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Real life data of ONC201 (dordaviprone) in pediatric and adult H3K27-altered recurrent diffuse midline glioma: Results of an international academia-driven compassionate use program

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ABSTRACT

Introduction: H3K27-altered diffuse midline gliomas (DMG) have limited therapeutic options and a very poor prognosis. Encouraging responses were observed in early clinical trials with ONC201. As ONC201 was unavailable in Europe, a compassionate use program supported by the French Authorities was launched for patients at progression after standard of care radiotherapy.

Methods: This program was developed by the French Society of Pediatric Oncology (SFCE) and Association des Neuro-Oncologues d'Expression Française in collaboration with the French National Agency For Medicines and Health Products Safety and Parents Associations.

Results: 174 patients (102 children, 72 adults) from 14 countries were treated from November 2021 to August 2023 at Gustave Roussy Institut (Villejuif, France). 37 % received a second course of irradiation at the time of relapse. Median duration of treatment was 57 days or 1,9 months (mo) (range 1–456 days). Median OS since diagnosis for the whole cohort was 466 days or 15,5 mo (112–2612 days); 426 or 14,2 mo (112–2612 days) and 590 or 19,6 mo (range 160–1881) for children and adults, respectively ($p = 0.001$). Median OS after ONC201 start was 143 days or 4,7 mo (1–711 days) for the whole cohort. Univariate and multivariable analysis identified site (thalamus) and age (older) as favorable prognostic factors. Reirradiation was associated with significantly longer survival after ONC201 start only in children.

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Conclusion: While the efficacy of ONC201 needs validation in a controlled randomized clinical trial, our real-life data support a better outcome for patients with thalamic tumors treated with ONC201. We demonstrated furthermore the feasibility of a successful academia-driven compassionate use program

1. Introduction

Diffuse midline gliomas (DMGs) are among the most challenging tumors to treat in children and adults. Approximately 90 % of cases harbor a lysine 28 to methionine mutation in histone H3 encoding genes [*HIST1H3B / H3C2* (H3.1) or H3F3A / *H3–3A* (H3.3)] [1–4]. Tumors showing typical DMG histology that lack H3K27M mutation can be detected by immunohistochemistry (IHC) using the overexpression of EZHIP and have been recently described as part of the DMG family [5]. The treatment of DMG is based mainly on radiotherapy both in adults and children. However, after an initial transient response, patients invariably progress with limited chances of being cured [6,7]. No major improvement has been achieved in treating these patients over the last 50 years, with a median overall survival of 9 - 12 months regardless of the treatment for pediatric patients and 23 months for adult ones [8–13].

ONC201 has recently emerged as a promising agent for treating DMGs, with signs of efficacy, mainly in adult patients with progressive DMG bearing H3K27M mutation [14]. ONC201 is a first-in-class small molecule that antagonizes the G protein-coupled receptor (GPCR) and dopamine receptors D2 (DRD2) and DRD3 [15–20].

ONC201 was developed in the USA by OncoceuticsTM and ChimerixTM, but until the initiation of the present program, the drug was not available in Europe for compassionate use.

Given the promising phase II results in adult gliomas with H3K27M mutations [14], the safe toxicity profile described in 2017 by Stein et al. in the first-in-human phase 1 trial of ONC201 [21], and the preliminary results in pediatric patients with DIPG [14], a compassionate use program was launched, but limited to the USA [21].

Thanks to a multi-stakeholder collaboration, an academia-driven program strongly supported by the French competent authority was set up to provide ONC201 access in Europe. Patient organizations waiting for access to new treatments and who were aware of the compassionate program in the US supported this program.

2. Methods

2.1. ONC201 expanded access program

The ONC201 expanded access program was approved by the French National Agency For Medicines and Health Products Safety.

The protocol is publicly available on the ANSM website (https://ansm.sante.fr/uploads/2021/11/02/20211102-put-pm-onc201.pdf), and more information for patients and parents is provided on the Gustave Roussy website (https://www.gustaveroussy.fr/fr/onc201). From a financial point of view, cross border health costs were covered by the European S2 mechanism of reimbursement (https://europa.eu/your-europe/citizens/health/planned-healthcare/right-to-treatment/index_en.htm) or by private funding.

2.2. ONC201 compounding

Due to the absence of the original pharmaceutical compound, Gustave Roussy Pharmacy developed a hospital preparation from a chemical compound that was requalified following ICH guidelines [22].

2.3. Patients

Patients with a progressive H3K27-altered DMG after upfront therapy, including radiotherapy, were eligible for the compassionate use program with no lower nor upper age limit for inclusion. H3K27 alterations were requested for treatment with ONC201, including: H3K27M mutations (identified by gene panel NGS or Whole Exome Sequencing); H3K27 trimethylation (3meH3K27) loss by immunohistochemistry (IHC); EZHIP overexpression at IHC (H3K27M wild-type). Pathology was confirmed by a central review (Neuro-Oncology Clinico-Pathology network, RENOCLIP). For patients coming from outside France, local pathology was accepted. Information regarding somatic TP53 mutations was collected when available. Location of primary tumor was defined as brainstem, thalamus or other midline, the latest in case the tumor developed in locations different from brainstem, pons, thalamus, including cerebellum and spinal cord.

Disease progression was defined as 1) tumor growth evidenced by imaging AND 2) neurological deterioration. We did not centrally review the images to confirm progression, but the peripheral radiologist report was accepted. Metastatic progression was also eligible. Post-radiotherapy complications, such as radionecrosis or pseudoprogression, had to be reasonably ruled out before inclusion.

To be included in the study, each case was discussed at the national Clinical Molecular Tumor Board (CMTB). Alternative therapeutic proposals were recommended whenever possible [23].

This compassionate use program is described in details in the PUT (Protocole d'Utilisation Therapeutique - Supplementary Materials).

Information on the program was provided to patients and legal representatives of children and adolescents. Data were collected via the information sheet for participation in the compassionate use program. According to the French clinical research regulation – Loi Jardé - their non-opposition was sought for collecting data.

2.4. Treatment

The treatment consisted of a dose of 375 mg/m2 of ONC201 (max 625 mg) rounded up as suggested in the therapeutic use protocol (PUT in the Supplementary Materials), once a week, on an empty stomach, in cycles of 28-days. The treatment was started after an adequate washout period of 5 half-life from the previous systemic treatment or after recovery from radiotherapy toxicity, if present. MRI imaging was performed in the local center every 8–12 weeks, as indicated in the official procedure. Treatment was continued until radiographic or clinical progression, unacceptable toxicity, or the patient/legal representative's decision to withdraw. In the case of clinical benefit, no toxicity, and lack of other therapeutic options, the treatment was carried out in selected cases after progression.

2.5. Safety

The referent physician assessed toxicity at baseline and before day 1 (D1) of every cycle, which consisted of blood tests, electrocardiogram (ECG), and clinical exam at baseline and D1C2 and then every three months. Toxicity was graded using the Toxicity Grading CTC AE version 5.

2.6. Efficacy and outcome

We calculated the duration of treatment from cycle 1 – day 1 (C1D1) of the ONC201 treatment to the last day of treatment for patients who ended the treatment. OS was defined as the interval between the date of diagnosis (defined on the date of the biopsy) and the date of death or last follow-up. Survival after ONC201 was defined as the interval between C1D1 of ONC201 treatment and the date of death or last follow-up. We

defined as long survivors (LS) those who had a survival after ONC201 start longer than the interval between diagnosis and first progression; the others were defined as short survivors (SS). We did not review any radiology information. Thus, it was not possible to obtain the overall response rate (ORR) nor progression-free survival (PFS) since ONC201 started.

Prism version 8 was used for statistical analyses. We used Kaplan–Meier methods to analyze survival and treatment duration, Log-Rank (Mantel-Cox) and Wilcoxon tests to compare the curves.

The comparison of the duration of the treatment and the survival between different groups was made using Log-rank test and the p value was considered significant if < 0.05. Fisher Exact test was used to compare subgroups within the whole population. A multivariable analysis was performed to check for the significance of parameters found in the univariate analysis. Variables with $p < 0.25$ at univariate analysis were included in the multivariable analysis. Stepwise selection was applied to select the only variables with a significant impact on survival.

3. Results

3.1. ONC201 compounding

The publications by Annereau et al. describe ONC201 compounding in detail. Fig. 1 depicts the process from compounding to delivery to the patient [22,24].

3.2. Patients

From November 2021 to August 2023, 174 patients from 14 countries and 69 centers received for ONC201 compassionate-use treatment after individual-case validation at the national CMTB or local multidisciplinary discussion for non-French patients. All the patients had to come to Gustave Roussy Institut to get the treatment. Median age at the time of inclusion was 14 years (range 2–73), with 72 patients $\geq$ 18 years and 102 $<$ 18 yrs. The distribution of patients by age categories is depicted in Fig. 2. As shown in Table 1, the primary tumor site was the brainstem in 87/174 (50 %), with a higher prevalence of brainstem location in children (71/102, 69 %) and thalamus/midline in adults (56/72, 77 %) ($p < 0.01$). Concerning the extension of disease, children/adolescents had a localized disease in 96/102 cases (94 %), whereas adults had in 9/72 cases (12 %) a metastatic disease at diagnosis (p 0.02). TP53 status was available for 131/174 patients (75 %),

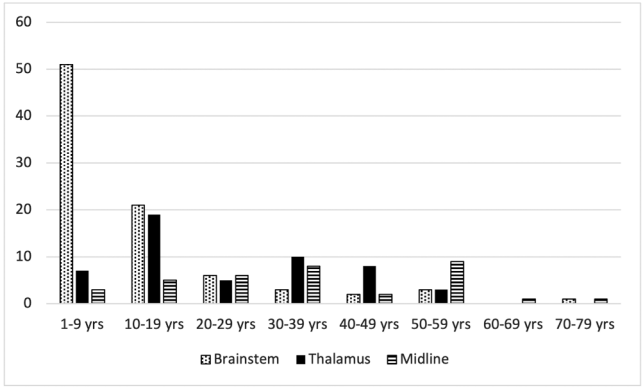

Fig. 2. Patients' distribution by age categories and location.

and the characteristics of the population by TP53 status are described in Table 2.

Upfront treatment included systemic therapy and radiotherapy in 141/174 (81 %), radiotherapy as single modality in 28/174 (16 %), systemic therapy and surgery in 3/174 (2 %), systemic therapy only in 2/174 (1 %).

At relapse, reirradiation was performed in 52/102 children and in 12/72 adults ($p < 0.01$), (Table 1).

At the time of ONC201 therapy, patients had a median of 1 disease progression (range 1–4). Overall, 64 patients (37 %) received a second course of irradiation in addition to ONC201 treatment at relapse, children in 52/102 cases (50 %) and adults in 12/72 cases (17 %) ($p < 0.01$).

3.3. Treatment and safety

All patients received ONC201 at a dose of 375 mg/m2 once a week. Toxicity assessment was available for 118/174 (68 %) patients, for 575 cycles. Overall, no treatment-related adverse event was reported for 99/118 patients; 16/118 had grade 1–2 toxicity, not limiting everyday life. A grade $\geq$ 3 toxicity was reported in 3/118 (3 %) cases: a case of grade 3 thrombocytopenia without bleeding during the first cycle and without recurrence during the following cycles; a case of grade 3 stiffness not surely related to the study treatment; a case of grade 4 tumoral bleeding during the first cycle not surely related to the study treatment. This

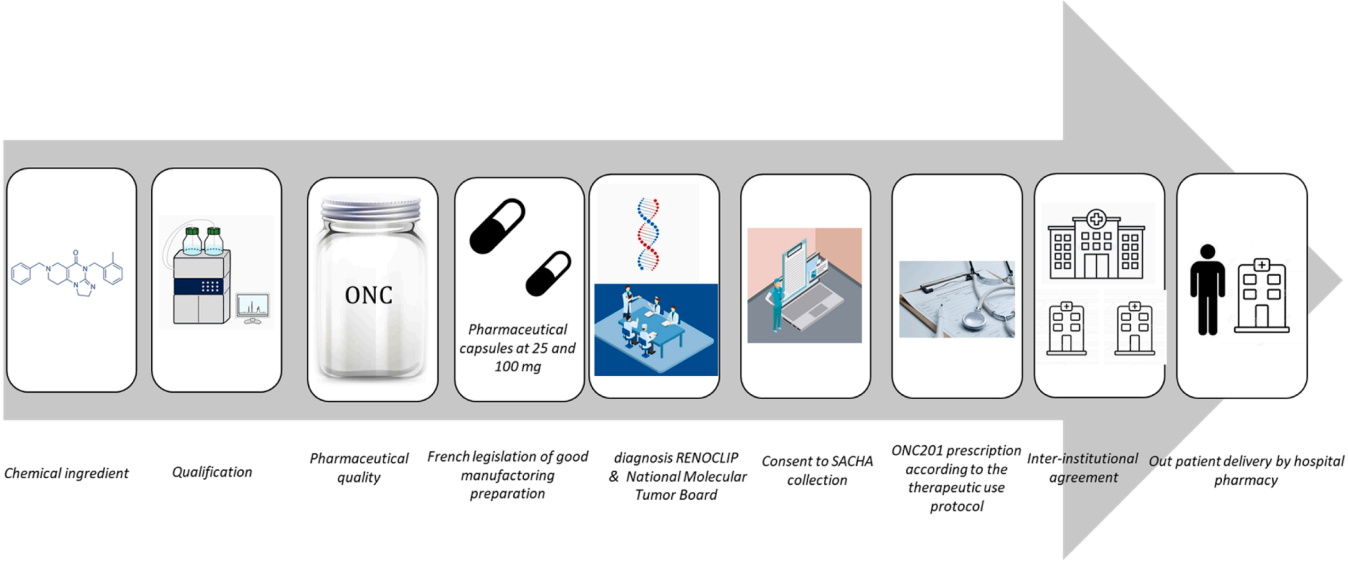

Fig. 1. Diagram of the global process from raw material to patient.

Table 1
Summary of the characteristics of the population. * Chi-square test. ° Fisher's test. ^Log-Rank test. # calculated on patients who ended the treatment.

Patients	Total n = 174	Children (< 18 yrs) n = 102	Adults (≥ 18 yrs) n = 72	*p*-value
Median age				
Yrs (range)	14 (2 –73)	8 (2 –17)	35 (18 –73)	/
Sex				
M	82	40	42	**0.01** *
F	92	62	30	
Site at diagnosis				
Brainstem	87	71	16	**< 0.01** *
Thalamus	52	23	29	
Other midline	35	8	27	
Extension at diagnosis				
Localized	155	96	59	**0.02**°
Metastatic	12	3	9	
Not known (spine imaging not performed)	7	3	4	
H3K27M				
Histology - Loss of 3meH3K27	20	13	7	0.5 *
Mutation	154	89	65	
H3.3 mutation	*141*	*78*	*63*	
H3.1 mutation	*5*	*5*	*/*	
Mutation not specified	*8*	*6*	*2*	
Site of progression				
Local-locoregional	123	76	47	0.08 *
Distant	45	25	20	
Not known	6	1	5	
Number of progressions				
n (range)	1 (1 –5)	1 (1 –5)	1 (1 –4)	/
Reirradiation				
Yes	64	52	12	**< 0.01** *
No	108	49	59	
Not known	2	1	1	
Median time to relapse				
days (range)	226 (26 –1355)	195 (46 –1355)	286 (26 –1268)	**0.0003**^
Median survival time after relapse				
days (range)	206 (17 –2395)	204 (22 –2395)	207 (17 –1209)	**0.003**^
Overall survival				
days (range)	466 (112 –2612)	426 (112 –2612)	590 (160 –1881)	**< 0.0001**^
Overall survival after ONC201 D1C1				
days (range)	143 (1 –711)	102 (1 –600)	122 (1 –711)	**0.002**^
Median duration of ONC201 treatment #				
days (range)	57 (1 –456)	62 (1 –456)	56 (13 –335)	0.4^

patient then recovered from the toxicity but ONC201 was stopped. No cases of grade 5 toxicity were recorded.

3.4. Efficacy and outcome

With a median follow-up from diagnosis of 453 days (or 15,1 months), (range 112–1881 days) and from ONC201 start of 144 days (or 4,8 months), (range 1–617 days), as of April 2024, 51/174 (29%) patients were still alive and on treatment, while 123 presented an event. The median duration of treatment was 57 days (or 1,9 months), (range 1–456 days) for the whole cohort, with no difference between children/adolescents and adults.

Table 2
Characteristics of the population by TP53 somatic mutation. * Chi-square test. ° Fisher's test. ^Log-Rank test. # calculated on patients who ended the treatment.

	TP53 Pathogenic mutation			
	Yes (n = 63)	No (n = 68)	Unknown (n = 43)	*p*-value
Age				
Adults	29	24	19	0.4 *
Children	34	44	24	
Sex				
M	38	29	15	**0.02** *
F	25	39	28	
Site at diagnosis				
Brainstem	27	37	23	0.1°
Thalamus	18	18	16	
Other midline	18	13	4	
Extension at diagnosis				
Localized	54	61	40	0.4°
Metastatic	7	4	1	
Not known	2	3	2	
Site of progression				
Local-locoregional	40	48	35	0.2°
Distant	18	20	7	
Not known	5	0	1	
Number of progressions				
n (range)	1 (1 –4)	1 (1 –4)	1 (1 –2)	/
Reirradiation				
Yes	16	30	18	**0.05**°
No	47	37	24	
Not known	0	1	1	
Median time to relapse				
days (range)	208 (56 –1127)	275 (26 –1355)	194 (76 –1268)	**0.005**^
Median survival time after relapse				
days (range)	193 (17 –1032)	206 (22 –2395)	113 (25 –440)	0.6^
Overall survival				
days (range)	428 (136 –1295)	529 (112 –2612)	463 (181 –1605)	0.7^
Median duration of ONC201 treatment #				
days (range)	56 (13 –315)	56 (1 –456)	75 (5 –416)	0.7^

Median OS for the whole cohort was 466 days (or 15,5 months) (range 112–2612 days); 426 days (or 14,2 months) (range 112–2612 days) and 590 days (or 19,6 months) (range 160–1881 days) for children and adults, respectively (p = 0.001) (Supplementary Figures 1–2a). Patients with thalamic vs brainstem tumor had an OS of 877 days (29 months) (range 136 – 2612 days) and 454 days (15 months) (range 112 – 1696 days), respectively (Supplementary Figure 2b and 2c). OS by TP53 status did not show any significant difference, but patients with TP53 mutation tended to progress earlier (Table 2 and Supplementary Figure 3).

Median OS after ONC201 D1C1 was 143 days (or 4,7 months) (range 1–711 days) for the whole cohort, with a 4-month OS of 57.5% (95%CI 49.3–64.8) and 1-yr OS of 15.5% (95%CI 9.5–22.9) (Supplementary Figure 4). Survival analysis showed a significant survival difference by age and site (Figs. 3 and 4). Reirradiation was significantly associated with longer survival after ONC201 start only in children (Fig. 5 and Supplementary Materials, Fig. 5a and b). Considering patients aged < 18 years with brainstem and thalamic location, the median OS after ONC201 D1C1 was 98 days (or 3,2 months) (range 6–385 days) and 180 days (or 6 months) (range 1–600 days) respectively (p = 0.07)

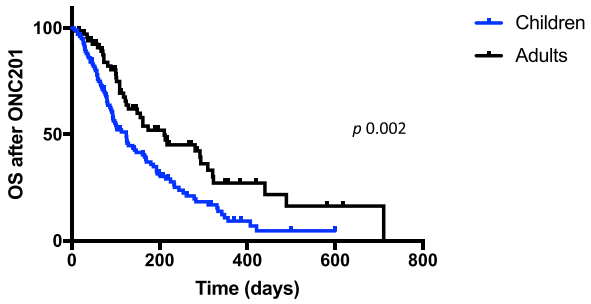

Fig. 3. Survival after ONC201 C1D1 by age. p 0.002 Log Rank.

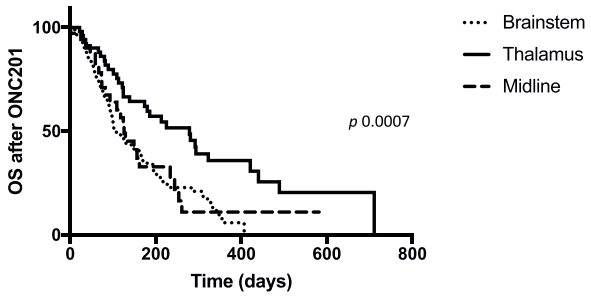

Fig. 4. Survival after ONC201 C1D1 by site. p 0.0007 Log Rank.

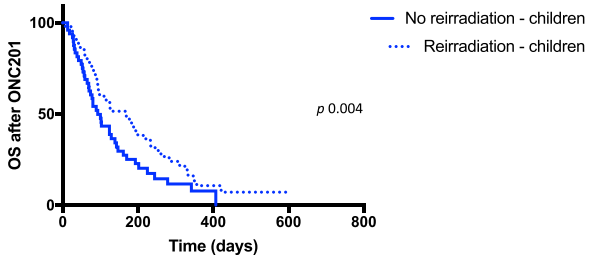

Fig. 5. Survival by reirradiation for the population aged < 18 yrs. p 0.004 Log Rank.

(Supplementary Materials, Figure 6). Including also adult patients in particular for thalamic location, OS after ONC201 D1C1 was 279 days (or 9,3 months) (range 2–711 days)). Median OS after ONC201 D1C1 by TP53 status showed no statistical difference between these two groups (Supplementary Materials, Fig. 3). In the univariate and multivariable analysis, the age at diagnosis (< or ≥18 years) and the site (brainstem, midline, thalamus) had a prognostic value on the outcome (Table 3). Analyzing LS and SS by age, location of the primary, extension of disease at diagnosis and progression, reirradiation, and TP53 status, only reirradiation was significantly more represented in LS group (p 0.01).

4. Discussion

When the ONC201 compassionate use project was launched, preliminary efficacy and safety data of ONC201 in diffuse midline gliomas in adults and children were available [8,14,21]. Given the unmet need for patients with DMG and the drug's excellent safety profile, this provided a strong rationale for setting up a compassionate use program for patients with progressive DMG and no therapeutic options.

In this context, we report the feasibility of a successful academia-driven compassionate use program ensuring access to an innovative experimental agent for patients with extremely poor prognoses when no clinical trial or compassionate use driven by Pharma is available. Indeed, the French legislation authorizes compounding preparations to treat patients in the absence of a suitable pharmaceutical form or no possible import, which was the case for ONC201 (Article L5121–1; articles R. 5121–146-2 et R. 5121–146-3 du Code de la santé publique).

This is the largest cohort of patients with DMG and treated with ONC201 published so far. In this population of 174 pediatric and adult patients, the median duration of ONC201 administration was comparable to the previous published experiences on 17 patients by Arrillaga-Romany [14] and on 14 patients after progression described by Chi et al. [8]. The extremely low rate of reported severe adverse events is also in line with the first phase I pediatric clinical trial of ONC201 [25] and other reports in literature [8,14,26]. This is important when considering the possibility of offering an outpatient treatment with an innovative, promising drug with respect to the quality of life for these patients with a very poor prognosis.

Considering the efficacy, limited to our real-life data not replacing a clinical trial, we observed that the median OS from ONC201 start was 143 days (4,7 months). Comparing the group at worse prognosis (patients aged < 18 years and with brainstem location) with a historical cohort published by Lobon et al., survival after ONC201 D1C1 in our analysis is superposable to that of the cohort of relapsed diffuse intrinsic pontine glioma (DIPG) not treated with ONC201 [27]. Pediatric patients with thalamic location showed a better OS after ONC201 D1C1, compared to that of brainstem location; in particular, the median OS for thalamic location was twice that of brainstem location. Including adult patients in the group of thalamic location, and comparing our cohort with that published by Koschmann et al. the median OS are superposable. Moreover they are better than the median OS after relapse of the historical controls not treated with ONC201 derived from Castel et al., Lobon-Iglesias et al., and an unpublished cohort from Gustave Roussy Institute, France [27].

Considering adult population, comparing our cohort of 48 patients with non-brainstem non-multifocal tumors treated with ONC201, with the cohort of 52 patients with the same characteristics described by Schulte et al. and treated with the standard therapy based on chemo-radiotherapy regimen, patients treated with ONC201 had a trend to

Table 3
Univariate and multivariable analysis. The age at diagnosis (< or ≥18 years) and the site (brainstem, midline, thalamus) had a prognostic value on the outcome.

Patient characteristics	N	Events	4-month OS (95%CI)	1-y OS (95%CI)	Univariate *p*-value	HR (95%CI)	Multivariable *p*-value
Age at diagnosis							
< 18 years	102	84	51.1 (40.8 −60.5)	9.2 (4.0 −17.2)	0.0022	1.57 (1.02 −2.41)	0.0409
≥ 18 years	72	39	67.5 (53.8 −78.0)	27.1 (14.5 −41.4)		1	
Re-irradiation							
No	108	73	55.0 (44.3 −64.4)	18.2 (9.9 −28.5)	0.7595	-	
Yes	64	50	60.1 (46.6 −71.2)	10.9 (4.1 −21.5)			
Site							
Brainstem	87	69	48.2 (36.8 −58.7)	5.8 (1.6 −14.1)	0.0007	1.90 (1.19 −3.05)	0.0092
Midline	35	23	56.4 (36.7 −72.1)	10.9 (2.0 −28.5)		2.12 (1.22 −3.69)	
Thalamus	52	31	73.2 (58.3 −83.5)	35.8 (20.8 −50.9)		1	
Presence of TP53							
Yes	63	44	58.2 (44.3 −69.8)	17.8 (8.0 −30.8)	0.7983	-	
No	68	48	58.1 (44.8 −69.3)	11.7 (4.0 −23.9)			

better survival with median OS 1066 days (35 months) vs 27.6 months for patients in the cohort by Schulte [10].

Moreover, our study allows a comparison between pediatric and adult patients. Survival and multivariable analysis showed that adults have a better OS and survival after ONC201 start than children. Concerning reirradiation, it may be a valuable option, especially for children. The same is not clear for the adult population, where the rate of reirradiated patients is too low to allow a reliable comparison. Moreover, comparing LS and SS, the only difference is due to reirradiation, more frequent in the LS group. Multivariable analysis failed to identify reirradiation as a risk factor associated with the outcome, possibly due to the lack of power in our study or because reirradiation is proposed more frequently to patients with tumor located in the brainstem, who have a worse prognosis.

Our data are difficult to compare with other series because of the heterogeneity of inclusion criteria and the different endpoints.

The limits of our study are those of a real-life program outside of a clinical trial with prospective real-world data collection. There was no central imaging review assessing tumor at diagnosis and its evolution under treatment, and progression-free survival after the start of ONC201 treatment could not be evaluated otherwise by considering the treatment duration. Moreover, the lack of extensive molecular data beyond H3 status, makes more challenging to perform further analysis to detect different outcome depending on genomic data. Toxicity was not collected for each patients and we could have missed very rare adverse events. From a financial point of view, unfortunately, the European S2 mechanism (https://europa.eu/youreurope/citizens/health/planned-healthcare/right-to-treatment/index_en.htm) did not work in all the cases to cover cross border health costs. Currently, patients affected by H3K27M DMG can be enrolled in BIOMEDE 2.0 trial (NCT05476939) and treated with ONC201 upfront. Moreover, the compassionate use program is still available for those who cannot access ONC201 in first-line treatment in the trial. Thanks to toxicity and safety results available since 2022 and officially published in 2024 [28], patients both treated in BIOMEDE 2.0 and in the compassionate use program are now exposed to a double dose of ONC201, hoping for a better efficacy.

In conclusion, we presented the results of our compassionate use program to give patients with a very poor prognosis and lack of dedicated available clinical trials access to a promising drug. We know that data collected within a compassionate use program cannot replace a structured controlled clinical trial, but the results of our work are encouraging in showing that new hypotheses and ideas can also come out from a compassionate use program.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115165.

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