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Randomized Phase II Trial of Vincristine-Irinotecan With or Without Temozolomide, in Children and Adults With Relapsed or Refractory Rhabdomyosarcoma: A European Paediatric Soft Tissue Sarcoma Study Group and Innovative Therapies for Children With Cancer Trial

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abstract

PURPOSE The VIT-0910 trial was conducted to evaluate efficacy and safety of the vincristine-irinotecan combination with and without temozolomide (VIT and VI, respectively) in relapsed or refractory rhabdomyosarcoma (RMS).

METHODS In this randomized European phase II trial, patients age 0.5-50 years received 21-day cycles combining vincristine (1.5 mg/m^2 once a day on day 1 and day 8) and irinotecan (50 mg/m^2 once a day from day 1 to day 5) with and without temozolomide (125 mg/m^2 once a day from day 1 to day 5 and 150 mg/m^2 once a day from cycle 2), until progression or unacceptable toxicity. The primary end point was objective response rate after two cycles. Secondary end points included best response, progression-free survival, overall survival, and adverse events. A Simon 2-stage design was initially planned to separately analyze 40 patients/arm. After amendment, the trial sample size was increased to 120 and a comparison between arms, adjusted for confounding factors, was added to the statistical plan (ClinicalTrials.gov, NCT01355445).

RESULTS Overall, 120 patients (60 per arm) were recruited in 37 European centers. The median age was 11 years (range, 0.75-45); 89% of patients had a relapsed RMS. The objective response rate was 44% (24 of 55 evaluable patients) for VIT versus 31% (18 of 58) for VI (adjusted odds ratio, 0.50; 95% CI, 0.22 to 1.12; $P = .09$). The VIT arm achieved significantly better overall survival (adjusted hazard ratio, 0.55; 95% CI, 0.35 to 0.84; $P = .006$) compared with VI, with consistent progression-free survival results (adj-hazard ratio, 0.68; 95% CI, 0.46 to 1.01; $P = .059$). Overall, patients experienced adverse events ≥ grade 3 more frequently with VIT than VI (98% *v* 78%, respectively; $P = .009$), including a significant excess of hematologic toxicity (81% *v* 61%; $P = .025$).

CONCLUSION The addition of temozolomide to VI improved chemotherapy efficacy for patients with relapsed RMS, with manageable increase in toxicity. VIT is considered the new standard treatment in these patients in the European paediatric Soft Tissue Sarcoma Group and will be the control arm in the next randomized trial.

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ASSOCIATED CONTENT

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Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

At the time of relapse, rhabdomyosarcoma (RMS) is generally refractory to treatment, leading to a poor overall survival (OS) of < 20%.[1] Main prognostic factors at relapse are the type of recurrence, previous radiotherapy treatment, initial tumor size, and time of relapse from diagnosis.[2] New systemic therapies are urgently needed to improve outcome of relapsed RMS.

The combination of vincristine and irinotecan (VI) using a 2-week regimen for irinotecan was highly active in newly diagnosed metastatic RMS, with an objective response rate (ORR) of 70%.[3] Subsequently,

CONTEXT

Key Objective

To our knowledge, this study, from the European paediatric Soft tissue Sarcoma study Group and the Innovative Therapies for Children with Cancer consortium, is the first European prospective randomized study testing chemotherapy combinations in relapsed and refractory rhabdomyosarcoma (RMS).

Knowledge Generated

The study showed that the addition of the chemotherapy drug temozolomide to vincristine and irinotecan chemotherapy improved tumor response and survival of patients with relapsed or refractory RMS. The study has defined the combination of vincristine, irinotecan, and temozolomide as a new standard chemotherapy treatment option for relapsed RMS.

Relevance

The combination of vincristine, irinotecan, and temozolomide is the standard (control) treatment in the recently launched European pediatric Soft tissue Sarcoma study Group Frontline and Relapse RMS study, which will test innovative combinations of new treatments combined with backbone chemotherapy in relapsed RMS.

this regimen was compared with a shorter schedule of irinotecan (1 × 5 days every 21 days) in the ARST0121 randomized phase II trial in first relapse or progression of RMS. No significant difference was observed between the longer and shorter regimens (ORR = 26% and 37%, respectively). The authors recommended the more convenient shorter regimen to be taken forward.[4]

Irinotecan, as a prodrug, is metabolized in vivo into its active metabolite SN-38, which acts as a topoisomerase I inhibitor, which is active in S-Phase of the cell cycle, leading to replication disruption. This mechanism of action supports its use in combination with alkylating agents such as temozolomide.[5,6] The dose-limiting toxicities of irinotecan (diarrhea) and temozolomide (myelosuppression) are nonoverlapping, and schedule-dependent synergy between these two drugs has been demonstrated in RMS mouse xenograft models.[7] When we designed the trial, the combination of vincristine and irinotecan with temozolomide (VIT) had not been evaluated prospectively in RMS. This European open-label, multicenter, randomized phase II trial evaluated the efficacy and safety of the combination of VI with or without temozolomide in patients with relapsed or refractory RMS.

METHODS

Trial Design

The VIT-0910 trial (ClinicalTrials.gov, NCT01355445) was an international open-label, randomized two-parallel group phase II trial conducted by the European paediatric Soft Tissue Sarcoma Group (EpSSG) and Innovative Therapies for Children with Cancer (ITCC), in 37 centers from five countries (Data Supplement, online only). Study protocol was approved by an independent ethics committee and the appropriate institutional review boards.

Patients

Key eligibility criteria included histologically confirmed RMS; relapsed, progressive, or refractory RMS in which standard treatments had failed; age 6 months to 50 years; Karnofsky or Lansky performance status ≥ 70%; life expectancy ≥ 3 months; and adequate organ function (details are given in the full Protocol, online only). Following the recommendation from the Independent Data Monitoring Committee (IDMC) on the basis of data analysis of the first 80 patients, the Protocol was amended in December 2015 to continue accrual in the trial in relapsed patients only.

Patients with previous exposure to irinotecan or temozolomide were not eligible.

Written informed consent was obtained from all patients and/or their parents or guardians before enrollment.

Random Assignment and Masking

The chemotherapy regimen VI or VIT was allocated by random assignment at study entry. Centralized random assignment software (TENALEA) was used, ensuring the concealment of the next patient allocation. Balanced 1:1 random assignment was based on a minimization algorithm taking into account disease status (relapsed or progressive in patients who have already shown a response to chemotherapy, here termed relapse) versus refractory (defined as progression after receiving chemotherapy without previous response) and country for the first 80 patients; for the 40 additional patients, all recruited in the relapse stratum, the algorithm also included previous radiotherapy (yes *v* no) and disease staging at study entry (metastases: yes *v* no). Patients and investigators were not blinded to treatment assignment, but the centralized retrospective radiologic review committee was blinded to group allocation.

Treatment

The study treatment consisted of 21-day cycles of VI or VIT. In the VIT arm, the starting dose of temozolomide was

125 mg/m^2 once a day from day 1 to day 5, escalating to 150 mg/m^2 once a day at cycle 2 for patients without grade ≥ 3 toxicity, on the basis of Kushner's published regimen in neuroblastoma.[8] Cefixime was recommended for prophylaxis of irinotecan gut toxicity. Treatment was continued until progression or unacceptable toxicity for up to 12 cycles. Further continuation of treatment was individually discussed for patients who did not experience disease progression after 12 cycles. Treatment schedule and chemotherapy details are given in Data Supplement.

Local therapy was allowed after two cycles; it was tailored to patient and tumor characteristics and included complete surgical removal wherever feasible, radiotherapy, or a combination of both.

Outcomes and Assessments

Tumor assessment on the basis of computed tomography or magnetic resonance imaging was performed every two courses during study treatment. After completion of study treatment, tumor evaluation was recommended every three months during the first 2 years, then every 6 months up to 6 years from study entry until disease progression.

The primary end point was ORR, ie, complete or partial response, after two cycles. Tumor response was evaluated using the three-dimensional WHO response criteria for the primary lesion and according to RECIST-1.1 criteria for metastatic sites.[9,10] Tumor evaluations until reported progression were reviewed by an independent response review committee. Clinical progression without radiologic confirmation, but which shortly led to death, was counted as progression.

Secondary efficacy end points included centrally reviewed best response over the whole study treatment duration (before local treatment if any), progression-free survival (PFS), and OS. PFS was defined as the time interval from the start of treatment to the date of tumor progression, relapse, or death from any cause. OS was defined as the time interval from the start of treatment until death from any cause.

Adverse events (AEs), evaluated by clinical and laboratory examinations at the beginning of each cycle of study treatment and weekly for hematologic tests, were graded according to NCI-CTCAE-v4.0. A grade ≥ 3 AE was classified as a severe AE.

Data cutoff was set at April 1, 2019.

Statistical Considerations

The trial was originally designed as a noncomparative randomized phase II trial. An Optimum Simon two-stage design on the basis of the objective response at two cycles was used to define the statistical rule and the sample size. Accounting for an 8% dropout rate, 40 patients in each arm were required to test the null hypothesis p0 ≤ 0.20 at a 1-sided alpha of 10% and ensure a 90%-power under the alternative hypothesis p1 ≥ 0.40. Following the IDMC recommendation to continue accrual in relapsed patients only, and assuming better outcomes in this stratum, the design parameters were revised (p0 = 0.35 and p1 = 0.55), leading to an increased sample size up to a total of 120 patients including 108 relapsed patients. On the basis of IDMC recommendations, another amendment was submitted in July 2018 to allow formal comparison of all end points between the randomly assigned groups.

Comparison of treatment arms was controlled for predefined covariates: disease status (relapse *v* refractory disease), disease staging at study entry (metastases: yes *v* no), and histologic subtype (alveolar *v* nonalveolar), using multivariate logistic regressions for the ORR at two cycles and the best response and using Cox models for the PFS and OS. Treatment effect estimates (odds ratio [OR] of failure and hazard ratio [HR], respectively) were estimated with their 95% CI and tested at a two-sided 5%-alpha level.

In addition to the Kaplan-Meier estimates of PFS and OS curves, we provided the adjusted survival curves estimated in the multivariate models.

The efficacy analysis was performed both on the entire study population and on the main subset of patients at relapse (study population after amendment). Heterogeneity of treatment effect across the main subgroups (on the basis of predefined covariates) was tested using interaction tests and illustrated by forest plots.

AEs were described by system organ class. Maximum grade observed over the whole treatment duration was tabulated per type of AE and illustrated using a butterfly plot. We estimated relative risk of severe AE in VIT compared with VI, overall and for each system organ class.

The analysis of response after two cycles included all patients who started study treatment except those with no imaging after two cycles (and no clinical progression). All patients with at least one tumor evaluation during the study treatment were included in the analysis of the best response. The primary analysis of survival outcomes (OS and PFS) was performed in the intention-to-treat population, including the entire follow-up duration regardless of possible nonstudy maintenance treatment. We performed a post hoc sensitivity analysis of PFS and OS by censoring the observations at the date of start of a systemic treatment other than planned study drugs, if a systemic treatment was administered before progression.

A two-sided *P* value < .05 was considered as significant for all VIT versus VI comparison tests.

All statistical analyses were performed using Stata software, version 15.0 (StataCorp LLC College Station).

RESULTS

Patient Characteristics

Overall, 120 patients were enrolled between March 2012 and April 2018: 60 in the VI arm and 60 in the VIT arm. All

but two patients in the VI arm started study treatment (Fig 1). As detailed in Table 1, we observed a nonsignificant excess of patients with unfavorable site of primary tumor, large tumor at diagnosis, and refractory disease and metastatic disease at study entry in the VIT arm compared with the VI arm. Additionally, there were slightly fewer patients with progression or early relapse (occurring in the 18 months from diagnosis) in the VIT arm than in the VI arm.

Efficacy Results on the Whole Population by Treatment Group

In the whole population, the ORR after two cycles was 44% in the VIT arm (24 of 55 evaluable patients) and 31% in the VI arm (18 of 58), significantly higher than the prespecified minimum efficacy threshold p0 = 20% in both arms (Table 2). Controlling for the prespecified covariates, the adjusted OR (aOR) was 0.50 (95% CI, 0.22 to 1.12) for the VIT arm compared with the VI arm, with a 2-sided $P = .09$.

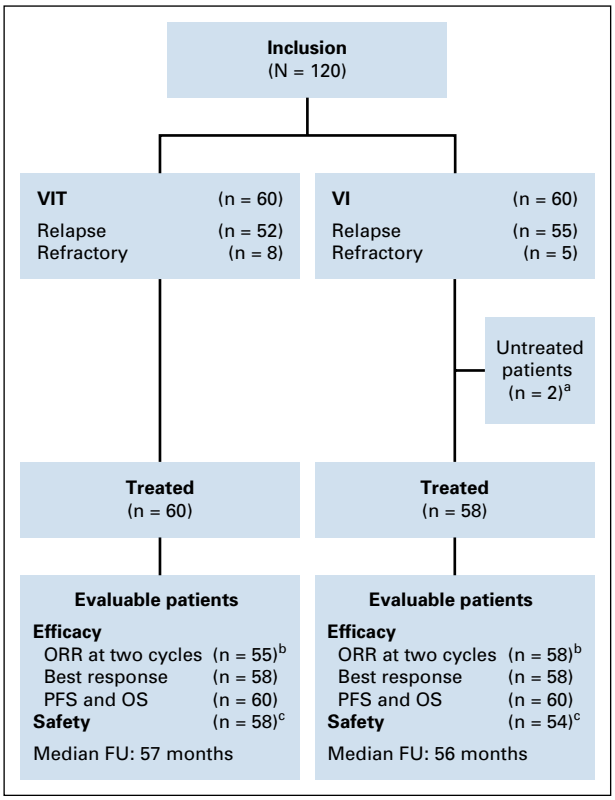

FIG 1. CONSORT diagram. [a]Two patients in the VI arm did not receive the study treatment: one because of patient's decision and the other because he was reviewed as ineligible for the study before start of treatment. [b]The primary outcome (ORR after two cycles) was not evaluable for five in the VIT arm with incomplete tumor evaluation and for two patients in the VI arm who did not start treatment. [c]One hundred twelve patients (58 in the VIT arm and 54 in the VI arm) were evaluable for safety. Eight patients were not evaluable for safety: two patients in the VI arm who did not receive the study treatment and six patients with missing safety data (two in the VIT arm and four in the VI arm). FU, follow-up; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; VI, vincristine and irinotecan; VIT, vincristine and irinotecan with temozolomide.

Considering the best response over the whole treatment duration, we observed significantly more objective responses in the VIT arm than in the VI arm (33 of 58, 57% *v* 22 of 58, 38%, aOR, 0.40; 95% CI, 0.18 to 0.88; 2-sided $P = .023$).

Overall, with a median follow-up of 57 months, 104 disease progressions or relapses were reported and 91 patients died, all but one from disease (Table 2 and Fig 2). In the multivariate Cox model adjusted for possible predefined confounding factors, the VIT arm was found to be associated with a reduction in the risk of progression or relapse compared with the VI arm, with an adjusted $HR_{PFS} = 0.68$, 95% CI, 0.46 to 1.01, which was nearly statistically significant ($P = .059$).

The VIT arm was associated with a significant reduction in the risk of death compared with the VI arm with an adjusted $HR_{OS} = 0.55$, 95% CI, 0.35 to 0.84, and $P = .006$.

In the sensitivity analysis censoring observations at the start date of other anticancer treatment, the benefit associated with VIT compared with VI appeared larger and significant in terms of PFS (adjusted-HR_{PFS}, 0.64; 95% CI, 0.42 to 0.98; $P = .039$) and stable and still significant in terms of OS (adjusted HR_{OS}, 0.59; 95% CI, 0.37 to 0.93; $P = .02$).

Efficacy Results in Patients at Relapse

As detailed in Table 2, the results were comparable when focusing on relapsed patients only. In this subgroup, the ORR after two cycles was 47% in the VIT arm (22 of 52), significantly higher than prespecified minimum efficacy threshold p0 = 35% (1-sided $P = .045$), whereas the ORR of 33% in the VI arm (18 of 55) was insufficient, leading to an adjusted OR of 0.53 (95% CI, 0.23 to 1.22; $P = .14$). The adjusted HR_{PFS} was 0.68 (95% CI, 0.45 to 1.03; $P = .069$), and the adjusted HR_{OS} was 0.57 (95% CI, 0.36 to 0.90; $P = .016$).

Subgroup Analyses

As illustrated by the forest plots (Data Supplement), we did not observe any significant heterogeneity of treatment effect across subgroups, neither for the objective response at two cycles nor for the PFS or the OS.

Treatments

The median number of cycles was 6 (range 1-18) for the VIT arm and 4 (range 1-26) for the VI arm (Table 3). The proportion of patients with a relative dose intensity < 0.8 was significantly higher in the VIT arm (47% *v* 22%; $P = .006$).

Overall, 55 patients discontinued treatment early because of progressive disease and 13 because of toxicity, with a nonsignificant trend for fewer early terminations because of progression and more because of toxicity in the VIT arm

TABLE 1. Patient and Tumor Characteristics

Characteristic	VIT (n = 60)	VI (n = 60)	Total (N = 120)	*P* VIT *v* VI
Age at inclusion				
Median (range)	12 years (9.1 months-45 years)	10.5 years (3 years-45 years)	11 years (9.1 months-45 years)	.94
Age group, years, No. (%)				.66
< 18	46 (77)	48 (80)	94 (78)	
≥ 18	14 (23)	12 (20)	26 (22)	
Primary site (at initial diagnosis), No. (%)				.23
Favorable[a]	8 (13)	13 (22)	21 (18)	
Unfavorable	52 (87)	47 (78)	99 (83)	
Histology, No. (%)				1
Alveolar	34 (57)	34 (57)	68 (57)	
Nonalveolar	26 (43)	26 (43)	52 (43)	
Tumor size at initial diagnosis, cm (MD = 1), No. (%)				.15
≤ 5	18 (31)	26 (43)	44 (37)	
> 5	41 (69)	34 (57)	75 (63)	
Previous chemotherapy with doxorubicin (MD = 1), No. (%)				.39
Yes	46 (77)	49 (83)	95 (80)	
No[b]	14 (23)	10 (17)	24 (20)	
Previous radiotherapy (MD = 3), No (%)				.43
Yes	47 (81)	51 (86)	98 (84)	
No	11 (19)	8 (14)	19 (16)	
Disease status at inclusion, No (%)				.38
Relapse	52 (87)	55 (92)	107 (89)	
Including first relapse	40	41	81	
Refractory	8 (13)	5 (8)	13 (11)	
Disease staging at inclusion, No (%)				.28
Local or locoregional progression	19 (32)	27 (45)	46 (38)	
Metastatic only	21 (35)	19 (32)	40 (33)	
Both	20 (33)	14 (23)	34 (28)	
Time interval between diagnosis and first relapse or progression				
Median time interval (months)	15.0 (2.1-76.6)	14.3 (0.3-67.8)	14.5 (0.3-76.6)	.34
Categories, years, No (%)				.26
< 1.5	35 (58)	41 (68)	76 (63)	
≥ 1.5	25 (42)	19 (32)	44 (37)	

Abbreviations: VI, vincristine and irinotecan; VIT, vincristine and irinotecan with temozolomide.

[a]Favorable sites included orbit (n = 7), head and neck nonparameningeal sites (n = 12), and genitourinary sites apart from bladder and prostate (n = 5).

[b]24 patients had not received doxorubicin before study entry; they had all received IVA courses (ifosfamide-vincristine-dactinomycin), and five patients received vinorelbine-cyclophosphamide.

(*P* = .30). Sixteen patients received 12 or more cycles of VIT/VI.

In addition, 17 patients had additional systemic therapy (Table 3) after stopping VI/T and before progression: 13 of 57 (23%) in the VIT arm and 4 of 55 (7%) in the VI arm (*P* = .02).

Among the 46 patients with local or locoregional disease at study entry, 20 had a local treatment (five surgery alone,

TABLE 2. Efficacy Results in Both Treatment Groups, in the Whole Population and Only in Patients Enrolled at Relapse

	Whole Population		Patients at Relapse	
Outcome	**VIT (n = 60)**	**VI (n = 60)**	**VIT (n = 52)**	**VI (n = 55)**
Response at two cycles				
Distribution of the response, No. (%)				
Complete response	5 (9)	2 (3)	5 (11)	2 (4)
Partial response	19 (35)	16 (28)	17 (36)	16 (30)
Stable disease	21 (38)	21 (36)	17 (36)	18 (33)
Progressive disease	10 (18)	19 (33)	8 (17)	18 (33)
Missing data	5	2	5	1
ORR at 2 cycles (95% CI)	44% (30 to 58%)	31% (20 to 45%)	47% (32 to 62%)	33% (21 to 47%)
1-sided *P* value (test *v* p0)[a]	< .0001	.018	.045	1.00
OR of failure[b]				
Unadjusted OR (95% CI)	0.58 (0.27 to 1.26)	1	0.57 (0.25 to 1.27)	1
2-sided *P* value	.17		.17	
Adjusted OR (95% CI)[c]	0.50 (0.22 to 1.12)	1	0.53 (0.23 to 1.22)	1
2-sided *P* value	.09		.14	
Best response over the whole treatment[d]				
Distribution of the response, No. (%)				
Complete response	9 (16)	4 (7)	9 (18)	4 (7)
Partial response	24 (41)	18 (31)	22 (44)	18 (33)
Stable disease	16 (27)	17 (30)	12 (24)	14 (26)
Progressive disease	9 (16)	19 (33)	7 (14)	18 (33)
Missing data	2	2	2	1
Best ORR (95% CI)	57% (43 to 70 to %)	38% (26 to 52%)	62% (47 to 75%)	40% (28 to 55%)
OR of failure[b]				
Unadjusted OR (95% CI)	0.46 (0.22 to 0.97)	1	0.43 (0.19 to 0.96)	1
2-sided *P* value	.042		.040	
Adjusted OR (95% CI)[c]	0.40 (0.18 to 0.88)	1	0.42 (0.19 to 0.93)	1
2-sided *P* value	.023		.032	
PFS				
No. and type of events				
Disease progression or relapse	52	52	44	48
Death as first event[e]	0	1	0	1
Median PFS (95% CI) in months	4.7 (4.1 to 8.5)	3.2 (2.4 to 7.3)	5.0 (4.2 to 10.0)	3.5 (2.4 to 7.4)
PFS rates (95% CI)				
at 6 months	45% (32 to 57)	42% (29 to 54)	50% (36 to 63)	44% (30 to 56)
at 1 year	33% (21 to 45)	28% (17 to 40)	36% (23 to 49)	29% (30 to 56)
at 2 years	18% (9 to 29)	15% (8 to 26)	19% (10 to 31)	16% (8 to 27)
HR				
Unadjusted HR (95% CI)	0.81 (0.55 to 1.19)	1	0.77 (0.51 to 1.16)	1
2-sided *P* value	.28		.22	
Adjusted HR (95% CI)[c]	0.68 (0.46 to 1.01)	1	0.68 (0.45 to 1.03)	1
2-sided *P* value	.059		.069	
PFS—censored at first other chemotherapy before progression				
No. and type of events				
Disease progression or relapse	42	50	35	46
Death as first event[e]	0	1	0	1
Median PFS (95% CI), months	4.8 (4.1 to 8.5)	3.2 (2.4 to 6.7)	7.6 (4.2 to 10)	3.5 (2.4 to 7.4)

(continued on following page)

TABLE 2. Efficacy Results in Both Treatment Groups, in the Whole Population and Only in Patients Enrolled at Relapse (continued)

	Whole Population		Patients at Relapse	
Outcome	**VIT (n = 60)**	**VI (n = 60)**	**VIT (n = 52)**	**VI (n = 55)**
PFS rates (95% CI)				
at 6 months	47% (34 to 60)	41% (29 to 53)	53% (38 to 66)	43% (30 to 56)
at 1 year	31% (18 to 44)	26% (15 to 38)	35% (21 to 49)	27% (15 to 39)
at 2 years	19% (9 to 32)	13% (5 to 24)	21% (10 to 36)	13% (6 to 25)
HR				
Unadjusted HR (95% CI)	0.74 (0.49 to 1.11)	1	0.68 (0.44 to 1.06)	1
2-sided *P* value	.14		.09	
Adjusted HR (95% CI)[c]	0.64 (0.42 to 0.98)	1	0.62 (0.39 to 0.96)	1
2-sided *P* value	.039		.03	
OS				
No. and cause of deaths				
Death because of disease progression	43	47	36	43
Death from another cause[e]	0	1	0	1
Median OS (95% CI), months	15.0 (10.0 to 21.2)	10.3 (7.1 to 12.6)	17.3 (11.7 to 22.9)	10.8 (7.4 to 14.9)
OS rates (95% CI)				
at 6 months	80% (67 to 88)	70% (57 to 80)	81% (67 to 89)	75% (61 to 84)
at 1 year	56% (42 to 67)	43% (30 to 55)	61% (46 to 73)	45% (32 to 58)
at 2 years	33% (21 to 45)	22% (12 to 34)	36% (22 to 49)	24% (13 to 36)
HR				
Unadjusted HR (95% CI)	0.71 (0.48 to 1.09)	1	0.69 (0.44 to 1.08)	1
2-sided *P* value	.12		.10	
Adjusted HR (95% CI)[c]	0.55 (0.35 to 0.84)	1	0.57 (0.36 to 0.90)	1
2-sided *P* value	.006		.016	
OS—censored at first other chemotherapy before event				
No. and cause of deaths				
Death because of disease progression	35	45	28	41
Death from another cause[5]	0	1		1
Median OS (95% CI), months	12.4 (9.8 to 17.3)	10.3 (7.1 to 12.6)	15 (9.8 to 22.3)	10.4 (7.4 to 12.6)
OS rates (95% CI)				
at 6 months	79% (66 to 88)	70% (56 to 80)	80% (65 to 88)	74% (60 to 84)
at 1 year	51% (36 to 64)	40% (27 to 53)	57% (40 to 70)	42% (29 to 55)
at 2 years	27% (15 to 41)	20% (10 to 31)	32% (17 to 47)	21% (11 to 33)
HR				
Unadjusted HR (95% CI)	0.73 (0.47 to 1.13)	1	0.67 (0.41 to 1.08)	1
2-sided *P* value	.15		.10	
Adjusted HR (95% CI)[c]	0.59 (0.37 to 0.93)	1	0.59 (0.36 to 0.96)	1
2-sided *P* value	.02		.03	

Abbreviations: HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; VI, vincristine and irinotecan; VIT, vincristine and irinotecan with temozolomide.

[a]The observed ORR after two cycles was tested against p0 = 20% when considering the whole study population and against p0 = 35% when focusing on patients at relapse, using one-sided test.

[b]Failure is defined as stable disease or progressive disease.

[c]All adjusted estimates of treatment effect (VIT compared with VI) are based on multivariable models including treatment and predefined covariates: histologic subtype (alveolar *v* nonalveolar), disease staging at study entry (metastases: yes *v* no), and disease status (relapse *v* refractory disease).

[d]Best response was based on tumor evaluations performed during study treatment or at the end of study treatment, before any local treatment, and before start of another systemic treatment if any.

[e]One patient died from surgical complications (hemorrhage) after hepatic transplant for a recurrent biliary duct rhabdomyosarcoma transplanted after seven VI courses.

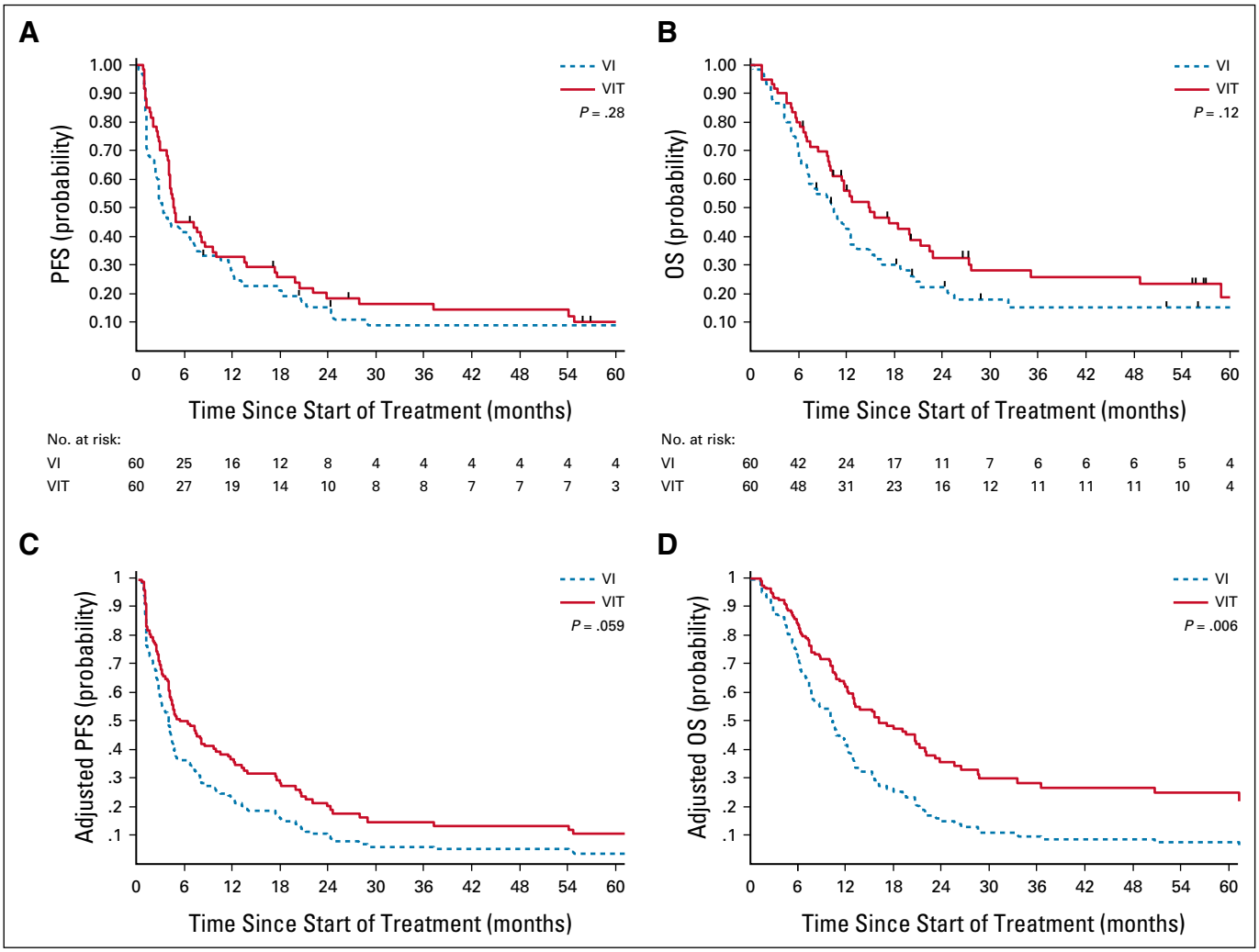

FIG 2. PFS and OS curves, by treatment group. Kaplan-Meier estimate of the (A) PFS and (B) the OS from start of study treatment. Adjusted curves of (C) PFS and (D) OS, estimated from the multivariable Cox models including treatment and predefined covariates: histologic subtype (alveolar *v* nonalveolar), disease staging at study entry (metastatic relapse or progression *v* locoregional disease), and disease status (relapse *v* refractory disease). OS, overall survival; PFS, progression-free survival.

seven radiotherapy alone, and eight both) with no significant difference between treatment groups ($P = .65$).

Safety

A significantly higher proportion of patients experienced a grade ≥ 3 AE in VIT compared with VI, both for all AEs (98% *v* 78%, respectively, $P = .009$) and also for AEs classified as related to study treatment (93% *v* 69%; $P = .002$).

There was also a significant excess of serious AEs classified as related to the study treatment in VIT arm (38% *v* 19%; $P = .023$).

We observed a significant excess of severe hematologic toxicity in VIT (81% *v* 61%; $P = .025$, Fig 3). Focusing on gastrointestinal events, we did not observe any significant difference in terms of grade ≥ 3 diarrhea (24% *v* 17%; $P = .33$) and grade ≥ 3 nausea and/or vomiting (26% *v* 17%; $P = .24$). There were no study treatment-related deaths.

DISCUSSION

This randomized European phase II trial suggests that, in patients with relapsed or refractory or relapsed RMS, the addition of temozolomide to vincristine and irinotecan improves chemotherapy efficacy. The ORR after two cycles in the VIT arm was 47% in patients at relapse, significantly higher than the predefined p0 = 35%, whereas the ORR rate was insufficient in the VI arm. Considering the best response over the whole treatment duration in the entire population, we observed significantly more objective responses in the VIT arm than in the VI arm. We also observed a nearly significant PFS benefit and a large and significant OS benefit for the VIT arm. The better outcomes with VIT were observed despite having a significant decrease in

TABLE 3. Treatment Characteristics

Treatment Characteristic	VI (n = 58)	VIT (n = 60)	P[a]
Total No. of VI/VIT cycles before progression (n = 118)			
Median (range)	4 (1-26)	6 (1-18)	.44
No. of cycles, No (%)			
< 12	50 (86)	52 (87)	
≥ 12	8 (14)	8 (13)	
Reasons for early termination of study treatment (< 12 cycles) (n = 101 and MD = 1), No. (%)			.30
Progression	30 (60)	25 (49)	
Toxicity	4 (7)	9 (15)	
Others	16 (32)	17 (33)	
Investigator decision	13	14	
Patient decision	3	3	
Reduced dose intensity for at least one study drug (Relative Dose Intensity, RDI < 0.8) (n = 118), No. (%)			.006
No	45 (78)	32 (53)	
Yes	13 (22)	28 (47)	
If yes (drugs with RDI < 0.8, potentially combined)			
Vincristine	8	15	
Irinotecan	9	16	
Temozolomide[b]	0	20	
Type of nonsystemic treatment performed before progression, overall (n = 112 and MD = 6), No. (%)			.88
None	33 (60)	37 (65)	
Radiation therapy alone	10 (18)	11 (19)	
Surgery alone	4 (7)	3 (5)	
Surgery and radiation therapy	8 (15)	6 (11)	
Timing of nonsystemic treatment (n = 42), No. (%)			.38
During VI/VIT chemotherapy[c]	15 (68)	11 (55)	
After the end of VI/VIT chemotherapy[d]	7 (32)	9 (45)	
Type of local treatment performed before progression, in patients with local or locoregional disease (n = 45 and MD = 1), No. (%)			.65
None	14 (54)	11 (58)	
Radiation therapy alone	3 (12)	4 (21)	
Surgery alone	3 (12)	2 (11)	
Surgery and radiation therapy	6 (23)	2 (11)	
Other systemic anticancer treatment administered before progression (n = 112 and MD = 6), No. (%)			.02
No	51 (93)	44 (77)	
Yes	4 (7)	13 (23)	
Vinorelbine-cyclophosphamide	4 (7)	6 (10)	
Others[e]	0 (0)	7 (12)	
Anticancer treatment administered after progression or relapse (n = 94 and MD = 10), No. (%)			.17
None	11 (25)	10 (20)	
Systemic treatment	24 (55)	19 (38)	
Surgery and/or radiation therapy	2 (4)	4 (8)	
Systemic treatment plus surgery and/or radiation therapy	7 (16)	17 (34)	

Abbreviations: VI, vincristine and irinotecan; VIT, vincristine and irinotecan with temozolomide.

[a]Chi-square test for qualitative variables and Student's *t*-test for quantitative variables.

[b]Relative dose intensity for temozolomide was calculated considering 125 mg/m^2/day for the first cycle and then 150 m g/m^2/day from the second cycle.

[c]Including three patients (2 in the VI arm and one in the VIT arm) who had surgery during VI/VIT courses and completed local treatment with radiation therapy delivered after VI/VIT courses.

[d]For the patients who had local treatment after VI/VIT courses, the median number of VI/VIT courses administered before local treatment was 5 (range 2-18).

[e]Seven patients allocated to VIT received after the end of VIT courses systemic anticancer treatment other than navelbine-cyclophosphamide before progression: two high-dose chemotherapy with busulfan-melphalan followed by stem-cell transplantation; one carboplatin etoposide, one pazopanib, two vincristine-dactinomycin-cyclophosphamide, and one oral etoposide.

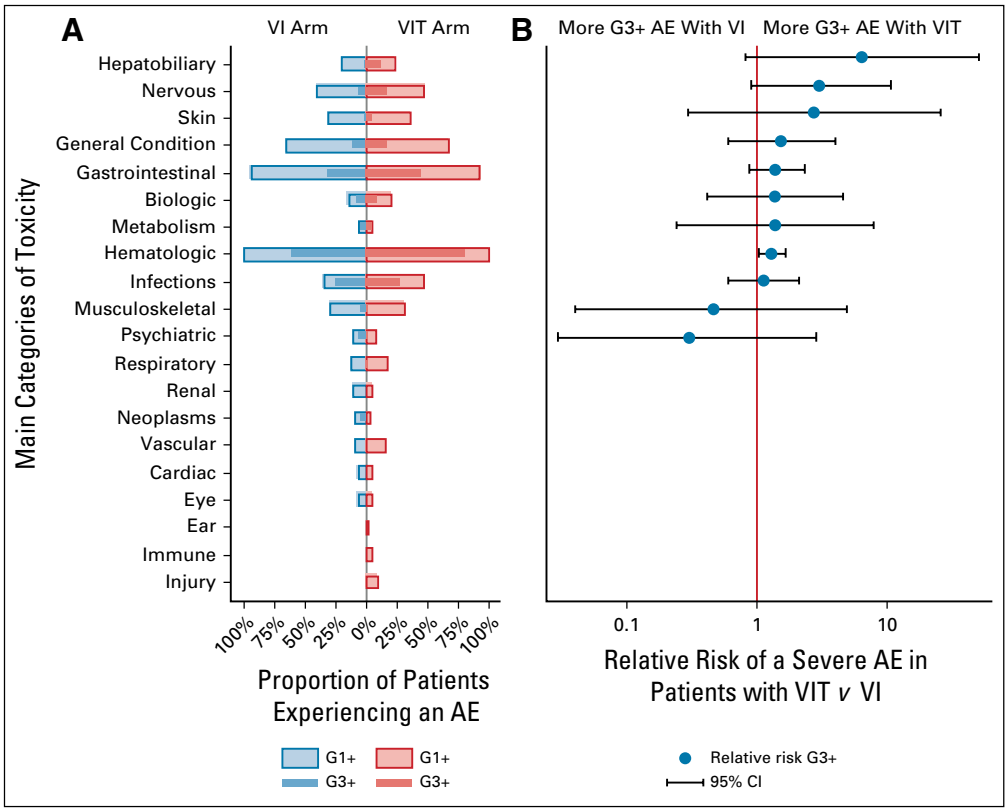

FIG 3. Safety analysis considering all reported AEs. (A) The butterfly plot showing the proportion of patients experiencing an AE, classified or not as related to study treatment, whatever the grade (light blue for VI and light red for VIT arm), and a severe AE, grade ≥ 3 (dark blue for VI and dark red for VIT arm) according to the random assignment group for the main categories of toxicity. (B) Displays the relative risk of a severe AE in patients with VIT relative to patients with VI, with 95% CIs for the main categories of toxicity. The toxicity items are regrouped by main categories (system organ class). Details of AEs are given in the Data Supplement. For each AE type, the analysis is based on the maximum grade observed over the whole maintenance treatment duration. The categories of AE are ordered by decreasing value of the relative risk of severe AE. Data Supplement illustrates the safety analysis focused on AEs classified as related to study treatment. AE, adverse event; G, grade; VI, vincristine and irinotecan; VIT, vincristine and irinotecan with temozolomide.

planned dose intensity, mainly because of toxicity. Overall, the significant excess of acute toxicity of the VIT combination, mostly hematologic toxicity, was manageable.

To our knowledge, this is the first randomized controlled trial evaluating VIT in the setting of progressive or relapsed RMS, and other published studies evaluating VIT in this setting were retrospective studies.[11,12] The VIT combination has also been prospectively evaluated in the ARST08P1 trial by the Children's Oncology Group (COG), in a non-randomized study evaluating VIT with lower doses of temozolomide as first-line treatment in metastatic RMS.[13] The authors concluded that the addition of temozolomide to intensive multiagent chemotherapy did not improve outcome for patients with metastatic RMS.

This study was the first EpSSG trial for patients with relapsed or refractory RMS, with the goal of defining the standard chemotherapy at relapse to which novel agents could be added or other innovative therapies compared. The control arm of the trial was based on the results of ARST0121 trial where the shorter schedule of irinotecan was found to be no different in efficacy from the protracted schedule.[4]

Although the study populations were not entirely comparable as our study also included patients with second or subsequent relapse (23% and 25.4% of the relapsed patients in the VIT and VI arm, respectively), the results of the VIT combination still compare favorably with the ARST0121 study.[1] In this risk-based therapy, the 6-month failure-free survival was 50% in patients with unfavorable features receiving multiagent chemotherapy (with or without tirapazamine), similar to the results in the VIT arm presented here (6-month PFS = 45% overall and 55% at first relapse or progression). When looking specifically at the comparable patient population (first relapse or progression), our results in the VIT arm (6-month and 24-month PFS 55% and 23%, respectively) are also quite similar to the results of ARST0921 trial comparing

temsirolimus and bevacizumab in combination with vinorelbine-cyclophosphamide (temsirolimus arm: 6- and 24-month PFS = 65% and 19%, respectively; bevacizumab arm: 50% and 7%).[14]

Although toxicity was deemed manageable in the VIT arm, the increased VIT toxicity raises the question of whether it is possible to add new targeted therapy or immunotherapy to this chemotherapy backbone. Such combinations should be tested in experienced early phase centers.

The planned dose of temozolomide was higher in the current trial than in the ARST08P1-COG trial, which concluded that adding temozolomide to multiagent chemotherapy did not improve outcome compared with historical controls.[13] In our trial, better outcomes on VIT were observed despite having a significant decrease in planned dose intensity, mainly because of toxicity. Whether a similar outcome would be observed with lower planned dose remains unknown.

We acknowledge several limitations of our study. First, the study was not initially designed to compare efficacy outcomes between treatment groups, leading, after amendment, to underpowered comparisons, both overall and even more in subgroups. On the basis of current knowledge, PFS would have been a more appropriate primary end point than ORR.[15] However, when the study was designed in 2012, assessment of objective response was still current practice in RMS. In addition, the study was based on the COG study published by Mascarenhas et al[4] in JCO in 2010, evaluating two different schedules of VI combination, using objective response as primary end point. Finally, we did evaluate PFS and OS as secondary end points. We also acknowledge that the use of several types of imaging and response criteria hampers optimal response assessment. Differences in treatment effect estimates between unadjusted and adjusted analyses also complicate the interpretation of the results; this is explained by slight imbalances in patient characteristics between treatment groups, which would have been avoided if the random assignment had been controlled for these prognostic factors. Another issue is the higher proportion of patients who received further chemotherapy after end of study treatment and before progression in the VIT arm compared with the VI arm, which may confuse the interpretation of survival outcomes. The reported OS results should be interpreted with care. However, OS remained significantly better for VIT and the improvement in PFS became statistically significant in the sensitivity analysis when observations were censored at the date of start of another anticancer treatment. Finally, we have no clear explanation for the larger effect on OS than on PFS of the VIT arm compared with the VI arm, as there was no significant difference of treatment modalities at progression or relapse. A similar finding was reported in the trial evaluating maintenance treatment in high-risk localized RMS.[16]

On the basis of our study results, the VIT combination is considered the new EpSSG standard treatment in patients with relapsed RMS who have previously received alkylating agent. We discounted the option of adding temozolomide to the first-line chemotherapy regimen in RMS because active cytotoxic drugs in RMS have reached a plateau in their capacity to prevent relapse and temozolomide would add an additional alkylating agent to cyclophosphamide and ifosfamide already used in front line. It was thus decided to pursue its evaluation in patients with relapsed or refractory disease.

The EpSSG has recently launched its new multiarm multistage frontline and relapse RMS study, and VIT will be the new standard control arm in relapsed patients. Depending on expected combination toxicity, experimental arms will include VI or VIT backbone, combined with innovative agents.

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DISCLAIMER

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DATA SHARING STATEMENT

The data set used and analyzed during the current study is available from the corresponding author on reasonable request.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase II Trial of Vincristine-Irinotecan With or Without Temozolomide, in Children and Adults With Relapsed or Refractory Rhabdomyosarcoma: A European Paediatric Soft tissue Sarcoma Study Group and Innovative Therapies for Children With Cancer Trial

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