GEINO-13

Phase II pilot, open, multicenter and prospective clinical trial to evaluate the safety and efficacy of Palbociclib (PD0332991), an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), in patients with recurrent Oligodendroglioma with preservation of the activity of the RB protein

FINAL STATISTICAL REPORT
TABLES, LISTS AND FIGURES

MFAR CLINICAL RESEARCH

GEINO GRUPO ESPAÑOL DE INVESTIGACIÓN EN NEUROONCOLOGÍA

xxth of xxxxxxx de xxxx (version xx)

SPONSOR

STUDY CHIEF INVESTIGATOR

MONITORING ORGANISATION (CRO)

INDEX

Tables:

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1. RESULTS (TABLES, LISTS AND FIGURES)

The database of the study was closed on the 10-10-2019.

1.1. STUDY POPULATION

1.1.1. SCREENED PATIENTS

A total of xx patients were screened and eventually xx patients fulfilled all the inclusion and exclusion criteria.

Table 1. Screened patients

		N	%
Hospital	Name		
	Total		
Fulfils every inclusion and none of the exclusion criteria	**Patient fulfils all the inclusion criteria and none of exclusion according to the protocol**		
	Patient does not fulfil the eligibility criteria		
	Total		

xx patients were considered evaluable for the study and the reason for non-evaluability was screening failure in all the cases.

Table 2. Evaluable patients

		N	%
Evaluable patients	**No**		
	Yes		
	Total		
Non evaluable reason	**Screening failure**		
	Total		

Table 3. Patients included and excluded from each hospital

		Evaluable patients					
		No		Yes		Total	
		N	%	N	%	N	%
Hospital	**Name**						
	….						

Those patients excluded from the analysis are listed in the following table.

Table 4. List of patients excluded from the analysis

Patient number	Hospital	Non evaluable reason	Fulfils every inclusion and none of the exclusion criteria
1			
2			
3			
4			
..			

DEMOGRAPHIC AND CLINICAL BASELINE CHARACTERISTICS

The median of the age was xx years and xx % were males.

Table 5. Age

	N	Mean	SD	Median	Min	Max
Age in years (at informed consent signature)						

Table 6. Gender and race

		N	%
Gender	**Men**		
	Female		
	Total		
Race	**White**		
	Hispanic		
	Total		

1.1.2. CLINICAL BASELINE CHARACTERISTICS

Table 7. Clinical data

		N	%
Performance Status (PS)	**0**		
	1		
	2		
	Total		

	N	Mean	SD	Median	Min	Max
Systolic blood pressure						
Diastolic blood pressure						
Weight						
Height						

Table 8. Analytical data

	N	Mean	SD	Median	Min	Max
Haemoglobin (g/dl)						
Platelets (x 10e9/L)						
Leukocytes (x 10e9/L)						
Neutrophils (x 10e9/L)						
Lymphocytes (x 10e9/L)						

Table 9. Biochemistry data

	N	Mean	SD	Median	Min	Max
Sodium (mmol/L)						
Potassium (mmol/L)						
Calcium (mg/dL)						
Magnesium (mg/dL)						
Glucose (mg/dL)						
Creatinine (mg/dL)						
AST (U/L)						
ALT (U/L)						
Total bilirubin (mg/dL)						
GGT (U/L)						
Alkaline Phosphatase (U/L)						
Albumin (g/dL)						
LDH (U/L)						

Table 10. Coagulation data

	N	Mean	SD	Median	Min	Max
TP value						
TTPA value						
Fib (mg/dL)						

Table 11. Thyroid function

	N	Mean	SD	Median	Min	Max
TSH value						
T3 value						

Table 12. ECG

		N	%
Qtc	**Unknown**		
	<450 mseg		
	450-480 mseg		
	Total		

1.1.3. CLINICAL TUMOUR CHARACTERISTICS

In the first surgery 16 patients (47.1%) had a tumour of grade 2 while 13 (38.2%) had a grade 3 tumour.

Table 13. First surgery characteristics

		N	%
Diagnosis with grade (First surgery)	**Oligoastrocytoma grade 2**		
	Oligoastrocytoma grade 3		
	Oligodendroglioma grade 2		
	Oligodendroglioma grade 3		
	Oligodendroglioma grade unknown		
	Diagnosis and grade unknown		
	Total		
Grade (First surgery)	**Grade 2**		
	Grade 3		
	Unknown		
	Total		
Anaplasia (First surgery)	**0**		
	1		
	2		
	4		
	Unknown		
	Total		
High cellularity (First surgery)	**No**		
	Yes		
	Total		
Endothelial proliferation (First surgery)	**No**		
	Yes		
	Total		
Necrosis (First surgery)	**No**		
	Yes		
	Total		
Mitosis (First surgery)	**No**		
	Yes		
	Total		
Nuclear anomalies (First surgery)	**No**		
	Yes		
	Total		

Table 14. List of patients with diagnosis in first surgery

Patient number	Hospital	Diagnosis with grade (First surgery)	Grade (First surgery)
1			
2			
3			
4			
5			
…			

In the last surgery, every patient (100%) was diagnosed with an oligodendroglioma grade 3.

Table 15. Last surgery characteristics

		N	%
Diagnosis with grade (Last surgery)	**Oligodendroglioma grade 3**		
	Total		
Grade (Last surgery)	**Grade 3**		
	Total		
Anaplasia (Last surgery)	**0**		
	1		
	2		
	3		
	4		
	5		
	Total		
High cellularity (Last surgery)	**No**		
	Yes		
	Total		
Endothelial proliferation (Last surgery)	**No**		
	Yes		
	Total		
Necrosis (Last surgery)	**No**		
	Yes		
	Total		
Mitosis (Last surgery)	**No**		
	Yes		
	Total		
Nuclear anomalies (Last surgery)	**No**		
	Yes		
	Total		

Table 16. Deletion

		N	%
Deletion 1p	**Yes**		
	Total		
Deletion 19q	**Yes**		
	Total		

In x patients (xx%) the surgery was not completed. Biopsy was performed in x patients (xx%) and craniotomy in XX patients (xx%).

Table 17. Surgery compliance

		N	%
Surgery	**No**		
	Yes		
	Total		
Type of surgery	**Biopsy**		
	Craniotomy		
	No applicable (Surgery not done)		
	Total		
Relapse location	**Bihemispheric**		
	Cingulate (right)		
	…. (Indicate locations)		
	Total		

The baseline barthel index mean was xx and the baseline minimental test mean was xx (data was available in xx patients).

Table 18. Baseline Barthel Index and Minimental test

	N	Mean	SD	Median	Min	Max
Barthel index (baseline)						
Mini mental test (baseline)						

1.2.3. PREVIOUS PATHOLOGIES

For 9 patients (26.5%) previous pathologies were not reported. In those patients with previous pathologies, seizures were the most common (n=7, 17.6%) previous pathology.

Table 19. Previous pathologies

		N	%
Previous pathologies	**No**		
	Yes		
	Total		

		N	%
Previous pathologies	.(Indicate previous pathologies. Exemples:		
	Fatigue		
	Cognitive disturbance		
	Muscle weakness left-sided		
	….		

Table 20. List of previous pathologies

	Pat. n.	Hospital	Previous pathology	Intensity	Action
1	01-003				
2	01-004				
3	01-006				
…	01-006				

Table 21. Time since diagnosis

	N	Mean	SD	Median	Min	Max
Time since 1st diagnosis until 1st cycle (months)						

1.2. EFFICACY ANALYSES

1.2.1. PRIMARY EFFICACY ANALYSES: PFS

At 6 and 9 months the estimated PFS was 21.23% (with 95% CI 11-40.97), at 12 months it was 16.99% (with 95% CI 7.71-37.43) and from 18 to 48 months it was 11.32% (with 95% CI 3.68-34.86).

The median of PFS was 2.84 months (with 95% CI 2.71-5.39).

Table 22. PFS estimated survival ratio

Progression Free Survival	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 9 months				
At 12 months				
At 18 months				
At 24 months				
At 30 months				
At 36 months				
At 42 months				
At 48 months				

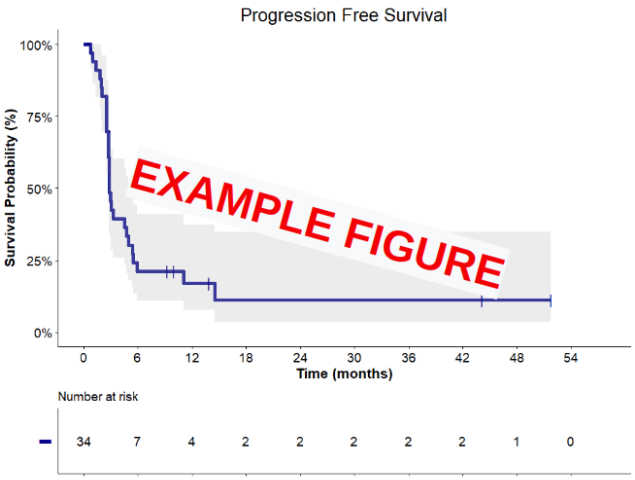
Note: Estimated using Kaplan-Meier product-limit method

Table 23. Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Progression Free Survival				

Note: Estimated using Kaplan-Meier product-limit method

Figure 1. Progression Free Survival



In the 28 patients with PD, the median until progression was 2.8 months.

Table 24. Time until PD/exitus (only pts with event)

Overall	Overall (N=xx)
Time until PD/Exitus	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

1.3.2. SECONDARY EFFICACY ANALYSES

1.2.2.1 OS

At 6 months the estimated OS was xx % (with xx% CI xx-xx), at 9 months it was xx % (with xx% CI xx-xx), at xx months it was ….

The median of OS was xxx months (with xx% CI xx-xx)

Table 25. OS estimated survival ratio

Overall Survival	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 9 months				
At 12 months				
At 18 months				
……				

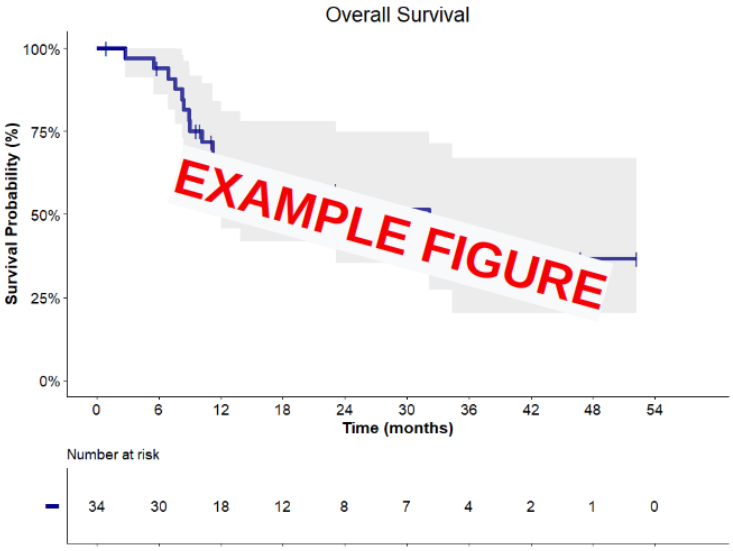
Note: Estimated using Kaplan-Meier product-limit method

Table 26. Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Overall Survival				

Note: Estimated using Kaplan-Meier product-limit method

Figure 2. Overall Survival



In those patients who died (n=xx), the median of follow-up was xx months.

Table 27. Time until exitus (only deaths)

Overall	Overall (N=xx)
Time until Exitus	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

In overall, the median of follow-up was xx months (minimum xx months and maximum of xx months).

Table 28. Time of follow-up (all patients)

Overall	Overall (N=xx)
Time until Exitus	
N	
Mean (95%CI)	
SD	

Overall	Overall (N=xx)
Median (95%CI)	
Range	

1.2.2.2 RESPONSES

13 patients (38.2%, with 95% CI 21.9-54.6), reached clinical benefit (all were Stable Disease).

Table 29. Best response and Clinical benefit rate

		N (%, 95% CI)
Best response rate	**CR**	
	SD	
	PD	
	No evaluated	
	Total	
Clinical benefit rate	**No**	
	Yes (CR or PR or SD)	
	No evaluable	
	Total	

In xx patients (xx%) the reason to end of treatment was PD; xx patients (xx%) were alive at the end of follow-up.

Table 30. Status at end of study

		N (%)
Current status	**End of treatment due to patient decision and patient is alive at end of follow-up**	
	End of treatment due to PD and patient is alive at end of follow-up	
	End of treatment due to PD and patient is exitus	
	End of treatment but reason not reported and patient is exitus	
	End of treatment due to lack of clinical benefit and patient is alive at end of follow-up	
	On treatment	
	Total	
End of treatment reason	**PD**	
	Toxicity (with PD)	
	Patient decision	
	On treatment	
	No clinical benefit	
	Total	
Status at end of follow-up	**Alive**	
	Exitus	
	Total	

1.2.2.3 RANO EVALUATION

xx patients (xx%) presented PD in RANO evaluations, xx (xx%) of them in the 2nd RANO, x (xx%) the 3rd, x (xx%) in the 5th and x (xx%) in the 6th.

Table 31. RANO Evaluation (I)

		N	%
RANO evaluation with PD	**Without PD in RANO**		
	2		
	3		
	5		
	6		
	Total		
Reason of PD with RANO	**Example:**		
	T1-Gd+:/ T2-FLAIR: / New lesions: New appearance/ Corticoids evolution (last 5 days): Stable/ Clinical evaluation (neurological): Stable		
	…		
	Total		

Table 32. RANO Evaluation (II)

		N	%
T1Gd+ (PD RANO)	NA or not reported		
	Decrease <5% or Increase < 25%		
	Increase >/= 25%*		
	Total		
T2/FLAIR (PD RANO)	NA or not reported		
	Increase		
	Stable		
	Total		
New lesions (PD RANO)	NA or not reported		
	New appearance		
	No		
	Total		
Corticoids evolution (PD RANO)	NA or not reported		
	Decrease		
	Increase		
	No corticoids		
	Stable		
	Total		
Clinical evaluation (PD RANO)	NA or not reported		
	Stable		
	Worsening		
	Total		

Table 33. List of patients with RANO progressions with details

Patient number	Evaluation RANO con PD	Reason of PD with RANO
1		Example: T1-Gd+:Increase >/= 25%*/ T2-FLAIR: Stable/ New lesions: No/ Corticoids evolution (last 5 days): No corticoids/ Clinical evaluation (neurological): Stable
2		
…		

1.2.2.4 USE OF CORTICOIDS

x patients (xx%) reported use of corticoids.

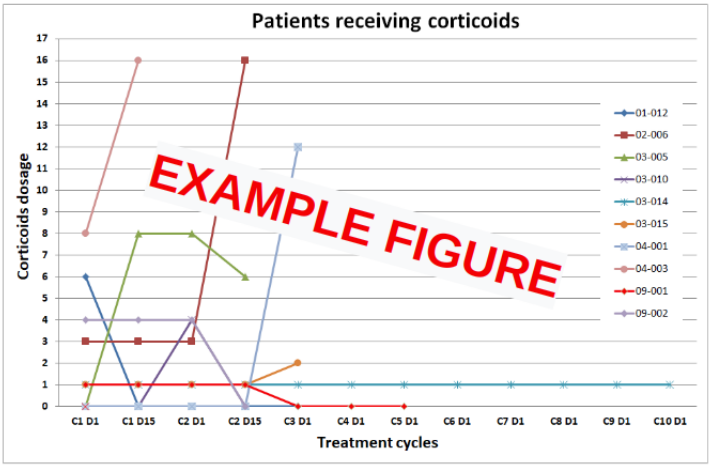
Table 34. Use of Corticoids

		N	%
Receive corticoids during treatment (cycles)	**No**		
	Yes		
	Total		
Changes in corticoids doses from baseline (during treatment cycles)	**No**		
	Increased		
	Increased with posterior decrease		
	Decreased		
	Stable		
	Total		

Table 35. List of patients receiving corticoids and Follow-up of dosage

Patient number	Receive corticoids during treatment (cycles)	Changes in corticoids doses from baseline (during treatment cycles)	C1 D1	C1 D15	C2 D1	C2 D15	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1
1	Yes	Example: Decreased/Increased/Stable													
2															
3	…….														

Figure 3. Use of corticoids



1.1.1.1 EVOLUTION OF MINIMENTAL TEST

The results of the minimental test for each patient (when available), is reported in the following table.

Table 36. Minimental Test: Results for each patient

Patient number	Baseline	C2 d1	C3 d1	C4 d1	C5 d1	C6 d1	C7 d1	C8 d1	C9 d1	C10 d1	C12 d1	C13 d1	C14 d1	C15 d1	C16 d1	C17 d1	C18 d1	C19 d1	C20 d1	C21 d1	C22 d1	C23 d1	End of treatment
….																							

Table 37. Minimental Test: Summary in each visit

	N	Mean (SD)	Median (Min-Max)
Test Minimental (baseline)			
Test Minimental (cycle 2 d1)			
Test Minimental (cycle 3 d1)			
Test Minimental (cycle 4 d1)			
Test Minimental (cycle 5 d1)			
Test Minimental (cycle 6 d1)			
Test Minimental (cycle 7 d1)			
Test Minimental (cycle 8 d1)			
Test Minimental (cycle 9 d1)			
Test Minimental (cycle 10 d1)			
Test Minimental (cycle 12 d1)			
Test Minimental (cycle 13 d1)			
Test Minimental (cycle 14 d1)			
Test Minimental (cycle 15 d1)			
Test Minimental (cycle 16 d1)			
Test Minimental (cycle 17 d1)			
Test Minimental (cycle 18 d1)			
Test Minimental (cycle 19 d1)			
Test Minimental (cycle 20 d1)			
Test Minimental (cycle 21 d1)			
Test Minimental (cycle 22 d1)			
Test Minimental (cycle 23 d1)			
Test Minimental (end of treatment)			

.

Table 38. Minimental Test: Comparison between visits and baseline

	N	Mean (SD)	Median (Min-Max)	p-valor[1]
Test Minimental (baseline) **Test Minimental (cycle 2 d1)**				
Test Minimental (baseline) **Test Minimental (cycle 3 d1)**				
Test Minimental (baseline) **Test Minimental (cycle 4 d1)**				
Test Minimental (baseline) **Test Minimental (cycle 5 d1)**				
Test Minimental (baseline) **Test Minimental (cycle 6 d1)**				
Test Minimental (baseline) **Test Minimental (cycle 7 d1)**				
Test Minimental (baseline) **Test Minimental (cycle 8 d1)**				
Test Minimental (baseline)				

Test Minimental (cycle 9 d1)
Test Minimental (baseline)
Test Minimental (cycle 10 d1)
Test Minimental (baseline)
Test Minimental (end of treatment)

1: Wilcoxon test

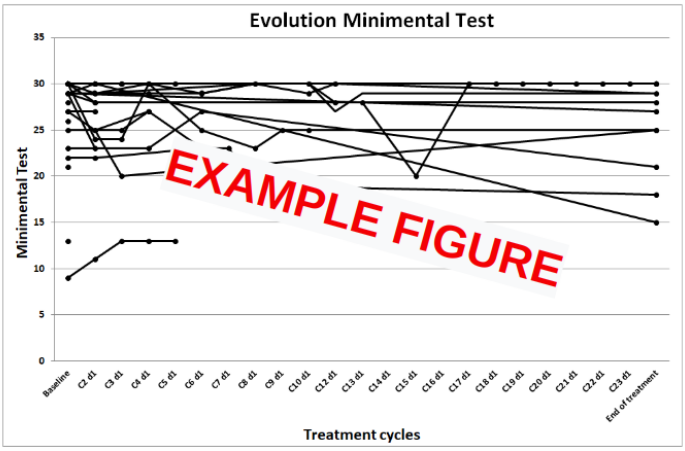


Figure 4. Minimental Test evolution

1.1.1.2 EVOLUTION OF BARTHEL INDEX

The results of the Barthel Index for each patient (when available), is reported in the following table.

Table 39. Barthel Index: Results for each patient

Patient number	Baseline	C2 d1	C3 d1	C4 d1	C5 d1	C6 d1	C7 d1	C8 d1	C9 d1	C10 d1	C11 d1	C12 d1	C13 d1	C14 d1	C15 d1	C16 d1	C17 d1	C18 d1	C19 d1	C20 d1	C21 d1	C22 d1	C23 d1	End of treatment
....																								

Table 40. Barthel Index: Summary in each visit

	N	Mean (SD)	Median (Min-Max)
Barthel Index (baseline)			
Barthel Index (cycle 2 d1)			
Barthel Index (cycle 3 d1)			
Barthel Index (cycle 4 d1)			
Barthel Index (cycle 5 d1)			
Barthel Index (cycle 6 d1)			
Barthel Index (cycle 7 d1)			
Barthel Index (cycle 8 d1)			
Barthel Index (cycle 9 d1)			
Barthel Index (cycle 10 d1)			
Barthel Index (cycle 11 d1)			
Barthel Index (cycle 12 d1)			
Barthel Index (cycle 13 d1)			
Barthel Index (cycle 14 d1)			
Barthel Index (cycle 15 d1)			
Barthel Index (cycle 16 d1)			
Barthel Index (cycle 17 d1)			
Barthel Index (cycle 18 d1)			
Barthel Index (cycle 19 d1)			
Barthel Index (cycle 20 d1)			
Barthel Index (cycle 21 d1)			
Barthel Index (cycle 22 d1)			
Barthel Index (cycle 23 d1)			
Barthel Index (end of treatment)			

The Barthel Index result in each visit was compared with the baseline result in those cases with results for at least 4 patients (for each pairwise comparison only those patients with measures in both visits could be compared). No statistically significant differences were found in any of the comparisons with baseline.

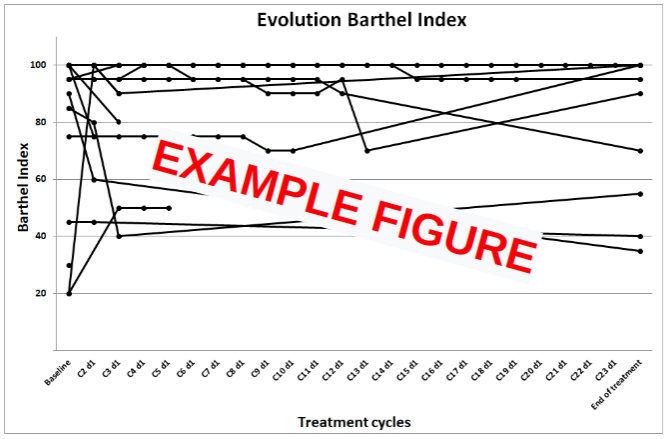
Table 41. Barthel Index: Comparison between visits and baseline

	N	Mean (SD)	Median (Min-Max)	p-valor[1]
Barthel Index(baseline) Barthel Index(cycle 2 d1)				
Barthel Index(baseline) Barthel Index(cycle 3 d1)				
Barthel Index(baseline) Barthel Index(cycle 4 d1)				
Barthel Index(baseline) Barthel Index(cycle 5 d1)				
Barthel Index(baseline) Barthel Index(cycle 6 d1)				
Barthel Index(baseline) Barthel Index(cycle 7 d1)				
Barthel Index(baseline)				

Barthel Index(cycle 8 d1)
Barthel Index(baseline)
Barthel Index(cycle 9 d1)
Barthel Index(baseline)
Barthel Index(cycle 10 d1)
Barthel Index(baseline)
Barthel Index(end of treatment)

1: Wilcoxon test

Figure 5. Barthel Index evolution



1.2. SAFETY ANALYSES

Every patient but one presented at least one adverse event during follow-up (n=xx, xx%). xx patients (xx%) presented at least one adverse event grade≥3 during follow-up. xx patients (x%) presented at least one toxicity (related AE) during follow-up. xx patients (xx%) presented at least one toxicity grade≥3 (related AE) during follow-up. xx patients (xx%) presented at least one SAE during follow-up, and none was reported as related to the treatment.

Table 42. Safety results summary

		N	%
AE	**No**		
	Yes		
	Total		
Adverse event grade≥3	**No**		
	Yes		
	Total		
Toxicity (any)	**No**		
	Yes		
	Total		
Toxicity grade≥3	**No**		
	Yes		
	Total		
SAE (any)	**No**		
	Yes		
	Total		
SAE related	**No**		
	Total		

1.2.1.

1.2.2. ADEVERSE EVENTS

The most frequent adverse event (any grade) were xxxxx (xx%, n=xx)....

Table 43. Frequencies of all adverse events

		N	%
Adverse event	**EXAMPLES:**		
	Neutrophil count decreased		
	Fatigue		
	Platelet count decreased		
	Anaemia		
	……		

%: calculated respect the total number of patients (N=34)

The most frequent adverse events, (at least in 10% of the patients, n=xx), are reported in the following table:

Table 44. Most frequent adverse events

		N	%
Specify Adverse events.	**No**	10	29.4%
EXAMPLE: Fatigue	**Yes**	24	70.6%
	Total	34	100.0%
……	**No**	14	41.2%
	Yes	20	58.8%

Total	34	100.0%

The most frequent adverse events with their respective grades are reported in the following table:

Table 45. Most frequent adverse events with grades

	No		G1		G2		G3		G4		Total	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Specify Adverse events.												
EXAMPLE: Fatigue												
……												

1.2.2. TOXICITIES

The most frequent toxicities (related AE of any grade) were xxx decreased (xx%, n=xx)....

Table 46. Frequency of Toxicities

		N	%
Adverse event	**Specify Advert event. EXAMPLE: Neutrophil count decreased**		
	….		

%: calculated respect the total number of patients (N=xx)

The most frequent toxicities (at least in 10% of the patients, n=x), are reported in the following table:

Table 47. Most frequent Toxicities

		N	%
Specify Advert event EXAMPLE: Neutrophil count decreased	**No**		
	Yes		
	Total		
…	**No**		
	Yes		
	Total		

The most frequent toxicities with their respective grades are reported in the following table:

Table 48. Most frequent Toxicities with grades

	No		**G1**		**G2**		**G3**		**G4**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Specify Advert event EXAMPLE: Neutrophil count decreased												
….												

1.2.3. **SERIOUS ADVERSE EVENTS**

Table 49. List of SAEs

	Patient number	Hospital	AE grade	Relation	Intensity	Action	SAE (any)
1							
2	…						
3	….						

1.3. ANNEX I: LIST OF ALL TOXICITIES

Table 50. List of all toxicities

Patient number	Hospital	AE grade	Relation	Intensity	Action	SAE (any)
1						
2						
3						
4						
...						

1.4. ANNEX II: ADDITIONAL RESULTS

In the event that the study coordinator considered evaluating the variables of a subgroup of patients (those of interest for the article), for example patients with progression free survival longer than 9 months **(low survivors**), some tables and graphs (PFS and OS) could be required

1.4.1. LONG SURVIVORS

Table 51. Long survivors

		N	%
Long survivor (PFS≥9m)	**No**		
	Yes		
	Total		

x patients were considered long survivors and are listed below:

List of long survivor patients (PFS≥9 months)

Table 52. Long survivors

	Patient number	Time until PD/Exitus	Progression Free Survival	Time until Exitus	Overall survival
1					
2					
3					
4					
5					
6					
7					

1.4.2. BASELINE AND TUMOUR CHARACTERISTICS VS LONG SURVIVORS

Those variables reported in table 1 of the article are reported below stratified by long survivors.

Table 53. Baseline and tumour characteristic vs. long survivors

		Long survivor (PFS≥9m)			p-value
		No (n=27)	Yes (n=7)	Total (n=34)	
Age, mean +/-SD years	**median (range)**				
	mean (SD)				
Gender, n (%)	**Male**				
	Female				
KPS, n (%)	**0**				
	1				
	2				
Barthel Index, n=31	**median (range)**				
	mean (SD)				
MMSE, n=31	**median (range)**				
	mean (SD)				
Prior treatments, n (%)	**Temozolomide**				
	Nitrosoureas				
	Radiotherapy				
Tumor characteristics at first surgery					
Diagnosis, n (%)	**Oligoastrocytoma**				
	Grade 2				
	Grade 3				
	Oligodendroglioma				
	Grade 2				
	Grade 3				
	Unknown				
	Not reported				
Time from first AO diagnosis to first cycle, median (range) months	**median (range)**				
	mean (SD)				
Corticoids use during treatment, n (%)					

1: T-test for independent samples; 2: Mann-Whitney U test; 3: Fisher exact test.

1.4.3. ADDITIONAL FIGURES

Figure 6. Progression Free Survival (R format)

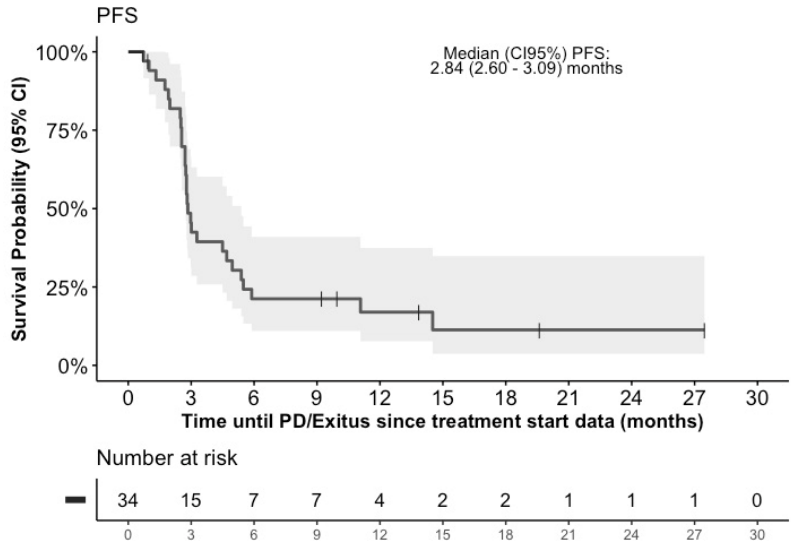


Figure 7. Overall Survival (R format)

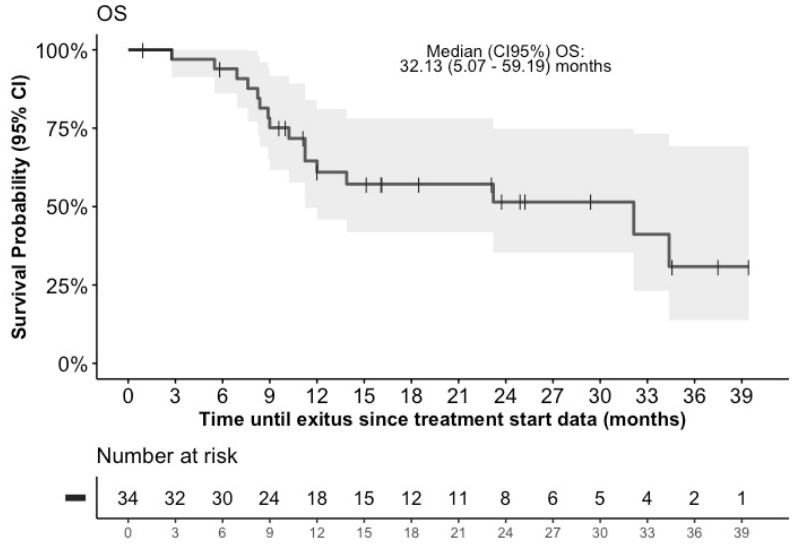


Figure 8. Swimmer plot: patient's follow-up

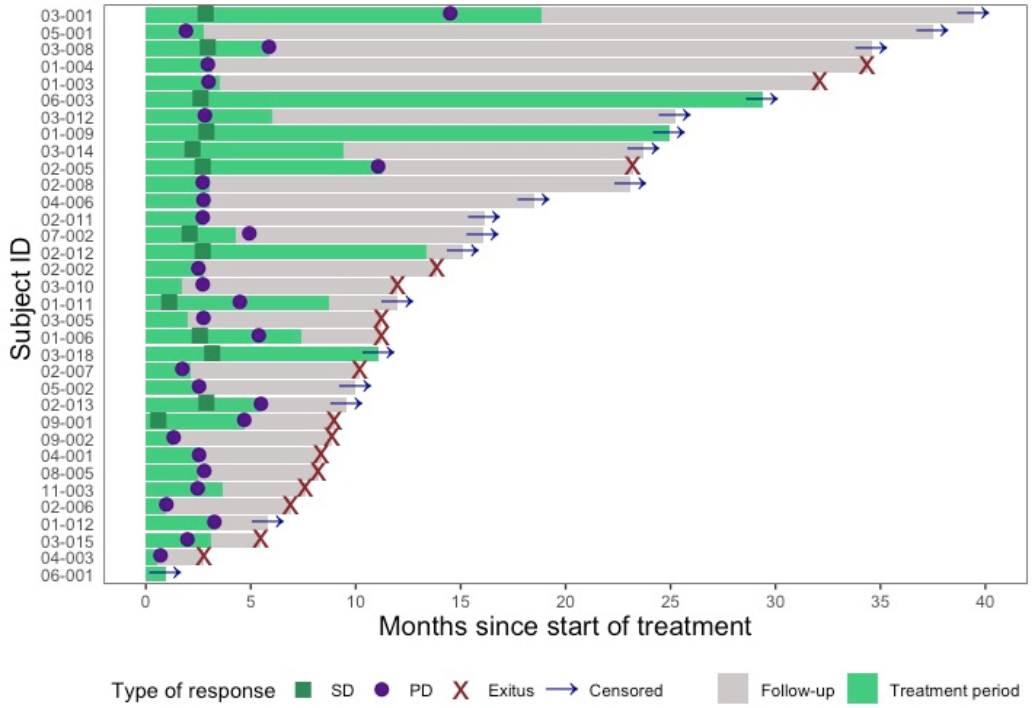
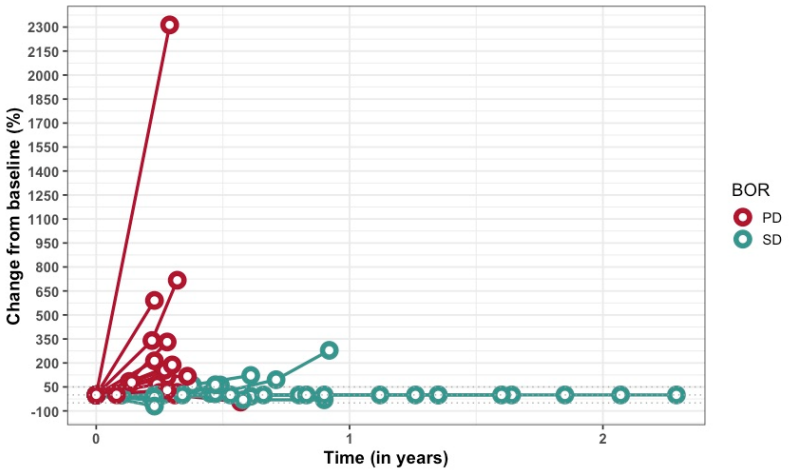


Figure 9. Spider plot: % change in lesions' measurements from baseline



Patient 04-001 had measurements that are considered outliers (too extreme) and the spider graph has been repeated excluding that patient to prevent skewing the results.

Figure 10. Spider plot: % change in lesions' measurements from baseline (excluding outlier value)