$  represented the normal AFP value.

TM decline was assessed through three distinct methods:

- Method 1<sup>1</sup> "Fizazi method"<sup>11</sup>: The decline rate was expressed as a theoretical number of weeks necessary to normalisation. That was called predicted time to normalisation (TTN):  $TTN = 3 a/b$ , with  $a = \log(M_0) - \log(M_N)$ ,  $b = \log(M_0) - \log(M_1)$ . TTN was either considered as a quantitative variable (number of weeks to normalisation) or a qualitative binary variable (favourable TM decline defined as:

TTN less than 9 weeks or normalised  $M_1$  value; or unfavourable TM decline: TTN of more than or equal to 9 weeks or increased  $M_1$  value).

- Method 2<sup>2</sup> "AFP change": Difference between AFP values at baseline and after the first chemotherapy course (expressed as  $\log_{10}$ ).<sup>5</sup>
- Method 3<sup>3</sup> "O-E AUC": Difference between the observed (O) and the expected (E) area under the curve (AUC), based on a 7-day AFP half-life.<sup>5</sup>

To evaluate a possible relationship between clinical parameters, TM decline and EFS, univariate Cox proportional hazard regression models were generated. Clinical covariates that were significant at a 20% alpha level in the univariate analysis were included in the multivariate model to test whether the TM decline was a potential independent prognostic factor. SAS version 9.4 software was used for all statistical analyses (SAS Institute Inc., Cary, NC, USA).

## 4 | RESULTS

### 4.1 | Patient and treatment characteristics

One hundred eighteen patients were enrolled in the TGM13 trial (Figure 1: consort diagram). Two patients in the HR2 group presented

**TABLE 2** Patient characteristics and outcomes

	Risk groups				Total
	IR1	IR2	HR1	HR2	
Number of patients	N = 20	N = 11	N = 30	N = 54	N = 115
Sex					
Male	1 (5%)	2 (18%)	12 (40%)	32 (59%)	47 (41%)
Female	19 (95%)	9 (82%)	18 (60%)	22 (41%)	68 (59%)
Age at diagnosis					
≤10 years	3 (15%)	11 (100.0%)	8 (27%)	24 (44%)	46 (40%)
>10 years	17 (85%)	0	22 (73%)	30 (56%)	69 (60%)
AFP at diagnosis					
<10,000 ng/ml	20 (100%)	10 (91%)	14 (47%)	36 (67%)	80 (70%)
≥10,000 ng/ml	0	1 (9%) <sup>a</sup>	16 (53%)	18 (33%)	35 (30%)
Presence of metastases					
No	20 (100%)	11 (100%)	30 (100%)	14 (26%)	75 (65%)
Yes	0	0	0	40 (74%)	40 (35%)
Primary tumour site					
Testis	1 (5%)	0	12 (40%)	24 (44%)	37 (32%)
Ovary	19 (95%)	0	18 (60%)	7 (13%)	44 (38%)
Sacroccygeal	0	8 (73%)	0	14 (26%)	22 (19%)
Mediastinum	0	0	0	4 (7%)	4 (4%)
Extragonadal other site	0	3 (27%)	0	5 (9%)	8 (7%)
Median follow-up (range) (years)	3.1 (1.0–5.5)	4.5 (0.2–5.9)	4.0 (1.6–5.2)	3.4 (0.2–5.6)	3.5 (0.2–5.9)
Events for EFS	2 (10%)	4 (36%)	1 (3%)	7 (13%)	14 (12%)
Metachronous contralateral disease	0	0	1 (3%) (testis)	0	1 (1%)
Progression/relapse	2 (10%)	3 (27%)	0	5 (9%)	10 (9%)
Death without progression	0	1 (9%)	0	2 (4%)	3 (3%)
5-year EFS (95% CI)	90% (66–97)	64% (30–85)	95% (72–99)	87% (74–94)	87% (80–92)
Deaths	0	1 (9%)	0	5 (9%)	6 (5%)
From tumour	0	0	0	3 (6%)	3 (3%)
From other causes	0	1 (9%)	0	2 (4%)	3 (3%)
5-year overall survival (95% CI)	100% (100–100)	91% (51–99)	100% (100–100)	91% (79–96)	95% (89–98)

Abbreviations: CI, confidence interval; EFS, event-free survival

<sup>a</sup>Despite AFP above 10,000 ng/ml, the patient was treated in the IR2 group due to their young age.

with an International Germ Cell Cancer Consensus Group (IGCCCG) poor prognosis testis tumour<sup>8</sup> and experienced an unfavourable TM decline after the first course of BEP. They hence received dose-dense (paclitaxel-BEP oxaliplatin) treatment according to the GETUG 13<sup>11</sup> and were consequently excluded from the analyses. One patient presented with an ovarian tumour with two contingents of GCT and sex cord stromal tumour and was, therefore, also excluded. Of the 115 remaining patients (68 females, 47 males), 20 were in the IR1, 11 in the IR2, 30 in the HR1 and 54 in the HR2 group (Table 2). The median age was 12.8 years (range: 0.4–18.9). Sixty-eight (59%) were female. The tumour sites were as follows: 44 ovarian tumours (four bilateral tumours and four relapses from a previous LR tumour), 37 testicular tumours (six relapses from a previous

LR tumour), 34 extragonadal tumours including 22 sacroccygeal (seven from a previous neonatal teratoma), four mediastinal and eight extragonadal other sites: four abdominal, two ear-nose-throat (ENT, one from previous ENT teratomas) and two perineal/vaginal tumours. Three had abnormal genetic backgrounds: one phenotypic female patient had a 46,XY karyotype with bilateral ovarian tumours, one phenotypic male had a 47,XXY karyotype (Klinefelter syndrome) with a mediastinal GCT and the third patient had Cowden syndrome with a metastatic testis tumour. Of the 84 patients in the HR group: 36 (43%) were treated with BEP, but when considering only the 15–18-year-old population in the HR group ( $n = 33$ ), the proportion of patients treated with BEP reached 88% ( $n = 29$ ).

**TABLE 3** Patients experiencing an event

Patient/age (years)	Tumour site	Risk group (type of chemotherapy)	Post-treatment status	Type of event	Delay from diagnosis (months)	Salvage treatment	Outcome + FU (months)
1/15	Testis	HR2 (BEP)	No CR	Peritoneal progression	4.5	TICE (1 course)	DOD; 13.8
2/0.8	ENT	IR2 (VBP)	No CR	Focal progression	4.4	VIP + HDCT + orbital exanteration + radiotherapy	NED; 71.3
3/1.5	Vagina	IR2 (VBP)	No CR	Focal progression	5.2	VIP + radiotherapy	NED; 30.1
4/10	Ovary	HR2 (VIP)	CR	Lymph nodes relapse	5.2	VBPA + lymphadenectomy + HDCT + radiotherapy	NED; 65.2
5/15	Abdomen	HR2 (BEP)	No CR	Lymph nodes progression	4.7	TICE	DOD; 12.5
6/15	Testis	HR1 (BEP)	CR	Contralateral testis	32.8	Orchiectomy + VIP	NED; 45.4
7/16	Testis	HR2 (BEP)	No CR	Death from bleomycin lung failure - no progression	9.1	T-BEP-oxaliplatin	DOT; 9.1
8/2.2	Mediastinum	HR2 (VIP)		Death from sepsis after course 1 - no progression	2.1		DOT; 2.1
9/2.5	Testis	HR2 (VIP)	CR	Metastatic relapse (lung)	5.8	VBPA + radiofrequency ablation + HDCT	NED; 33.6
10/14	Ovary	IR1 (VBP)	CR	Lymph nodes relapse	4.5	VIP + HDCT + lymphadenectomy	NED; 65.8
11/17	Mediastinum	HR2 (BEP)	CR	Metastatic relapse (brain)	4.4	Palliative care	DOD; 6.9
12/1	Sacroccygeal	IR2 (VBP)	CR	Local relapse	7.3	VIP + tumorectomy + radiotherapy + HDCT	NED; 42.7
13/0.7	Abdomen	IR2 (VBP)		Death from surgery complication after course 2 - no progression	1.9		DOT; 1.9
14/14.5	Ovary	IR1 (VBP)	No CR	Metastatic progression (liver)	9.7	(second-line VBPA) + VIP + radiofrequency ablation + HDCT	NED; 41.6

Abbreviations: BEP, bleomycin-etoposide-cisplatin; CR, complete remission; DOD, death of disease; DOT, death of toxicity (grey lines); FU, follow-up; HDCT, high-dose chemotherapy; NED, no evidence of disease; TICE, taxol-ifosfamide-carboplatin-etoposide; VBP, vinblastine-bleomycin-cisplatin; VBPA, vinblastine-bleomycin-cisplatin-adriamycin; VIP, etoposide-ifosfamide-cisplatin.

## 4.2 | Post-treatment assessment and outcomes

At the end of the first-line treatment, nine (7%) patients received a second-line treatment for non-remission. The 5-year FFS was 81% (95% CI: 73%–87%).

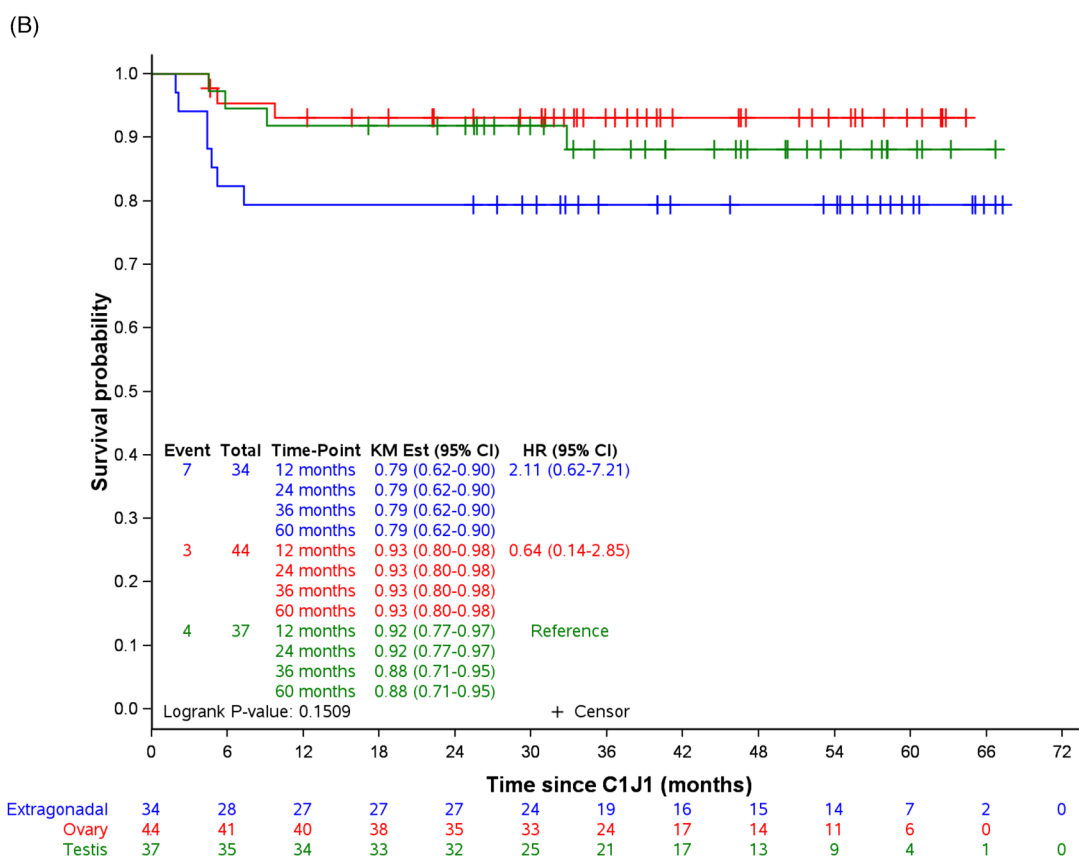
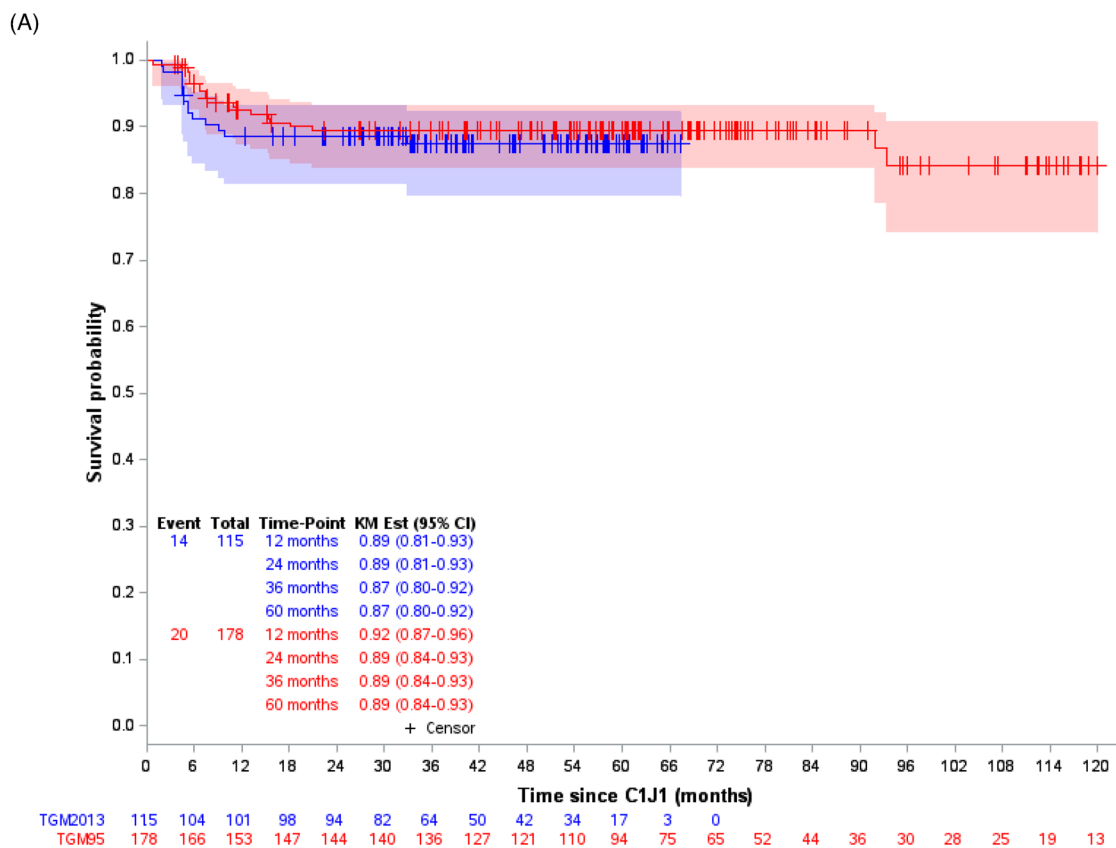
After a median follow-up of 3.5 years (0.2–5.9), a total of 14 events (five relapses, five progressions, one contralateral testicle tumour and three deaths) were reported (Table 3) and no secondary malignancies.

Three deaths occurred without previous disease progression (Table 3, grey lines) either from sepsis (patient 8), post-surgical com-

plications from a growing teratoma (patient 13) or bleomycin-induced lung toxicity (patient 7; cumulative dose of bleomycin reaching 540 mg during second-line treatment).

The 5-year EFS and OS were 87% (95% CI: 80–92) and 95% (95% CI: 89–98), respectively, for the whole population and were comparable (log-rank  $p$ -value for EFS = .561) to those previously reported in the TGM95 protocol (Figure 2A).

The 5-year EFS differed significantly according to the risk group: 90% (95% CI: 66–97), 64% (95% CI: 30–85), 95% (95% CI: 72–99) and 87% (95% CI: 74–94) for IR1, IR2, HR1 and HR2, respectively (log-rank test  $p$  = .02). The 5-year OS were 100%, 91% (95% CI: 51–99),



**FIGURE 2** (A) Event-free survival in the TGM95 and TGM13 protocols. (B) Event-free survival by tumour site in the TGM13 protocol

100% and 91% (95% CI: 79–96) in the IR1, IR2, HR1 and HR2 groups, respectively (log-rank test  $p$ -value = .18).

Depending on the tumour site (Figure 2B), the EFS were inferior, albeit not significantly for extragonadal tumours: the 5-year EFS was 79% (95% CI: 62–90) compared to testicular (5-year EFS 88%; 95% CI: 71–95) or ovarian tumours (5-year EFS 93%; 95% CI: 80–98); log-rank test  $p$ -value = .15.

### 4.3 | Tumour marker decline analyses

Analysis of TM decline (Table 4) showed a prognostic impact of TTN on the EFS after adjustment on tumour site and baseline AFP level: each additional week needed for TM normalisation negatively impacted the EFS (HR = 1.003 [1.000–1.007],  $p$  = .04).

According to TTN qualitative analysis,<sup>12</sup> the EFS (Figure S1) was better albeit non-significantly so in the group of favourable TM decline ( $n$  = 63): 5-year EFS 92% (95% CI: 81–96) compared to the group of unfavourable decline ( $n$  = 44): 84% (95% CI: 69–92) HR = 0.46 (0.15–1.44),  $p$  = .17. Similarly, method 2 'AFP change', after adjustment on tumour site and baseline AFP level, revealed a prognostic impact, albeit non-significant of a log10 variation on EFS (HR = 3.39 [0.92–12.56],  $p$  = .07). Method 3 'O-E AUC' failed to demonstrate a significant impact of TM decline on EFS: HR = 1.19 (95% CI: 0.75–1.90),  $p$  = .45.

### 4.4 | Treatment burden and toxicity

The mean total cumulative dose of cisplatin per patient, including second-line and salvage treatments, was 382 mg/m<sup>2</sup> in the TGM13 protocol, while it was 512 mg/m<sup>2</sup> in the TGM95 protocol. With a median delay of 33 months (range: 2–65 months) from diagnosis to the last toxicity assessment, 114 patients had renal assessments, nine (8%) experienced nephrotoxicity, and all were grade 1 (Schwartz-estimated GFR 89 to 60 ml/min/1.73 m<sup>2</sup>) (Table S1). These nine patients received a total median dose of 455 mg/m<sup>2</sup> (range: 300–600 mg/m<sup>2</sup>) of cisplatin and a total dose of 10 g/m<sup>2</sup> (range: 0–24 g/m<sup>2</sup>) of ifosfamide. With a median delay of 10.3 months from diagnosis to the last toxicity assessment (range: 1–63), 112 patients had audiometric assessments, of whom 19 (17%) experienced ototoxicity, 12 of which were Brock grade 1, three were grade 2, one was grade 4 and three were not graded. The patients with grade 4 ototoxicity had received 400 mg/m<sup>2</sup> cisplatin and a salvage treatment with a high dose of carboplatin (TICE regimen<sup>13</sup>) in addition to the first-line treatment.

## 5 | DISCUSSION

With a fixed and reduced number of chemotherapy courses compared to the previous French experience<sup>5</sup> and consequently lower cumulative doses of cisplatin administered to the patients, the 5-year EFS and FFS of the current study remained excellent and similar to those of

the previous protocol TGM95, with the follow-up exceeding the HR period of relapse.<sup>14</sup> It is, therefore, probable that three or four courses of cisplatin-based chemotherapy are enough to cure most patients, and this number has hence been adopted by most of the cooperative paediatric and adult protocols. Risk group stratification relied on the results of the previous TGM95 protocol and was designed before the publication of the revised paediatric GCT classification published in 2015.<sup>6</sup> Interestingly, similarities regarding the detrimental impact of age above 10 years (11 years in the revised classification) and an extragonadal side were observed in both analyses. Conversely, levels of TMs were not considered in the revised classification, whereas they had an impact in a previous French series<sup>7</sup> and thus were incorporated in the current trial.

As already reported in the paediatric<sup>6,7,15</sup> and adult literature on GCTs,<sup>8</sup> extragonadal tumours have a higher risk of progression. In the current series, the 5-year EFS was inferior in the IR2 group (extragonadal tumours treated with VBP) compared with the other risk groups. The inferiority of VBP compared with BEP was reported in the late 1980s for adults with bulky disease.<sup>16</sup> By contrast, the outcomes in the IR1 group (where only gonadal tumours were treated with VBP) were excellent. We can hence conclude that the VBP regimen is suitable in children with IR gonadal tumours, but it is not sufficient to cure IR extragonadal tumours.

Five second malignancies were observed in the TGM95 protocol, leading to one death, whereas none were reported in the current protocol, which can, not surprisingly, be explained by a limited follow-up duration.

In adults, a randomised controlled trial has reported a similar efficacy of BEP versus VIP,<sup>17</sup> and it underpinned the rationale for letting the investigator choose between these regimens. In the adolescent and young adult population, the BEP combination has been clearly favoured, probably encouraged by less reported hematologic and gonadal toxicity with the BEP regimen compared to VIP<sup>17</sup> and increasing collaboration between paediatricians and oncologists, through shared multidisciplinary team boards.

TM decline is a strong prognostic factor in adults with poor-risk testicular GCT.<sup>12</sup> Whether or not it can apply in the paediatric area is still to be seen. In the TGM95 protocol, where the number of chemotherapy courses was dependent on TM normalisation, the impact of TTN on the outcomes was not demonstrable.<sup>5</sup> In the current protocol, where a fixed number of courses was applied, we found that there was a significant impact of TTN on EFS and a larger even non-significant impact of 'AFP change' on prognosis, although, as the study was not calibrated for this endpoint, the small sample size and the paucity of events precluded accurate identification of the best method for TM decline assessment. Other methods to evaluate the impact of TM decline on prognosis may be more suitable than TTN and are currently assessed through an international meta-analysis in paediatric GCTs. Nevertheless, the entire concept of using early TM decline as a prognostic factor is debatable, as resistant clones may be selected through chemotherapy cycles, thus preventing the TM decline to follow the logarithmic decrease predicted in the initial 3 weeks of treatment.

**TABLE 4** Univariate and multivariate analysis of TM decline adjusted on clinical parameter to predict EFS

Parameter	Factor label	Events/N	Univariate analysis		Multivariate analysis (model 1 <sup>a</sup> )		Multivariate analysis (model 2 <sup>b</sup> )	
			Hazard ratio (95% CI)	p-Value	Hazard ratio (95% CI)	p-Value	Hazard ratio (95% CI)	p-Value
Method 1								
FIZAZI quantitative (weeks)		11/103	1.028 (1.003–1.053)	.028	1.003 (1.000–1.007)	.0453		
Method 1								
FIZAZI qualitative (9 weeks cut-off)				.183				
	Unfavourable TM decline	7/44	1					
	Favourable TM decline	5/63	0.458 (0.145–1.445)					
Method 2: AFP change (log)		11/105	2.875 (0.86–9.59)	.086			3.390 (0.92–12.56)	.0676
Method 3: O-E AUC		11/105	1.195 (0.75–1.90)	.453				
Age at diagnosis				.794				
	≤10 years	6/46	1					
	>10 years	8/69	0.868 (0.31–2.50)					
AFP level at diagnosis				.080		.0485		.0574
	<10,000 ng/ml	13/80	1		1		1	
	≥10,000 ng/ml	1/35	0.162 (0.02–1.24)		0.119 (0.014–0.986)		0.128 (0.015–1.067)	
Extent of disease				.921				
	Non-metastatic	9/73	1					
	Metastatic	5/42	0.946 (0.32–2.82)					
Primary tumour site				.179		.1842		.0515
	Testis	4/37	1		1		1	
	Ovary	3/44	0.637 (0.14–2.85)		1.42 (0.28–7.13)		1.47 (0.30–7.30)	
	Extragenadal	7/34	2.110 (0.62–7.21)		3.68 (0.83–16.18)		5.94 (1.27–27.7)	

Abbreviations: CI, confidence interval; EFS, event-free survival; O-E AUC, difference between the observed (O) and the expected (E) area under the curve (AUC); TM, tumour marker.  
<sup>a</sup>Model 1: Multivariate Cox model to test the prognostic impact of method 1 (FIZAZI quantitative decline method) when adjusted on clinical parameters shown to be prognostic at 20% alpha level in the univariate model.  
<sup>b</sup>Model 2: Multivariate Cox model to test the prognostic impact of method 2 (AFP change) when adjusted on clinical parameter shown to be prognostic at 20% alpha level in the univariate model.

The main goal of this therapy-decreasing protocol was to spare patients from potential long-term sequelae. For various reasons (higher median age, genetic background and possibly the modalities of cisplatin infusion), patients treated with the same cumulative dose of cisplatin can experience less hearing loss when treated for a GCT than for other tumour types such as hepatoblastoma or neuroblastoma.<sup>18,19</sup> However, the frequency of cisplatin-induced audiologic and nephrologic toxicity has not been systematically reported in GCT protocols, including the TGM95. With cisplatin-related toxicity being dose-dependent and increasing with higher cumulative doses,<sup>20</sup> we expect the long-term sequelae to be inferior in the TGM13 compared to the TGM95 protocol. In the literature, as in the current series, grade 3 and 4 ototoxicity and nephrotoxicity were rare with four courses of cisplatin-based chemotherapy.<sup>11,20</sup>

## 6 | CONCLUSION

Risk-adapted strategy with fixed three or four courses of cisplatin-based chemotherapy leads to a high cure rate and presumably less potential treatment-related toxicity. The VBP scheme appears to be insufficient for extragonadal tumours. Quantitative analysis of TM decline suggests a significant impact of TTN on prognosis, but this deserves a larger study, possibly through international meta-analysis.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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## SUPPORTING INFORMATION

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