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ORIGINAL RESEARCH ARTICLE

Phase I/II Study of the CDK2/9 Inhibitor Fadraciclib in Combination with Chemotherapy in Children with Advanced Malignancies: Arm K of the AcSé-ESMART Trial

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Abstract

Background Cyclin-dependent kinase (CDK) dysregulation is common in pediatric cancers. The dual CDK2/9 inhibitor fadraciclib has shown preclinical antitumor activity, alone and in combination, supporting clinical evaluation in children.

Objective Arm K of the AcSé-ESMART proof-of-concept phase I/II platform trial aimed to define the recommended phase II dose (RP2D), pharmacokinetics, antitumor activity and predictive biomarker(s) of fadraciclib in combination with temozolomide in pediatric patients with recurrent/refractory solid malignancies.

Patients and Methods Fadraciclib was administered intravenously once on Day 1 ± Day 15, and temozolomide orally on Days 1–5. Dose escalation of fadraciclib followed the continuous reassessment method starting at 135 mg/m^2/day on Day 1, equivalent to 70% of the adult RP2D; temozolomide was given at the pediatric RP2D dose of 150 mg/m^2/day. The cohort was enriched for patients with molecular alterations in cell cycle pathways.

Results Twelve patients were enrolled and treated (median age: 12.1 years, range 4.0–17.9). Main diagnoses were sarcoma and central nervous system tumors. Dose-limiting toxicities and main treatment-related adverse events were hematologic. The final tolerated intravenous fadraciclib dose could be estimated at 135 mg/m^2 on Day 1 or Day 1 and 15 as the trial was closed prematurely following emerging adult data and the company's shift from an intravenous to a new oral formulation. No objective response was observed; two patients with ependymoma and extra-cerebral malignant rhabdoid tumor had stable disease for 6 and 9 cycles, respectively.

Conclusions This pediatric study was the first to explore the CDK2/9 inhibitor fadraciclib. Fadraciclib combined with temozolomide showed a manageable safety profile with limited clinical activity.

Trial registry ClinicalTrials.gov NCT2813135. Registered on: 24 June 2016.

1 Introduction

There is still a high unmet medical need to provide more effective treatments for the 20% of children with cancer who are not currently cured [1]. Precision cancer medicine programs aim to adapt rescue treatments to the biological features of recurrent or refractory tumors, and to move the most promising agents into earlier lines of therapy, including front-line therapy, where relevant. Successful treatments have already been defined for small populations exhibiting

Key Points

AcSe-ESMART is the first trial to investigate the safety and anti-tumor activity of fadraciclib in children with relapsed/refractory tumors.

Fadraciclib combined with temozolomide was tolerable in children; adverse events were predominantly hematologic.

Limited activity in patients whose tumors had cell cycle–related molecular alterations may in part be related to the intravenous formulation and absence of prolonged exposure to fadraciclib.

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unique actionable key driver events [2, 3]. However, most patients have complex cancers that mandate adapted combination strategies [4–7].

The pediatric precision cancer medicine platform trial AcSé-ESMART (European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors; ClinicalTrials.gov identifier: NCT02813135) was developed as a proof-of-concept, phase I/II trial, designed to explore targeted agents in a molecularly guided and enriched pediatric cancer patient population [8, 9].

Among the broad range of molecular targets under investigation in AcSé-ESMART are cyclin-dependent kinases (CDKs). These enzymes regulate two fundamental processes in cancer cells: cell-cycle progression and transcription [10]. Dysregulation of CDKs, through genetic or epigenetic changes, drives unchecked cell growth and is recognized as one of the hallmarks of cancer [11]. Although clinical development initially concentrated on CDK4/6 inhibitors in adult breast cancer, the focus has expanded toward other CDKs, notably CDK7, CDK9, CDK12, CDK13, and CDK2 [12]. Pediatric malignancies such as sarcomas, central nervous system (CNS) tumors (e.g., medulloblastoma, ependymoma, high-grade glioma), acute leukemias, and neuroblastomas frequently harbor aberrations in these pathways [13–17]. In addition, *MYCN* gene–amplified tumors heavily depend on increased transcription of specific oncogenes for their survival. This reliance makes them potentially more vulnerable to drugs that target transcriptional kinases such as CDK7 [18]. In addition, the presence of an intact Rb gene is noteworthy, as Rb is a crucial gatekeeper at the G1-S checkpoint. By preserving Rb function, CDK inhibition can further block cell-cycle progression in tumors that rely on Rb phosphorylation [19].

Fadraciclib (CYC065) has emerged as a prime example of a dual inhibitor targeting both CDK2 and CDK9 [20]. By inhibiting CDK9, fadraciclib diminishes the phosphorylation of RNA polymerase II and thereby reduces the transcription of oncogenes and survival factors essential for many aggressive tumors. Meanwhile, inhibition of CDK2 disrupts cell-cycle progression at the G1-to-S phase transition, compounding the anti-proliferative impact [21, 22].

Preclinical studies have consistently shown that fadraciclib induces significant cytostatic effects across a variety of pediatric tumor models, showing synergy when combined with chemotherapies or targeted agents [23, 24]. In *MYCN*-amplified neuroblastoma, fadraciclib reduces cell viability and promotes apoptosis in vitro, and in xenograft models; these effects are markedly enhanced when combined with temozolomide, indicating a synergistic mechanism [24]. Similarly, in acute myeloid and lymphoblastic leukemia models, fadraciclib exerts cytotoxicity with further additive benefits observed when paired with cytarabine [20, 23]. Although data in other pediatric solid tumors such as sarcomas are more limited, early studies suggest that fadraciclib may also be useful [25].

Fadraciclib was first evaluated in a first-in-human phase I trial administered as a 4-hour intravenous infusion once every 3 weeks, establishing a recommended phase II dose (RP2D) of 192 mg/m^2 with predominantly hematologic dose-limiting toxicities. Pharmacokinetics showed increasing exposure with dose and an average half-life of approximately 1.6–3.9 hours. Pharmacodynamic assessments included RNA polymerase II phosphorylation reduction and MCL1 levels suppression observed at the RP2D [26]. This adult IV experience provided the rationale for selecting an intermittent IV dosing approach in pediatric Arm K and informed the choice of the starting dose in combination with temozolomide. Subsequently, alternative adult schedules were explored, including a 1-hour IV regimen and oral dosing [27] [28]. Although objective responses in monotherapy were infrequent, stable disease was observed in 20 out of 31 evaluable patients in the oral monotherapy fadraciclib adult trial (NCT04983810) [27], and early combination studies with cytarabine or venetoclax have shown promising synergistic effects and clinical trials are ongoing [29]. Together with robust preclinical data, these findings supported advancing fadraciclib into pediatric clinical trials.

Arm K of the AcSé-ESMART trial aimed to evaluate the CDK2/9 inhibitor fadraciclib in combination with temozolomide in patients with solid pediatric malignancies, which harbored specific molecular alterations targetable directly or indirectly by fadraciclib. A parallel sub-protocol, Arm L, combining fadraciclib with cytarabine, was planned in patients with hematologic malignancies but did not enroll. Therefore, Arm L design details are provided in the electronic supplementary material (ESM) and Supplementary Table 1, and the present manuscript focuses on Arm K.

2 Patients and Methods

2.1 Study Population and Eligibility of AcSé-ESMART

Patients were eligible if they had a relapsed/refractory solid or hematologic malignancy and had undergone advanced molecular tumor profiling (i.e. whole exome [WES], whole transcriptome [WTS] sequencing) from on-purpose biopsy at treatment failure, or exceptionally at diagnosis, prior to inclusion. Main inclusion criteria were age <18 years at inclusion or young adults with a pediatric-type cancer, evaluable or measurable disease, Karnofsky or Lansky performance status ≥70, and adequate organ function. Key exclusion criteria included symptomatic CNS metastases, disease that could significantly alter oral drug absorption,

unresolved ≥CTCAE grade 2 treatment-related toxicity, systemic anticancer therapy within 21 days prior to the first dose (or within 5 half-lives, whichever was shorter); radiotherapy within 21 days or within 6 weeks for therapeutic mIBG doses or craniospinal irradiation and major surgery within 21 days.

Reports and the sequencing details from the prior national or international molecular tumor boards were reviewed within the weekly AcSé-ESMART tumor board to confirm eligibility and arm assignment.

Written informed consent/assent of patients and parents/legal representatives was obtained prior to any study procedure.

2.2 Study Design of Arm K

This study arm K was conducted within the AcSé-ESMART platform trial, which encompasses multiple molecularly driven sub-protocols. Candidates for Arm K were patients considered suitable for temozolomide therapy whose tumors exhibited one or more specific genetic alterations involving disruptions to cell cycle pathways, potentially rendering them susceptible to treatment with fadraciclib. These alterations included *MYCN* amplification or increased MYCN oncoprotein expression, *MYC* aberrations or increased MYC oncoprotein expression, SMARCB1/INI1 loss, *SMARCA4* loss or mutations, *ARID1A* mutations, *MLL* aberrations, amplifications of *MCL1*, *CCND1* (Cyclin Ds), *CCNE1* (Cyclin Es), *HDM2*, and other cell cycle gene abnormalities such as *CDK4/6* amplification, deletion of *CDKN2A* and/or *CDKN2B*, or other alterations in the D-cyclin-CDK4/6-INK4a-Rb pathway with a wild-type *Rb* gene.

Prior treatment with temozolomide or a CDK inhibitor was allowed given that use here would be in combination with temozolomide. Prophylactic use of hematopoietic growth factors was not permitted.

The primary objective of the phase I part was to determine the RP2D of fadraciclib in combination with temozolomide in children/adolescents with recurrent or refractory malignancies harboring specific molecular alterations; the phase II part was to determine the activity of the combination in this population.

The trial was approved by independent ethics committees and national medical authorities, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

2.3 Treatment and Dose Levels

Fadraciclib was provided by Cyclacel and administered intravenously over 4 hours either on Day 1 only (DL1) or on Days 1 and 15 (DL2 and DL3). Temozolomide was given orally once daily (QD) at the pediatric RP2D of 150 mg/m^2/day on Days 1–5 of a 28-day cycle. The starting dose level (DL1) was fadraciclib 135 mg/m^2 on Day 1 and temozolomide 150 mg/m^2/day, with planned escalations of fadraciclib to 135 mg/m^2 on Day 1 and Day 15 (DL2), then 150 mg/m^2 on Day 1 and Day 15 (DL3). The temozolomide dose was not escalated. In case of intolerability of DL1, de-escalation to fadraciclib 96 mg/m^2 and temozolomide 150 mg/m^2/day (DL-1) or 100 mg/m^2/day (DL-2) were explored (ESM Supplementary Table 2; Table 4).

2.4 Statistical Design

Dose escalation was guided by the Continual Reassessment Method (CRM) targeting a 25% risk of dose-limiting toxicity (DLT), using a one-parameter power model with Bayesian inference and a weakly informative Normal prior (SD = 1). The prior skeleton of the dose-toxicity model was parameterized with $\alpha_{-2} = 0.025$, $\alpha_{-1} = 0.05$, $\alpha_1 = 0.12$, $\alpha_2 = 0.25$, and $\alpha_3 = 0.40$. Hematologic DLTs were defined as grade 3 or higher thrombocytopenia requiring transfusions for >7 days, grade 4 neutropenia for >7 days, or documented infection during a grade 4 neutropenic episode [30]. Non-hematologic DLTs were defined as grade 3 or higher adverse events, non-tolerable grade 2 toxicities, or any grade toxicity resulting in <75% administration of the planned dose. The DLT period was the first cycle. Patients were evaluable for the dose escalation phase if they had received ≥75% of the dose of both drugs in cycle 1 or had DLT. The starting dose was fixed at level 1, and escalation was planned to be halted when 10 patients had been treated at a single dose or if excessive toxicity was observed. If doses d_1, d_{-1}, and d_{-2} proved excessively toxic, enrollment required a minimum of 9 patients (3+3+3). Up to 22 patients were to be enrolled during the dose-escalation phase, with an expansion cohort of up to 10 additional patients (maximum 32 patients overall). These 10 additional patients correspond to the second step of a Fleming two-stage design ($\alpha = \beta = 10\%$) with the objective response hypotheses of H0 <10% and Ha >30% (total of 20 patients). The first step includes the 10 patients treated at the RP2D during the dose escalation. If at least one objective response was observed then stage 2 was to be initiated. If four or fewer objective responses were observed from 20 patients then this suggested the absence of activity.

R package and SAS v9.2 software were used.

2.5 Study Evaluations

Safety assessments were performed throughout the study. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.03). Response assessment was scheduled every two cycles according to the tumor type (Response Evaluation Criteria In Solid Tumors (RECIST)

version 1.1 [31] for solid tumors, Response Assessment in Neuro-Oncology (RANO) [32] for high-grade glioma and International Neuroblastoma Response Criteria (INRC) [33] for neuroblastoma.

2.6 Pharmacokinetics

Limited lithium heparinate blood sampling (2 mL) for fadraciclib pharmacokinetic (PK) analysis was collected during Cycle 1 on Day 1 (pre-dose and prior to administration of temozolomide, 4 h, 6 h, 24 h post-dose).

3 Results

3.1 Patient Characteristics and Molecular Alterations Reported

Twelve patients were enrolled between May 2021 and November 2022 and were treated in Arm K. Patients' demographics and baseline characteristics are listed in Table 1.

Median age at inclusion was 12.1 years (range 4.0–17.9), 8 (66.7%) were male. Six patients had sarcomas (osteosarcoma [$n = 3$], ossifying fibromyxoid tumor [$n = 2$], CIC::DUX4 sarcoma [$n = 1$]), four CNS tumors (diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype [$n = 1$], diffuse midline glioma, H3 K27-altered [$n = 1$], CNS embryonal tumor, not elsewhere classified (NEC), with PLAGL2 amplification [$n = 1$], and supratentorial ependymoma, ZFTA fusion-positive [$n = 1$]), one neuroblastoma, and one extra-cerebral malignant rhabdoid tumor. Sixty-seven percent had metastatic disease at study entry. Patients had received a median of three prior lines of treatment (range 1–8); all had received chemotherapy, including temozolomide in four patients; nine also underwent surgical resection and nine radiation therapy. None had received prior treatment with a cell cycle inhibitor.

All patients enrolled had a molecular alteration in their tumor involving disruption of cell cycle pathways, which was required as molecular enrichment for Arm K (Table 2). Six patients harbored alterations in genes directly related to the cell cycle kinases or cyclins (in their tumors): four in *CDKN2A* or *CDKN2B*: *CDKN2A/CDKN2B* focal homologous deletion in one patient, a *CDKN2A* pathogenic mutation associated with loss of heterozygosity [LOH] in two (one of whom also carried a sub clonal deleterious mutation in SETD2, an epigenetic tumor suppressor that plays a role in regulating cell cycle progression) or with *MYC* and *CCNE1* amplification in one. In addition, a second patient had *CCNE1* amplification together with a break point in *TP53*, and one patient demonstrated *CCND1* and *CDK4* co-amplification. In total, two patients had *MYC* amplifications, both also had alterations in homologous repair deficiency genes, and one patient had *MYCN* amplification. One patient harbored a *CIC::DUX4* fusion that disrupts transcriptional regulation, leading to uncontrolled cellular proliferation. Two patients exhibited alterations in *SMARCB1*, a critical gatekeeper molecule of the cell cycle: one with a rearrangement and one with a pathogenic mutation with LOH. Additionally, one patient carried a deleterious mutation in *SETD2* in the absence of other known cell-cycle gene alterations.

3.2 Dose-Limiting Toxicity and Recommended Phase II Dose

Eleven patients were evaluable for DLT; one patient with osteosarcoma passed away due to disease progression before completing the DLT observation period (Table 3). Two of the first four evaluable patients in DL1 (fadraciclib 135 mg/m^2 on Day 1 and temozolomide 150 mg/m^2 on Days 1–5) experienced dose-limiting myelosuppression, and DL-1 (fadraciclib 96 mg/m^2/temozolomide 150 mg/m^2) was initiated. No DLT was observed in four evaluable patients at DL-1. Thus, the dose level was re-escalated to DL1 and the subsequent three evaluable patients did not present with any DLT. The study was terminated prematurely due to a decision by the pharmaceutical company, based on emerging PK data from the ongoing adult trials, to switch the development from the intravenous to an oral formulation of fadraciclib. Despite this interruption, the toxicity probability estimated at each dose level using the CRM design may suggest that DL1 (0.204 [0.056–0.415]) and DL2 (0.353 [0.152–0.563]) are potentially candidates for RP2D (targeted toxicity of 25%) considering the uncertainty associated with these two estimates based on the 11 patients treated in the dose escalation (Table 4).

3.3 Study Treatment and Treatment-Related Adverse Events

Overall, 32 cycles of fadraciclib with temozolomide were administered to 12 patients (median 2; range 1–9). Ten patients discontinued treatment due to disease progression confirmed radiographically, one due to parental choice, and one due to early death related to clinical disease progression.

All adverse events possibly related to study treatment throughout the overall treatment duration are presented according to dose level in Table 5. Main treatment-related adverse events were hematologic, mainly thrombocytopenia (all grades 25%; G3–4 25%), anemia (all grades 25%; G3–4 8%), and neutropenia (all grades 17%; G3–4 8%). Two patients (17%) reported nausea and vomiting (grade 1–2). Both patients experiencing DLTs in cycle 1 had dose reduction in cycle 2; none of the treatment cycles after cycle 1 required delay.

Table 1 Patients' characteristics included in Arm K ($n = 12$)

Demographic category	Total patients, $N = 12$
Age at study entry (years)	
Median (Q1 ; Q3)	12.1 (6.8 ; 15.8)
Range	4.0 ; 17.9
Age at diagnosis (years)	
Median (Q1 ; Q3)	10.5 (4.0 ; 14.0)
Range	0.6 ; 16.2
Gender	
Male	8 (66.7%)
Female	4 (33.3%)
Performance status: Lansky Play Scale/Karnofsky Score	
100%	4 (33.3%)
90%	4 (33.3%)
80%	2 (16.7%)
70%	2 (16.7%)
Histological diagnosis	
Sarcoma	
Osteosarcoma	3 (25.0%)
Ossifying fibromyxoid tumor (OFMT)	2 (16.6%)
CIC::DUX4 sarcoma	1 (8.3%)
Other solid tumors	
Neuroblastoma	1 (8.3%)
Extra-cerebral malignant rhabdoid tumor	1 (8.3%)
Central nervous system tumors	
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	1 (8.3%)
Diffuse midline glioma, H3 K27-altered	1 (8.3%)
CNS embryonal tumor, NEC, with PLAGL2 amplification	1 (8.3%)
Supratentorial ependymoma, ZFTA fusion-positive	1 (8.3%)
Time between initial diagnosis and inclusion (years)	
Median [range]	1.9 [0.8 ; 2.9]
Metastatic at study entry	
Yes	8 (66.7%)
No	4 (33.3%)
Prior anticancer treatment	
Prior treatment lines: median [range]	3 [2–8]
Systemic lines of treatment: median [range]	2 [1–3]
Chemotherapy	2 [1–3]
Prior cell cycle inhibitor	0 (0.0%)
Prior temozolomide	4 (33.3%)
High-dose regimen with stem cell rescue	1 (8.3%)
Radiation therapy	9 (75.0%)
Surgical resection	9 (75.0%)

NEC not elsewhere classified

3.4 Antitumor Activity

No objective tumor response was observed across the 12 patients treated at the two-dose levels. Two patients had stable disease; one patient with supratentorial ependymoma (ZFTA fusion-positive) for six cycles and one patient with an extra-cerebral malignant rhabdoid tumor for nine cycles of fadraciclib with temozolomide. Both patients subsequently discontinued treatment due to disease progression.

The female patient with supratentorial ependymoma ZFTA fusion-positive, diagnosed in September 2019 with a left parietal supratentorial region lesion, had presented

Table 2 Molecular characteristics and outcome in all patients included in Arm K ($n = 12$)

Pat no	Diagnosis	DL	DLT	Molecular alterations in cell cycle	Other alterations reported in the MTB report	Total cycles received	Best response
K-01	Ossifying fibromyxoid tumor	1	No	*CDKN2A/B* 0.23 Mb focal homozygous deletion	*BCOR* homozygous intragenic deletion; *ZC3H7B* homozygous deletion; *MAP3K14* mutation; *CTPS2* mutation	2	PD
K-02	Osteosarcoma	1	No	*MYC* amplification	*RAD21* mutation; *COX6C* mutation; *UBR* mutation; *WWTR1* amplification; *BAX* mutation; *CEBPA* mutation; *CIC* mutation; *ERCC2* mutation; *PPP2R1A* deletion	1	PD
K-03	Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype (frontoinsular)	1	Yes	*CDKN2A c.172C>T* p.*(Arg58*) VP VAF 45% with LOH;* *SETD2* c.1858C>T p.(Arg620*) VP VAF 7%	*TP53* mutation; *EGFR* mutation; *BCOR* mutation; *NF2* mutation; chromosome 7 polysomy	2	PD
K-04	Diffuse midline glioma, H3 K27-altered (cerebellum)	1	Yes	*CCND1* amplification (21.3 copies); *CDK4* amplification (5.2 copies)	*TP53* mutation; *H3F3A* mutation	2	PD
K-05	CIC::DUX4 sarcoma	−1	No	*CIC::DUX4*	*JAK1* mutation; *EML4* mutation	1	PD
K-06	Supratentorial ependymoma, ZFTA fusion-positive	−1	No	*CDKN2A* c.225_243dup p.(Val82ArgfsTer44) VP VAF 88% with LOH	*PTCH1* mutation and LOH; *ZFTA* fusion	6	SD
K-07	Extra-cerebral malignant rhabdoid tumor	−1	No	*SMARCB1* exon 6 and TLE6 intron 13 rearrangement		9	SD
K-08	Neuroblastoma	−1	No	*MYCN* amplification (9 copies)	*FGFR3* mutation	2	PD
K-09	Ossifying fibromyxoid tumor	1	No	*SMARCB1* c.1130G>A exon 9 p.(Arg377His) VP, VAF 59% with LOH	*TET2* mutation	2	PD
K-10	Osteosarcoma	1	No	*CCNE1* amplification (13 copies)	TP53 gene break	2	PD
K-11	CNS embryonal tumor, with PLAGL2 amplification (thalamic/ hemispheric)	1	No	*SETD2* c.691delA p.(Ser231fs) VP VAF 50%	*BCOR* mutation; *DNMT3B* amplification; *ASXL1* amplification; *PLAGL2* amplification; *ASXL1::NECAB3* fusion	2	PD
K-12	Osteosarcoma	1	NE	*MYC* amplification (13 copies); *CDKN2A* c.176T>G exon 2 p.(Val59Gly) VP VAF 66%; *CCNE1* amplification (6 copies)	*RAD54L* mutation	1	PD

CNS central nervous system, *DL* dose level, *DLT* dose-limiting toxicity, *LOH* loss of heterozygosity, *MTB* molecular tumor board, *NE* non-evaluable, *PD* progressive disease, *SD* stable disease, *VAF* variant allele frequency, *VP* pathogenic variant

Table 3 Dose-limiting toxicities per dose level in all patients enrolled in arm K ($n = 12$)

Dose level	Treatment per 28-day cycle: Fadraciclib day 1 Temozolomide day 1–5	Enrolled/treated	DLT/evaluable for DLT	DLTs
DL1	Fadraciclib 135 mg/m^2/d Temozolomide 150 mg/m^2/d	4/4	2/4	K-03 G3 thrombocytopenia lasting >7 days and necessitating transfusion K-04 G4 neutropenia, G3 thrombocytopenia lasting >7 days and necessitating transfusion
DL−1	Fadraciclib 96 mg/m^2/d Temozolomide 150 mg/m^2/d	4/4	0/4	
DL1	Fadraciclib 135 mg/m^2/d Temozolomide 150 mg/m^2/d	4/4	0/3*	

*One patient was not DLT-evaluable due to death from disease progression before completion of cycle 1

DL dose level, *DLT* dose-limiting toxicity, *G* Grade

Table 4 Dose levels of arm K and probabilities of toxicity after 11 patients treated and evaluable for DLT in dose-escalation

Dose level	Treatment over a 28-day cycle		Probability of toxicity with lower and upper credible limits of toxicity rates ($n = 11$)
DL−2	Temozolomide 100 mg/m^2 QD Day 1–5	Fadraciclib 96 mg/m^2/d iv Day 1	0.063 [0.007–0.217]
DL−1	Temozolomide 150 mg/m^2 QD Day 1–5	Fadraciclib 96 mg/m^2/d iv Day 1	0.106 [0.017–0.289]
DL1	Temozolomide 150 mg/m^2 QD Day 1–5	Fadraciclib 135 mg/m^2/d iv Day 1	0.204 [0.056–0.415]
DL2	Temozolomide 150 mg/m^2 QD Day 1–5	Fadraciclib 135 mg/m^2/d iv Day 1 & 15	0.353 [0.152–0.563]
DL3	Temozolomide 150 mg/m2 QD Day 1–5	Fadraciclib 150 mg/m^2/d iv Day 1 & 15	0.503 [0.288–0.684]

DLT dose-limiting toxicity, *iv* intravenously, *QD* once-daily dosing

with two previous metastatic relapses, treated with surgical resections and radiotherapy. Whilst receiving fourth-line treatment with sirolimus and irinotecan, she experienced a new local and metastatic relapse that included meningeal and bilateral frontal involvement, leading to enrollment in the AcSé-ESMART trial. On a biopsy performed at that point, whole exome and RNA sequencing confirmed the ZFTA rearrangement and identified a homozygous deletion of *NUTM2A*, an inactivating *CDKN2A* mutation and a *PTCH1* variant.

The male patient with an extra-cerebral malignant rhabdoid was initially diagnosed in March 2020 with a tumor in the costal region. Following extensive chemotherapy and the EZH2 inhibitor tazemetostat, he underwent a third-line treatment for metastatic relapse in the METRO-PD1 trial (nivolumab in combination with 3 metronomic chemotherapy [34], for 6 months, after which he progressed further and was enrolled in the AcSé-ESMART trial. Molecular profiling from diagnosis revealed a key rearrangement of *SMARCB1*, along with additional genetic alterations.

Overall, the median progression-free survival was 1.75 months [95% CI 0.8–2.6] and the median overall survival was 5.9 months [95% CI 2.9–7.0] in all treated patients.

3.5 Pharmacokinetics

PK sampling for fadraciclib was performed with a total of 94 blood sample collections on Day 1 and Day 2 of cycle 1 from the 12 patients receiving study treatment at 96 mg/m^2 ($n = 4$), and 135 mg/m^2 ($n = 8$) on Day 1. Despite prior agreement, and sample collection as per protocol, the Cyclacel laboratory leadership unfortunately declined to proceed with the PK analysis following discontinuation of the intravenous formulation development for adults.

Table 5 Maximum adverse events per patient possibly related to fadraciclib and temozolomide during overall duration and a total of 32 cycles in 12 patients treated

CTCAE v4.0 term	DL-1 ($n = 4$)			DL1 ($n = 8$)			Total ($n = 12$)		
	All grades n (%)	Grade n (%)		All grades n (%)	Grade n (%)		All grades n (%)	Grade n (%)	
		3	4		3	4		3	4
Hematologic disorders									
Anemia	1 (25)			2 (25)	1 (13)		3 (25)	1 (8)	
White blood cell decreased	1 (25)			1 (13)			2 (17)		
Neutrophil count decreased				2 (25)		1 (13)	2 (17)		1 (8)
Lymphocyte count decreased				1 (13)			1 (8)		
Platelet count decreased	1 (25)		1 (25)	2 (25)		2 (25)	3 (25)		3 (25)
Febrile neutropenia				1 (13)	1 (13)		1 (8)	1 (8)	
Gastrointestinal disorders									
Nausea	1 (25)			1 (13)			2 (17)		
Vomiting				2 (25)			2 (17)		
Constipation				1 (13)			1 (8)		
General disorders and administration site									
Fatigue				1 (13)			1 (8)		
Anorexia	1 (25)						1 (8)		
Pain	1 (25)						1 (8)		
Infusion site extravasation	1 (25)						1 (8)		
Investigations									
GGT increased	1 (25)						1 (8)		
Hyponatremia	1 (2%)			1 (13)			1 (8)		
Hypokalemia				1 (13)			1 (8)		
Hypertriglyceridemia				1 (13)			1 (8)		
Nervous system disorders									
Vasovagal reaction	1 (25)	1 (25)					1 (8)	1 (8)	
Skin disorders									
Pruritus				1 (13)			1 (8)		

GGT γ-glutamyl transferase, *NCI-CTCAEv4.0* National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

4 Discussion

This is the first-in-child evaluation of the dual CDK2/9 inhibitor fadraciclib in combination with temozolomide in a molecularly enriched pediatric population. The safety profile was favorable and manageable, primarily characterized by hematologic adverse events; as the trial was closed prematurely, the final tolerable intravenous fadraciclib dose could be estimated at 135 mg/m^2 on Day 1 or Day 1 and 15. In the 12 heavily pretreated children with advanced solid tumors, no objective responses were observed, albeit that two patients on treatment experienced stable disease for several months.

In a limited number of 32 treatment cycles administered to the 12 enrolled patients, the main treatment-related adverse events and dose-limiting toxicities were hematologic. Thrombocytopenia G3–4 occurred in 25% of patients, neutropenia and anemia G3–4 in 8% each. DLTs at the initial dose level at 70% of the BSA-equivalent adult q3 weeks dose of fadraciclib and the RP2D of temozolomide included grade 3 prolonged thrombocytopenia for >7 days in two patients, necessitating platelet transfusions in one patient associated with grade 4 neutropenia. Hematologic toxicity and DLTs were also reported in adult phase I trials of single-agent fadraciclib [26–28] but align also with the known toxicity profile of temozolomide-based regimens [35]. This is further in line with the toxicities described for other cyclin inhibitors evaluated in children to date, such as ribociclib, palbociclib, and abemaciclib [36–39]. Non-hematologic events were rare in our pediatric cohort, a more favorable experience compared with that seen in adults [26–28].

Given the premature study closure, an RP2D could not be formally established with the pre-planned level of certainty.

Nonetheless, the CRM-based toxicity probability estimates, together with the observed DLTs, suggest that DL1 (fadraciclib 135 mg/m^2 Day 1 + temozolomide 150 mg/m^2 Days 1–5) and DL2 (fadraciclib 135 mg/m^2 Days 1 and 15 + temozolomide 150 mg/m^2 Days 1–5) are candidate dose levels, acknowledging the uncertainty of these estimates and the limited clinical evaluation of the Day 15 schedule.

Strong promising preclinical evidence for dual inhibition of CDK2/9 in both solid and hematologic tumors prompted us to start this first-in-child fadraciclib trial in combination with active doses of chemotherapy. Rare partial responses to fadraciclib as a single agent were observed in the adult population (e.g., in one patient with *MCL1*-amplified endometrial carcinoma and another with T-cell lymphoma harboring a *CDKN2A* mutation [27, 28]). Therefore, we included only patients whose tumors exhibited genetic alterations in the cell-cycle pathways based on evidence in adults or in preclinical studies possibly associated with sensitivity to CDK2/9 inhibition and its combination. Nevertheless, no patient demonstrated objective tumor responses within our study. Importantly, in adults with advanced solid tumors and lymphoma, fadraciclib monotherapy administered either by 1-hour IV infusion or orally on days 1, 2, 8, and 9 every 3 weeks demonstrated only modest activity, whereas oral fadraciclib given 3–5 days per week for 3–4 days out of every 4 weeks or daily for 4 consecutive weeks has led to stable disease in 62% of patients [27, 28]. Also, further preclinical evidence suggests that maintaining uninterrupted inhibition of the target is essential for fadraciclib's antitumor efficacy. In model systems, once the drug was removed, phosphorylation of RNA Pol II and Mcl-1 expression returned to baseline, and further cell death was not observed [40]. These findings underscore the importance of sustaining therapeutically active levels of the CDK9 inhibitor for at least 10–12 hours in clinical settings. Consequently, there is a growing hypothesis that continuous or protracted dosing may be required to achieve potent transcriptional suppression of oncogenic drivers. Therefore, the RP2D of oral fadraciclib in adults was defined at 100 mg twice per day for weeks 1–4 of 28-day cycles [27], and a phase II trial was launched [41], whereas the development of the intravenous formulation was discontinued. Unfortunately we could not proceed with the PK analysis, which, despite the limited numbers of patients, would have been helpful especially for any further pediatric development of a potential future oral solution of fadraciclib. This highlights a common issue still faced in pediatric oncology drug development, where alterations to the adult drug development program by pharmaceutical sponsors or partners can (and very unfortunately do) impact negatively on access to innovative therapies for children. To mitigate against similar situations in future pediatric oncology trials, academic sponsors may consider (i) upfront agreements securing completion and/or transfer of key bioanalytical deliverables (including the option to run analyses at an independent laboratory if support is withdrawn); (ii) protected funding for essential correlative studies (PK/PD/biomarkers); and (iii) contingency plans for formulation/schedule changes with clear data and sample access to enable analysis and reporting even if the development program changes.

A key rationale for investigating CDK inhibitors in pediatric cancers is the high frequency of cell-cycle dysregulation in tumors of high unmet need for new approaches to therapy such as sarcomas, high-grade CNS tumors, neuroblastoma, and various leukemias [14, 15]. Fadraciclib offers a mechanistic rationale for use in this setting. However, meaningful clinical benefit depends on identifying the optimal schedule, synergistic combination partners, and reliable biomarkers. Comparable challenges have arisen with other pediatric CDK inhibitors, particularly CDK4/6 inhibitors, which have shown limited single-agent efficacy in children [36, 42, 43]. As a result, these agents are often combined with various chemotherapies (e.g., reinduction protocols, topoisomerase inhibitors, or alkylators) in an effort to improve outcomes, although in several of these trials, the combination with cytotoxic chemotherapy has been intolerable at dose levels where responses might be expected, and most pediatric trials have reported stable disease rather than objective remissions to date [37–39].

Multiple CDK2 and CDK9 inhibitors are under clinical development, primarily in adults, with ongoing efforts to assess their safety and efficacy in the pediatric population. Table 6 summarizes all CDK2 and CDK9 inhibitors currently in clinical development, their clinical status, and any reported pediatric trials. Despite their potential utility in pediatric cancers, the absence of pediatric investigational plans for these inhibitors reflects the frustrating yet regulatorily compliant delays to new drug development for children and young people with cancer created by waivers and deferrals within the current EU regulatory framework, alongside a persistent focus on adult-first development incentives instead of a child-first development approach.

Our experience contributed to discussions at the ACCELERATE multi-stakeholder 12th Pediatric Strategy Forum on CDK4/6, CDK7 and CDK9 inhibitors, which was held in Amsterdam in October 2023, with a view to making recommendations on the optimal development of these agents [44].

Currently, no clinically validated biomarker exists (in children or in adults) to predict response to CDK inhibition, despite extensive preclinical work suggesting heightened susceptibility in tumors harboring cell-cycle aberrations [45–48]. Accordingly, our trial enrolled a relatively broad patient population enriched for hypothesized cell-cycle abnormalities, such as *MYC/MYCN* amplifications, *CDKN2A*/B deletions, or *SMARCB1* alterations. While two participants (one with ependymoma carrying a *CDKN2A* mutation and one with extra-cerebral malignant rhabdoid tumor harboring a *SMARCB1* rearrangement), experienced stable disease, the other ten patients, who had various genetic backgrounds (e.g. *MYC/N* amplifications, *CDKN2A/B* alterations, or *CCNE1/CCD1/CDK4* amplifications), derived no

Table 6 Overview of CDK2 and CDK9 inhibitors: clinical trials in adults and children

Compound	Company	Target	Adult trials	Formulation	Pediatric trials	PIP
Fadraciclib (CYC065)	Cyclacel	CDK2/9	6 studies (NCT05817890 NCT04983810 NCT05168904 NCT03739554 NCT02552953 NCT04017546)	IV/oral	Phase I/II in relapsed/refractory tumors: Fadraciclib + TMZ Fadraciclib + cytarabine (NCT02813135 ESMART trial, terminated)	No
Flavopiridol (Alvocidib)	Tolero/ Sumitomo	Pan-CDK 1st generation CDK 1/2/4/6/(9)	65 studies Phase I/II	IV/oral	Phase I monotherapy in relapsed/refractory solid tumors or lymphoma (NCT00012181 terminated) Phase I monotherapy in relapsed/refractory leukemia NCT00101231 terminated) Phase I monotherapy in advance solid tumors. T1287 oral prodrug (NCT03604783 terminated). >12 years old	No
KB-0742	Kronos Bio	CDK9	1 study Phase I/II	Oral	Phase I/II in relapsed/refractory solid tumors or NHL in monotherapy (NCT04718675; terminated). >12 years old Development of agent terminated due to toxicity in adults	No
Seliciclib (Roscovitine)	Cyclacel	Pan-CDK 1st generation (CDK 1/2/5/7)	7 studies Phase I/II	Oral	No	No
Dinaciclib (MK-7965)	MSD	Pan-CDK 2nd generation (CDK 1/2/5/9)	18 studies Phase I/II/III	IV	No	No
Riviciclib hydrochloride (P276-00)	Piramol	Pan-CDK 2nd generation (CDK 1/2/4/6/9)	11 studies Phase I/II	IV	No	No
Zotiraciclib (TG02 / SB1317)	Tragara	CDK/JAK2/FLT3 (CDK 1/2/7/9)	7 studies Phase I/II	Oral	No	No
Roniciclib	Bayer	Pan-CDK 2nd generation (CDK 1/2/3/4/6/7/9)	9 studies phase I/II	Oral	No	No
PHA-793887	Nerviano	Pan-CDK 2nd generation (CDK 1/2/4)	9 studies phase I/II	IV	No	No
RGB-286638	Agennix	Pan-CDK 2nd generation (CDK 1/2/3/4/5/8/(6/7)	2 studies phase I	IV	No	No
Atuveciclib	Bayer	CK9	2 studies Phase I	Oral	No	No
Enitociclib	Bayer	CK9	2 studies Phase I	IV	No	No
SNS-032	Sunesis	Pan-CDK 2nd generation (CDK 2/7/9) + mTORC1/2 in AML	3 studies Phase I	IV/oral	No	No
AT-7519	Astex	Pan-CDK 2nd generation	3 studies Phase I/II	IV	No	No
AZD-4573	AstraZeneca	CDK9	3 studies Phase I/II	IV	No	No
PF-07104091	Pfizer	CDK2	2 studies Phase I/II	Oral	No	No

Last data review: November 2025

AML acute myelogenous leukemia, *CDK* cyclin-dependent kinase, *IV* intravenous, *mTORC* mammalian Target of Rapamycin Complex, *NHL* non-Hodgkin lymphoma, *PIP* Pediatric Investigation Plan, *TMZ* temozolomide

benefit. It remains unclear whether the stable disease in these two individuals reflected genuine molecular sensitivity to CDK2/9 blockade or merely a slower natural course of their disease or an effect of temozolomide (both had not received it previously). Additionally, despite *MYCN*-amplified neuroblastoma being the disease with the most robust preclinical data for activity in vitro and in vivo, including in combination with temozolomide, only one patient with

neuroblastoma was enrolled in Arm K, and this patient had progressive disease. Whilst there are many strengths to tumor agnostic exploratory signal-seeking platform trials, it may also be helpful once the RP2D has been confirmed in a mixed cohort to pull out histology specific expansion cohorts (as was done for Ewing sarcoma in Arm D of the ESMART trial), thereby utilizing the platform trial infrastructure to obtain additional disease-specific data to take forward in subsequent trials.

Our ESMART trial design included also a second fadraciclib arm (Arm L), investigating fadraciclib plus cytarabine in hematologic malignancies, but it did not enroll any patients. The failure to accrue is likely explained by the availability of multiple alternative rescue options for children with relapsed or refractory leukemias (including hematologic stem cell transplantation and CAR-T cell options), combined with the challenges of finding a sufficiently enriched population for an investigational regimen. These same difficulties have been encountered in multiple pediatric precision-oncology trials, including other arms of ESMART (just 2 out of 297 patients enrolled so far overall had a leukemia), where strict molecular criteria need to be balanced against the small potential enrollment pool as is the case for MLL (KMT2A)-rearranged leukemia. These observations suggest that, whilst leukemia patients can benefit from precision medicine approaches, trial design often needs to be distinct from that used for solid-tumor platform cohorts. Possible approaches include broader molecular eligibility criteria, regimens integrated into salvage backbones, evaluated in post–cellular-therapy settings, or used as maintenance in complete remission, which may be more likely to accrue while still enabling biomarker-driven questions.

In conclusion, although this phase I/II study did not yield objective responses, it established first data on the safety and feasibility of combining fadraciclib with temozolomide in pediatric patients and underscores the possible value of a more prolonged dosing regimen to fully exploit dual CDK2/9 inhibition. Future development of transcriptional CDK inhibitors for children should emphasize combination strategies supported by robust preclinical evidence, dosing schedules that maintain prolonged target inhibition, age-appropriate formulations, and biomarker-driven enrollment criteria.

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Declarations

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Conflicts of interest ARS has had an advisory role for Eusapharma and SANOFI and an IDMC role for Miltenyi Biotec. LVM has had an advisory role for Alligator Biosciences, Bayer, DayOne Biopharmaceuticals, Illumina and Merck KGaA, and IDMC roles for Eisai and Merck. NA had an advisory role for MERCK and Norgine and receives grants (institution) from Bristol Myers Squibb and drugs for a trial from Bristol Myers Squibb, Pierre Fabre, MERCK, Pfizer and travel support from Roche, Novartis, Alexion; he has IDMC roles for ITM Radiopharma. SA has an advisory role for research funding support for FORE pharmaceutical, Lilly and Ipsen and is co inventory of a patent for temozolomide oral suspension. IA has had an advisory role for Alexion. SD has had an IDMC role for Orphelia Pharma. BG has had an advisory role for AstraZeneca, and IDMC roles for Roche and Novartis. EK, JR, SN, ET, CB, and GLT declare no conflict of interest that might be relevant to the contents of this manuscript.

Ethics Approval This study was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to Participate Written informed consent was obtained from parents, patients, or legal representatives.

Consent for Publication Not applicable.

Availability of Data and Material Data from this clinical trial are available from the authors and can be requested by completing the data request form for Gustave Roussy clinical trials at https://redcap.gustaveroussy.fr/redcap/surveys/?s=DYDTLPE4AM. The trial steering committee and the sponsor will review the requests on a case-by-case basis. A specific agreement between the sponsor and the researcher may be required for data transfer.

Code Availability Not applicable.

Authors' Contributions All authors contributed to collection and assembly of data, and to data analysis and interpretation. All authors critically reviewed the manuscript, provided final approval, and agreed to be accountable for all aspects of the work.

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