[redacted]

Phase II multicenter clinical trial to evaluate the efficacy and safety of ibrutinib in combination with rituximab, gemcitabine, oxaliplatin, and dexamethasone followed by ibrutinib as maintenance treatment in patients with diffuse large B-cell lymphoma refractory to the treatment or relapsing, non-candidates to receive a TACM.

STATISTICAL ANALYSIS REPORT

26th of April 2021 (version 1.0)

[redacted]

TITLE

Phase II multicenter clinical trial to evaluate the efficacy and safety of ibrutinib in combination with rituximab, gemcitabine, oxaliplatin, and dexamethasone followed by ibrutinib as maintenance treatment in patients with diffuse large B-cell lymphoma refractory to the treatment or relapsing, non-candidates to receive a TACM.

SPONSOR

[redacted]

COORDINATORS

[redacted]

MONITORING ORFANISATION

[redacted]

INDEX

LIST OF ABBREVIATIONS

Abbreviations	Term explanation
AE	Adverse Event
CR	Complete response
eCRF	Case Report Form
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
GEL/TAMO	Grupo Español de Linfoma/Trasplante Autólogo de Médula Ósea
HLA	Human Leukocyte Antigen
LDCBG	Linfoma difuso de células B grandes
LNH	Linfoma no Hodgkin
NA	Not aplicable
ND	Not Done
OR	Overall Response
OS	Overall survival
PET	Positron Emission Tomography
PR	Partial Response
PD	Progression disease
PFS	Progression Free Survival
R-GEMOX	Rituximab-GEMOX
SAE	Serious Adverse Event
SD	Stable Disease
UK	Unknown

1. DEFINITIONS

1.1. POPULATIONS FOR ANALYSIS

The analysis populations are defined as:
- **Population of all treated patients**: defined as all patients receiving at least 1 dose of study drug.
- **Population with evaluable response**: defined as all patients with measurable disease at baseline, receiving at least 1 dose of study drug, and having at least 1 adequate post-baseline disease evaluation. An adequate disease assessment is defined as having sufficient evidence to correctly indicate whether or not disease progression has occurred. Patients who have died from progression are also considered to have had an adequate evaluation.
- **Safety population:** defined as all patients receiving at least 1 dose of study drug, which is the same definition as for the population of all treated patients.

1.2. EFFICACY ANALYSIS

Efficacy analysis: final analysis of the primary endpoint, ORR (CR + PR) after 4 cycles, can be carried out 4 months after the last patient was enrolled, and will be based on the population of all treated patients. Response rates with confidence intervals (95% interval) will be presented. The TRG will be evaluated in accordance with local and centralized PET / CT evaluations.

Overall survival, PFS, event-free survival, and duration of response are defined as follows (Cheson et al., 2007):
Overall survival (OS): defined as the time between entry into the trial and death from any cause. It will be analyzed using the Kaplan-Meier method. Data on patients withdrawn from the study or unavailable for follow-up will be censored on the date of the last contact.
Progression-free survival (PFS). It is defined as the time elapsed from the inclusion of the first patient in the study until the progression of the disease or death from any cause.
Event-free survival (EFS). It is defined as the time elapsed from inclusion in the trial to lymphoma progression, treatment failure, or death from any cause. It will be analyzed using the Kaplan-Meier method.
Duration of response. It will be calculated from the date there is an indication of CR or PR to the date of disease recurrence or progression. It will be analyzed using the Kaplan-Meier method.

2. RESULTS

2.1. POPULATIONS

2.1.1. Patients registered in the eCRF

Table 1. Patients registered by hospital

		N	%
Hospital			
	Total		
Analyzable	Yes		
	No		
	Total		

2.1.2. Analyzable patients

Table 2. Not analyzable patients

No.	Study Subject ID	Hospital	Reason

Table 3. Analyzable patient by hospital

		Analyzable					
		No		Yes		Total	
		N	%	N	%	N	%
Hospital							
	Total						

2.1.3. Analysis populations

Table 4. Analysis population

		N	%
Treated patient population	Yes		
	Total		
Available response patient population	Yes		
	No		
	Total		
Reason considered response not available	At least one post-baseline evaluation		
	Death due to progression		
	Total		

Table 5. List of patients excluded from Available response patient population

	Study Subject ID	Hospital	Available response patient population	Reason considered response available (or not)	Overall survival	Reason of Death	Specify reason of Death
1							
2							
3							
4							

2.2. BASELINE CHARACTERISTICS

Table 6. Gender

		N	%
Gender (Baseline)	Male		
	Female		
	Total		

Table 7. Age

	N	Mean	SD	Median	Min	Max
Age (years)						

Vital signs

Table 8. Vital signs 1

	N	Mean	SD	Median	Min	Max
Systolic blood pressure (Baseline)						
Diastolic blood pressure (Baseline)						
Temperature (Baseline)						
Weight (Baseline)						
Height (Baseline)						

Table 9. Vital signs 2

		N	%
ECOG (Baseline)	0		
	1		
	2		
	Total		
B symptoms (Baseline)	Yes		
	No		
	Total		
Pre-existing condition, relevant signs or symptoms (Baseline)	Yes		
	No		
	Total		

All relevant previous events are listed in ANNEX 1: RELEVANT PREVIOUS EVENTS (page 40), and the following table contains those events present in at least 5% of the patients.

Table 10. Most frequent relevant previous events (present in at least 5% of patients)

		N
Relevant previous events		

Table 11. Previous medication

		N	%
Previous medication	Yes		
	No		
	Total		

All previous medications are listed in ANNEX 2: PREVIOUS MEDICATION (page 40), and the following table contains those medications present in at least 5% of the patients.

Table 12. Most frequent previous medication (present in at least 5% of patients)

		N
Previous medication		

2.3. DIAGNOSIS

Table 13. Time from diagnosis and age at diagnosis

	N	Mean	SD	Median	Min	Max
Time from diagnosis to study inclusion (months)						
Age at diagnosis						

Table 14. Local histological diagnosis, centralized and agreement

		N	%
Histological subtype at diagnosis, local (Baseline)	LDCBG without specification		
	Others[1]		
	LDCBG specified[2]		
	Total		
2: LDCBG specified	LDCGB rich in T		
1: Others	Follicular lymphoma		
		N	%
Histological subtype at diagnosis, centralized review (Baseline)	LDCBG without specification		
	Others[3]		
	NA		
	ND		
	Total		
3: Others	CD5+ B lymphoma		
	Could not be determined with submitted sample		
	MO cylinder biopsy without evidence of neoplastic infiltration		
		N	%
Agreement in histology at diagnosis	No		
	Yes		
	Total		

Table 15. Patients without agreement in Histological type at diagnosis

	Study Subject ID	Hospital	Diagnosis date (Baseline)	Histological subtype at diagnosis, local (Baseline)	Histological subtype at diagnosis, centralized review (Baseline)	Agreement in histology at diagnosis
1						
2						
3						
4						

1.1.1. Diagnosis: Immunohistochemical type of LDCBG

Table 16. Immunohistochemical type of LDCBG at diagnosis

		N	%
Immunohistochemical type at diagnosis, local (Baseline)	no-CGB		
	Others		
	UK		
	Total		
Immunohistochemical type of LDCBG at diagnosis, centralized review (Baseline)	CGB		
	no-CGB		
	NA		
	ND		
	UK		
	Total		
Agreement in immunohistochemical at diagnosis	Non-CGB local and centralized		
	Non-CGB local and CGB centralized		
	Non-CGB local and missing centralized		
	Missing local and centralized		
	Other local and missing centralized		
	Total		
Agreement in immunohistochemical at diagnosis	Yes		
	No		
	Total		

Table 17. Patients without agreement in Immunohistochemical type of LDCBG at diagnosis

	Study Subject ID	Hospital	Diagnosis date (Baseline)	Immunohistochemical agreement at diagnosis (Yes/No)	Immunohistochemical agreement at diagnosis
1					
2					
3					
4					
5					

1.1.2. Diagnosis: Other histological data

Other histological data at diagnosis.

Table 18. Other histological data

		N	%
Nanostring result at diagnosis (Baseline)	ABC		
	Not done		
	NA		
	ND		
	UK		
	Total		
Lymphoma stage at diagnosis (Baseline)	I		
	II		
	III		
	IV		
	ND		

	UK	
	Total	
ECOG diagnosis (Baseline)	0	
	1	
	2	
	3	
	ND	
	UK	
	Total	
LDH at diagnosis (Baseline)	Normal	
	Increased	
	ND	
	UK	
	Total	
IPI diagnosis (Baseline)	0-1	
	2	
	3	
	4	
	5	
	ND	
	UK	
	Total	

1.1.3. Current lymphoma exploration

Table 19. Current lymphoma exploration

		N	%
Adenopathy (Baseline)	Yes		
	No		
	Total		
Specify adenopathy (Baseline)	Example: Bilateral supraclavicular, Axillary, mediastinal, hilar…		
	Total		
Hepatomegaly (Baseline)	Yes		
	No		
	Total		
Splenomegaly (Baseline)	Yes		
	No		
	Total		
Lymphomatous involvement (Baseline)	Yes		
	No		
	Total		
Specify Lymphomatous involvement (Baseline)	Example: Bone, liver and bone marrow…		
	Total		

1.1.4. Current stage: Rebiopsy and other current results

Table 20. Histological, molecular and current stage

		N	%
Rebiopsy (Baseline)	Yes		
	No		
	Total		
Current nanostring result (Baseline)	CGB		
	ABC		
	Not done		
	NA		
	ND		
	UK		
	Total		
Current lymphoma clinical stage (Baseline)	I		
	II		
	III		
	IV		
	NA		
	ND		
	UK		
	Total		
Current Bone marrow biopsy - histological affectation (Baseline)	Yes		
	No		
	NA		
	ND		
	UK		
	Total		
Current cytometry involvement (Baseline)	Yes		
	No		
	NA		
	ND		
	UK		
	Total		

1.1.5. Current histology: diagnosis and agreement

Table 21. Current Histological subtype

		N	%
Current, local histological subtype (Baseline)	LDCBG without specification		
	LDCBG specified		
	NA		
	ND		
	UK		
	Total		
Specify other histological subtypes current, local (Baseline)	Example: LDCBG gastric…		
	Total		
Current histological subtype, centralized review (Baseline)	LDCBG without specification		
	Others		
	NA		
	ND		

	UK	
	Total	
Specify other current histological subtypes, centralized review (Baseline)	Example: Lymphoma B of the marginal zone/Lymphoma B with plasmocellular differentiation…	
	Total	
Current concordance in Histology at diagnosis	No	
	Yes	
	Total	

Table 22. Patients without agreement in current histology diagnosis

	Study Subject ID	Hospital	Current, local histological subtype (Baseline)	Specify other histological subtypes current, local (Baseline)	Current histological subtype, centralized review (Baseline)	Specify other current histological subtypes, centralized review (Baseline)
1						
2						
3						

1.1.6. Current Immunohistochemistry: diagnosis and agreement

Table 23. Agreement current immunohistochemical diagnosis

		N	%
Current immunohistochemical type, local (Baseline)	no-CGB		
	NA		
	ND		
	UK		
	Total		
Immunohistochemical type of current LDCBG, centralized review (Baseline)	CGB		
	no-CGB		
	NA		
	ND		
	UK		
	Total		
Current immunohistochemical agreement	No		
	Yes		
	Total		

Table 24. Patients without agreement in current immunohistochemical diagnosis

	Study Subject ID	Hospital	Current immunohistochemical agreement	Current immunohistochemical type, local (Baseline)	Immunohistochemical type of current LDCBG, centralized review (Baseline)
1					
2					
3					
4					

1.1.7. Global diagnosis

Table 25. Agreement current immunohistochemical diagnosis

		N	%
Global local diagnosis	no-CGB		
	Total		
Global centralized diagnosis	no-CGB		
	CGB		
	LDCBG without specification		
	Others: Follicular lymphoma, Lymphoma B with plasmocellular differentiation…		
	ND		
	UK		
	Total		
Global agreement	No		
	Yes		
	Total		

Table 26. Patients without agreement in current immunohistochemical diagnosis

	Study Subject ID	Hospital	Global local diagnosis	Global centralized diagnosis
1				
2				
3				

1.2. PREVIOUS TREATMENTS LYMPHOMA

Table 27. Number of previous treatment lines

		N	%
Number of previous treatment lines (Baseline)	1		
	2		
	3		
	4		
	5		
	Total		

	N	Mean	SD	Median	Min	Max
Number of previous treatment lines (Baseline)						

Table 28. Previous treatment: 1st line

		N	%
Best response previous treatment line 1 (Baseline)	CR		
	PR		
	SD		
	PD		
	ND		
	UK		
	Total		
Relapse or previous progression line 1 (Baseline)	Yes		
	No		
	NA		
	ND		
	Total		
First line treatment (Baseline)	Example: R- CHOP, Rituximab, Splenectomy…		
	Total		

Table 29. Previous treatment: 2nd line

		N	%
Best response previous treatment line 2 (Baseline)	CR		
	PR		
	SD		
	PD		
	NA		
	UK		
	Total		
Relapse or previous progression line 2 (Baseline)	Yes		
	No		
	NA		
	UK		
	Total		
Second line treatment (Baseline)	NA		
	Example: R-ESHAP, R-DHAP		
	Total		

Table 30. Previous treatment: 3rd line

		N	%
Best response previous treatment line 3 (Baseline)	PR		
	SD		
	PD		
	NA		
	UK		
	Total		
Relapse or previous progression line 3 (Baseline)	Yes		
	No		
	NA		
	Total		
Third line treatment (Baseline)	NA		
	Example: BeGEV + Transplant		
	Total		

Table 31. Previous treatment: 4th line

		N	%
Best response previous treatment line 4 (Baseline)	PR		
	PD		
	NA		
	UK		
	Total		
Relapse or previous progression line 4 (Baseline)	Yes		
	NA		
	Total		
Fourth line treatment (Baseline)	NA		
	Example: Prednisone + Brentuximab		
	Total		

1.3. AUTOLOGOUS STEM CELL TRANSPLANT

Table 32. Autologous stem cell transplant

		N	%
Autotransplantation (Baseline)	Yes		
	No		
	Total		
Situation autotransplantation (Baseline)	1st CR		
	1st PR		
	2nd CR		
	2nd PR		
	Others		
	NA		
	Total		
Specify other (Baseline)	Example: PD located in right axillar region…		
	Total		
Best response autotransplantation (Baseline)	CR		
	PR		
	PD		
	NA		
	UK		
	Total		

Response duration (Baseline)	Example: 0, 3, 6, 9…	
	NA	
	UK	
	Total	
Relapse or progression (Baseline)	Yes	
	NA	
	Total	

Table 33. Response duration (autologous stem cell transplant)

	N	Mean	SD	Median	Min	Max
Response duration (Baseline)						

1.4. ALEOGENIC TRANSPLANT HEMATOPOIETIC PROGENITORS

Table 34. Allogenic transplant hematopoietic progenitors

		N	%
Allotransplant (Baseline)	No		
	Total		

1.5. EXTRANODAL AND NODAL AFFECTATION

Table 35. Extranodal Affectation

		N	%
Extranodal affectation at diagnosis (Baseline)	Yes		
	No		
	ND		
	Total		
Locations extranodals (Baseline)	ND		
	Example: 0, 1, 2, 3…		
	Total		
Specify extranodal affectation (Baseline)	Example: Bone, Lung, Bone marrow…		
	Total		

Table 36. Nodal Affectation

		N	%
Nodal affectation at diagnosis (Baseline)	Yes		
	No		
	ND		
	Total		
Nodal locations (Baseline)	ND		
	Example: 0, 1, 2, 3…		
	Total		
Specify nodal affectation (Baseline)	Example: Bilateral adrenal burky mass, Retroperitoneal…		
	Total		

1.6. BASELINE ANALYTICS

1.6.1. HEMOGRAM

Table 37. Baseline analytics: Hemogram

	N	Mean	SD	Median	Min	Max
Hemoglobin Value (Baseline)						
Leukocytes Value (Baseline)						
Lymphocytes Value (Baseline)						
Monocytes Value (Baseline)						
Eosinophils Value (Baseline)						
Neutrophils Value (Baseline)						
Platelets Value (Baseline)						

1.6.2. BIOCHEMISTRY

Table 38. Baseline analytics: Biochemistry

	N	Mean	SD	Median	Min	Max
Creatinine Value (Baseline)						
Urea Value (Baseline)						
Urate Value (Baseline)						
Sodium Value (Baseline)						
Potassium Value (Baseline)						
Calcium Value (Baseline)						
Glucose Value (Baseline)						
Protein Value (Baseline)						
Albumin Value (Baseline)						
LDH Value (Baseline)						
Gamma globulin Value (Baseline)						
Meta2-seric microglobulin Value (Baseline)						
OSTP/ALT Value (Baseline)						
OSOT/AST Value (Baseline)						
FA Value (Baseline)						
GGT Value (Baseline)						
BIL Value (Baseline)						
IgG Determination Value (Baseline)						
IgA Determination Value (Baseline)						
IgM Determination Value (Baseline)						

1.6.3. COAGULATION TEST

Table 39. Baseline analytics: Coagulation test

	N	Mean	SD	Median	Min	Max
TTP Value (Baseline)						
TP Value (Baseline)						
Fibrinogen Value (Baseline)						

1.6.4. IPI

Table 40. Baseline analytics: IPI

		N	%
IPI (Baseline)	0		
	1		
	2		
	3		
	4		
	5		
	UK		
	Total		

	N	Mean	SD	Median	Min	Max
IPI (Baseline)						

1.6.5. LYMPHOMA SITUATION

Table 41. Baseline analytics: Lymphoma situation

		N	%
Situation lymphoma (Baseline)	Partial Response		
	Refractory disease		
	Relapse early untreated (<1 year after diagnosis)		
	Relapse late untreated		
	UK		
	Total		

1.6.6. SEROLOGY

Table 42. Baseline analytics: Serology

		N	%
HIV antibodies (Baseline)	Negative		
	Total		
Hepatitis C (Baseline)	Positive		
	Negative		
	UK		
	Total		
RNA VHC (Baseline)	Negative		
	NA		
	ND		
	UK		
	Total		
HbsAg (Baseline)	Positive		
	Negative		
	NA		
	ND		
	UK		
	Total		

Anti Hbc (Baseline)	Positive		
	Negative		
	ND		
	UK		
	Total		
Anti Hbs (Baseline)	Positive		
	Negative		
	ND		
	UK		
	Total		
DNA VHB (Baseline)	Positive		
	Negative		
	NA		
	ND		
	UK		
	Total		

1.7. OTHER TESTS

1.7.1. OTHER TESTS: PREGNANCY

Table 43. Other test: Pregnancy

		N	%
Pregnancy test at inclusion (Baseline)	Negative		
	NA		
	ND		
	UK		
	Total		

1.7.2. OTHER TESTS: CARDIOLOGY TEST

Table 44. Other test: Cardiology test

		N	%
ECG at inclusion (Baseline)	Without significative alterations		
	Significative alterations		
	NA		
	ND		
	UK		
	Total		
Cardiac ventricular ejection fraction (Baseline)	Yes		
	No		
	NA		
	ND		
	UK		
	Total		
Technique FE (Baseline)	Ecocardio		
	MUGA		
	NA		
	ND		
	Total		
Result FE (Baseline)	Normal		
	Total		

1.7.3. OTHER TESTS: COMORBIDITIES QUESTIONNAIRE

Table 45. Comorbidities questionnaire: Item results

		N	%
CRS-G comorbidity scale has been done (Baseline)	Yes		
	No		
	Total		
Hearth (Baseline)	Example: 0, 1…		
	Total		
Hypertension (Baseline)	Example: 0, 1…		
	Total		
Hematopoietic vascular (Baseline)	Example: 0, 1…		
	Total		
Respiratory (Baseline)	Example: 0, 1…		
	Total		
ORL (Baseline)	Example: 0, 1…		
	Total		
Upper GI apparatus (Baseline)	Example: 0, 1…		
	Total		
Lower GI apparatus (Baseline)	Example: 0, 1…		
	Total		
Liver (Baseline)	Example: 0, 1…		
	Total		
Renal (Baseline)	Example: 0, 1…		
	Total		
Genitourinary (Baseline)	Example: 0, 1…		
	Total		
Skeletal muscle (Baseline)	Example: 0, 1…		
	Total		
Nervous system (Baseline)	Example: 0, 1…		
	Total		
Endocrine-metabolic system and breast (Baseline)	Example: 0, 1…		
	Total		
Psychiatric problems (Baseline)	Example: 0, 1…		
	Total		
GAH (Baseline)	Yes		
	No		
	NA		
	ND		
	Total		

Table 46. Comorbidities questionnaire: Scores

		N	%
Number of categories that have scored: of the total of 14 categories, count those that have not received a score of 0	Example: 0, 1…		
	Total		
Total score (adding all the points)	Example: 0, 1…		
	Total		
Severity index (total score/number of categories that have scored)	Example: 0, 1…		
	Total		

Number of categories that have scored with a score>=3	Example: 0, 1…	
	Total	
Number of categories that have scored with score 4	Example: 0, 1…	
	Total	

	N	Mean	SD	Median	Min	Max
Score > 0 (Baseline)						
Score (Baseline)						
Severity index (Baseline)						

1.8. TREATMENT COMPLIANCE

Table 47. Treatment compliance Induction: Received cycles/completed

		N	%
Number of induction cycles received	Example: 1.00, 2.00…		
	Total		
Number of induction cycles received complete (according to protocol)	Example: 1.00, 2.00…		
	Total		
Patients with delayed induction cycles	No		
	Yes		
	Total		
% of induction cycles received complete (according to protocol)	% of induction cycles received		
	Total		
Number of induction cycles received with delay	Example: 1.00, 2.00…		
	Total		
% of induction cycles received with delay	% of induction cycles received with delay.00		
	Total		
No. of induction cycles delayed due to hematological toxicity	Not delayed cycle due to hematological toxicity		
	Example: 1.00, 2.00…		
	Total		

	N	Mean	SD	Median	Min	Max
Number of induction cycles received						
Number of induction cycles received complete (according to protocol)						
% of induction cycles received complete (according to protocol)						
Number of induction cycles received with delay						
% of induction cycles received with delay						
No. of induction cycles delayed due to hematological toxicity						

Table 48. Ibrutinib dosage

		N	%
Minimum dose of ibrutinib received per patient	560mg/day		
	420mg/day		
	280mg/day		
	Total		
Ibrutinib dose reduced	No		
	Yes		
	Total		

Table 49. Treatment duration

	N	Mean	SD	Median	Min	Max
Treatment duration (months)						

1.9. END OF TREATMENT

Table 50. End of treatment

		N	%
Treatment ends	**Yes**		
	Total		
Reason end of treatment (End of treatment)	**Progression**		
	Unacceptable toxicity		
	End of maintenance		
	Investigator criteria		
	Patient withdrawal of continuing with treatment		
	Others		
	Total		
Specify Other/Unacceptable toxicity or Investigator criteria	**Example: Allogeneic transplant, Cardiac complications…**		
	Total		

1.10. EFFICACY: RESPONSE

1.10.1. SUMMARY RESPONSE AT 4TH CYCLE AND AFTER INDUCTION IN TREATED PATIENTS

Table 51. Summary of local response in the 4th cycle, 6-8th cycles in local evaluation (treated patients) and ORR

	After 4th cycle N (%)	After induction N (%)	ORR (as Best Overall Response)
Complete response (CR)			
Partial response (PR)			
Global response (GR=CR+PR)			
Stable disease (SD)			
Progression			
Not evaluated due to lack of follow-up at cycle 6-8			
Not evaluated due to other reasons			
Total			

1.10.2. RESPONSE AT 4TH CYCLE IN TREATED PATIENTS

Table 52. Response at 4th cycle in local evaluation (treated patients)

		N (%, CI 95%)
Local evaluation CT scan 4th cycle	CR	
	PR	
	SD	
	Progression	
	Study ends due to Exitus without CT scan 4th cycle	
	Study ends due to IC withdrawal without CT scan 4th cycle	
	Total	
CR or PR at 4th cycle in local evaluation	PR or CR	
	No PR or CR	
	Total	

Table 53. Response at 4th cycle in centralized evaluation (treated patients)

		N (%, CI 95%)
Centralized evaluation CT scan 4th cycle	CR	
	PR	
	SD	
	Progression	
	Study ends due to Exitus without CT scan 4th cycle	
	Study ends due to IC withdrawal without CT scan 4th cycle	
	Without centralized response CT scan 4th cycle (local available)	
	Total	
CR or PR at 4th cycle in centralized evaluation	PR or CR	
	No PR or CR	
	Without centralized response CT scan 4th cycle (local available)	
	Total	

1.10.3. RESPONSE AT 4TH CYCLE IN PATIENTS FROM AVAILABLE RESPONSE POPULATION

Table 54. Response at 4th cycle in local evaluation (evaluable assessment)

		N (%, CI 95%)
Local evaluation CT scan 4th cycle	CR	
	PR	
	SD	
	Progression	
	Study ends for Exitus without CT scan 4th cycle	
	Total	
CR or PR at 4th cycle in local evaluation	PR or CR	
	No PR or CR	
	Total	

Table 55. Response at 4th cycle in centralized evaluation (evaluable assessment)

		N (%, CI 95%)
Centralized evaluation CT scan 4th cycle	CR	
	PR	
	SD	
	Progression	
	Study ends for Exitus without CT scan 4th cycle	
	Without centralized response CT scan 4th cycle (local available)	
	Total	
CR or PR at 4th cycle in centralized evaluation	PR or CR	
	No PR or CR	
	Without centralized evaluation	
	Total	

1.10.4. RESPONSE AT 6-8TH CYCLE IN TREATED PATIENTS

Table 56. Response at 6-8th cycle in local evaluation (treated patients)

		N (%, CI 95%)
Local evaluation CT scan 6-8th cycle	CR	
	PR	
	SD	
	Progression	
	Study ends for Exitus without CT scan 6-8th cycle	
	Study ends for IC withdrawal without CT scan 6-8th cycle	
	Without CT scan 6-8th cycle due to lack of follow-up	
	Total	
CR or PR at 6-8th cycle in local evaluation	PR or CR	
	No PR or CR	
	Without CT scan at 6-8th cycle due to lack of follow-up	
	Total	

Table 57. Response at 6-8th cycle in centralized evaluation (treated patients)

		N (%, CI 95%)
Centralized evaluation CT scan 6-8th cycle	Positive*	
	Negative*	
	Progression in PET-TAC 4th cycle centralized (without evaluation at 6-8th cycle)	
	Ends study due to Exitus without CT-scan 6-8th cycle	
	Ends study due to withdrawal of IC without CT-scan 6-8th cycle	
	Without CT-scan 6-8th cycle due to lack of follow-up	
	Without centralized evaluation 6-8th cycle (local available)	
	Without centralized evaluation 6-8th cycle	
	Total	
CR or PR at 6-8th cycle in centralized evaluation	Positive (Response)*	
	Negative (No response)*	
	Without CT scan at 6-8th	
	Total	64

1.10.5. RESPONSE AT 6-8TH CYCLE IN PATIENTS FROM AVAILABLE RESPONSE POPULATION

Table 58. Response at 6-8th cycle in local evaluation (evaluable assessment)

		N (%, CI 95%)
Local evaluation CT scan 6-8th cycle	CR	
	PR	
	SD	
	Progression	
	Study ends for Exitus without CT scan 6-8th cycle	
	Without CT scan 6-8th cycle due to lack of follow-up	
	Total	
CR or PR at 6-8th cycle in local evaluation	PR or CR	
	No PR or CR	
	Without CT scan at 6-8th cycle due to lack of follow-up	
	Total	

Table 59. Response at 6-8th cycle in centralized evaluation (evaluable assessment)

		N (%, CI 95%)
Centralized evaluation CT scan 6-8th cycle	Positive*	
	Negative*	
	Progression in PET-TAC 4th cycle centralized (without evaluation at 6-8th cycle)	
	Ends study due to Exitus without CT-scan 6-8th cycle	
	Without CT-scan 6-8th cycle due to lack of follow-up	
	Without centralized evaluation 6-8th cycle (local available)	
	Without centralized evaluation 6-8th cycle	
	Total	
CR or PR at 6-8th cycle in centralized evaluation	Positive (Response)*	
	Negative (No response)*	
	Without CT scan at 6-8th	
	Total	

1.1.1. ORR IN TREATED PATIENTS

Table 60. ORR in local evaluations (treated patients)

		N (%, CI 95%)
Best Overall Response (including CT-scans after EOT)	CR	
	PR	
	SD	
	Relapse	
	Progression	
	Study ends due to Exitus without CT scan 4th cycle and after	
	Study ends due to IC withdrawal without CT scan 4th cycle and after	
	Total	

BOR: CR or PR (including CT-scans after EOT)	No	
	Yes	
	Total	

Table 61. ORR in centralized evaluations (treated patients)

		N (%, CI 95%)
BOR: CR or PR as Positive/Negative* (including CT-scans after EOT) centralized	No	
	Yes	
	Total	

1.10.6. ORR IN PATIENTS FROM AVAILABLE RESPONSE POPULATION

Table 62. ORR in local evaluations (evaluable assessment)

		N (%, CI 95%)
Best Overall Response (including CT-scans after EOT)	CR	
	PR	
	SD	
	Relapse	
	Progression	
	Study ends due to Exitus without CT scan 4th cycle and after	
	Total	
BOR: CR or PR (including CT-scans after EOT)	No	
	Yes	
	Total	

Table 63. ORR in centralized evaluations (evaluable assessment)

		N (%, CI 95%)
BOR: CR or PR as Positive/Negative* (including CT-scans after EOT) centralized	No	
	Yes	
	Total	

1.11. EFFICACY: SURVIVAL

1.11.1. OVERALL SUVIVAL IN TREATED PATIENTS

Table 64. Overall survival in treated patients

Estimated OS	N events	N at risk	% patients without exitus	CI 95%	% with exitus
at 6 months					
at 12 months					
at 24 months					

	N events (%)	Median	Min-Max	Standard error	CI 95%
Estimated OS					

Table 65. Overall survival in treated patients: Events and death reason

		N (%; CI 95%)
Overall survival	Alive	
	Death	
	Total	
Death reason	Lymphoma/Progression	
	Toxicity	
	Others	
	Not specified	
	Total	

Specify death reason	N (%)
Example: CART-T therapy, Nosocomial respiratory infection	

Table 66. Follow-up time in treated patients

	N	Mean (SE)	Median (Min-Max)
Time until Death or last follow-up (from inclusion)			

1.11.1.1 OVERALL SUVIVAL IN COMPLETE RESPONDERS (TREATED PATIENTS)

Table 67. Overall survival in complete responders (treated patients)

Estimated OS	N events	N at risk	% patients without Death	CI 95%	% with Death
at 6 months					
at 12 months					
at 24 months					

	N events (%)	Median	Min-Max	Standard error	CI 95%
Estimated OS					

Table 68. Overall survival in complete responders (treated patients): Events and death reason

		N (%; CI 95%)
Overall survival	Vivo	
	Death	
	Total	
Death reason	Lymphoma/Progression	
	Others	
	Total	

Specify death reason	N (%)
Example: Respiratory insufficiency due to progression…	

Table 69. Follow-up time complete responders (treated patients)

	N	Mean (SE)	Median (Min-Max)
Time until exitus or last follow-up (from inclusion)			

1.1.1. OVERALL SUVIVAL IN AVAILABLE RESPONSE POPULATION

Table 70. Overall survival in available response population

Estimated OS	N events	N at risk	% patients without exitus	CI 95%	% with Death
at 6 months					
at 12 months					
at 24 months					

	N events (%)	Median	Min-Max	Standard error	CI 95%
Estimated OS					

Table 71. Overall survival in available response population: Events and death reason

		N (%; CI 95%)
Overall survival	Vivo	
	Death	
	Total	
Death reason	Lymphoma/Progression	
	Others	
	Not specified	
	Total	

Specify death reason	N (%)
Example: CART-T therapy, Respiratory insufficiency due to progression…	

Table 72. Follow-up time in available response population

	N	Mean (SE)	Median (Min-Max)
Time until exitus or last follow-up (from inclusion)			

1.1.1.1 OVERALL SUVIVAL IN COMPLETE RESPONDERS (AVAILABLE RESPONSE POPULATION)

Table 73. Overall survival in complete responders (available response population)

Estimated OS	N events	N at risk	% patients without exitus	CI 95%	% with exitus
at 6 months					
at 12 months					
at 24 months					
	N events (%)	Median	Min-Max	Standard error	CI 95%
Estimated OS					

Table 74. Overall survival in complete responders (available response population): Events and death reason

		N (%; CI 95%)
Overall survival	Vivo	
	Death	
	Total	
Death reason	Lymphoma/Progression	
	Others	
	Total	
		N (%)
Specify death reason	Others: Probable septic shock with multi-organ failure (post-haploidentical transplantation)	
	Others: Respiratory insufficiency due to progression	

Table 75. Follow-up time complete responders (available response population)

	N	Mean (SE)	Median (Min-Max)
Time until exitus or last follow-up (from inclusion)			

1.11.2. PROGRESSION FREE SURVIVAL IN TREATED PATIENTS

Table 76. Progression Free Survival in treated patients

Estimated PFS	N events	N at risk	% of patients without PFS	CI 95%	% with PD
at 6 months					
at 12 months					
at 24 months					
	N (%)	Median	Min-Max	Standard error	CI 95%
Estimated PFS					

Table 77. PFS in treated patients: Events and PD assessment

		N (%; CI 95%)
Progression Free Survival	Vivo sin PD	
	PD	
	Death	
	Total	
PD assessment		N (%)
	PD assessment	

1.11.2.1 PFS IN COMPLETE RESPONDERS (TREATED PATIENTS)

Table 78. Progression Free Survival in complete responders (treated patients)

Estimated PFS	N events	N at risk	% of patients without PFS	CI 95%	% with PD
at 6 months					
at 12 months					
at 24 months					
	N (%)	Median	Min-Max	Standard error	CI 95%
Estimated PFS					

Table 79. PFS in complete responders (treated patients): Events and PD assessment

		N (%; CI 95%)
Progression Free Survival	Vivo sin PD	
	PD	
	Death	
	Total	
PD assessment		N (%)
	PD assessment	

1.11.3. PROGRESSION FREE SURVIVAL IN AVAILABLE RESPONSE POPULATION

Table 80. Progression Free Survival in available response population

Estimated PFS	N events	N at risk	% of patients without PFS	CI 95%	% with PD
at 6 months					
at 12 months					
at 24 months					
	N (%)	Median	Min-Max	Standard error	CI 95%
Estimated PFS					

Table 81. PFS in available response population: Events and PD assessment

		N (%; CI 95%)
Progression Free Survival	Vivo sin PD	
	PD	
	Death	
	Total	
		N (%)
PD assessment	PD assessment	

1.11.3.1 PFS IN COMPLETE RESPONDERS (AVAILABLE RESPONSE POPULATION)

Table 82. Progression Free Survival in complete responders (available response population)

Estimated PFS	N events	N at risk	% of patients without PFS	CI 95%	% with PD
at 6 months					
at 12 months					
at 24 months					
	N (%)	Median	Min-Max	Standard error	CI 95%
Estimated PFS					

Table 83. PFS in complete responders (available response population): Events and PD assessment

		N (%; CI 95%)
Progression Free Survival	Vivo sin PD	
	PD	
	Death	
	Total	
		N (%)
PD assessment	PD assessment	

1.11.4. EVENT FREE SURVIVAL IN TREATED PATIENTS

Table 84. EFS in treated patients

Estimated EFS	N events	N at risk	% patients without event	CI 95%	% patients with event
at 6 months					
at 12 months					
at 24months					
	N (%)	Median	Min-Max	Standard error	CI 95%
Estimated EFS					

Table 85. EFS in treated patients: Events

		N (%; CI 95%)
Type of events	Alive (without event)	
	PD	
	Death	
	Therapeutic failure (Toxicity)	
	Total	

1.11.4.1 EFS IN COMPLETE RESPONDERS (AVAILABLE RESPONSE POPULATION)

Table 86. EFS in available response population

Estimated EFS	N events	N at risk	% patients without event	CI 95%	% patients with event
at 6 months					
at 12 months					
at 24months					
	N (%)	Median	Min-Max	Standard error	CI 95%
Estimated EFS					

Table 87. EFS in available response population: Events

		N (%; CI 95%)
Type of events	Alive (without event)	
	PD	
	Death	
	Therapeutic failure (Toxicity)	
	Total	

1.11.5. RESPONSE DURATION IN TREATED PATIENTS

Table 88. TAC at which the CR or PR is reached (treated patients)

		N	%
TAC at which the CR or PR is reached	Cycle X		
	Total		

Table 89. Response duration (treated patients)

	N	Mean (SD)	Median (Min-Max)
Time since CR/PR until PD/exitus or censored			

1.11.5.1 PFS FROM RESPONSE (CR or PR) IN TREATED PATIENTS

Table 90. PFS from response until PD/exitus (estimated by Kaplan-Meier) (in treated patients)

Estimated PFS from response	N events	N at risk	% of patients without event	CI 95%	% of patients with event
at 6 months					
at 12 months					
at 24 months					

	N (%)	Median	Min-Max	Standard error	CI 95%
Estimated PFS from response					

Table 91. PFS from response (in treated patients): Events

		N (%; CI 95%)
PFS from response events	Alive without PD	
	PD	
	Exitus without previous PD	
	Total	
Pts with response longer than 12m	No	
	Yes	
	Total	

1.1.1. COMPLETE RESPONSE DURATION IN TREATED PATIENTS

Table 92. TAC at which the CR is reached (treated patients)

		N	%
TAC at which the CR is reached	Cycle X		
	Total		

Table 93. CR duration (treated patients)

	N	Mean (SD)	Median (Min-Max)
Time since CR until PD/exitus or censored			

1.1.1.1 PFS FROM COMPLETE RESPONSE IN TREATED PATIENTS

Table 94. PFS from CR until PD/exitus (estimated by Kaplan-Meier) (in treated patients)

Estimated PFS from CR	N events	N at risk	% of patients without event	CI 95%	% of patients with event
at 6 months					
at 12 months					
at 24 months					

	N (%)	Median	Min-Max	Standard error	CI 95%
Estimated PFS from CR					

Table 95. PFS from response (in treated patients): Events

		N (%; CI 95%)
PFS from CR events	Alive without PD	
	PD	
	Death without previous PD	
	Total	
Pts with CR longer than 12m	No	
	Yes	
	Total	

PARTIAL RESPONSE DURATION IN TREATED PATIENTS

Table 96. TAC at which the PR is reached (treated patients)

		N	%
TAC at which the PR is reached	Cycle X		
	Total		

Table 97. PR duration (treated patients)

	N	Mean (SD)	Median (Min-Max)
Time since PR until PD/exitus or censored			

1.1.1.2 PFS FROM PARTIAL RESPONSE IN TREATED PATIENTS

Table 98. PFS from PR until PD/exitus (estimated by Kaplan-Meier) (in treated patients)

Estimated PFS from PR	N events	N at risk	% of patients without event	CI 95%	% of patients with event
at 6 months					

at 12 months					
at 24 months					
	N (%)	Median	Min-Max	Standard error	CI 95%
Estimated PFS from PR					

Table 99. PFS from response (in treated patients): Events

		N (%; CI 95%)
PFS from PR events	PD	
	Death without previous PD	
	Total	
Pts with PR longer than 12m	No	
	Yes	
	Total	

1.2. SAFETY: TOXICITY

As per protocol, the following definition is used to determine which adverse events are considered as toxicities:

"Adverse event related to drug use

An adverse event is considered to be drug-related if the attribution is possible, probable, or very probable, based on the definitions provided below. (see page 54 of the protocol)".

Table 100. Toxicities

		N (%, IC 95%)
AE	No	
	Yes	
	Total	
Toxicity: AE related to the treatment (possible, probable or definitively)	No	
	Yes	
	Total	
AE grade ≥3	No	
	Yes	
	Total	
Hematological Toxicity	No	
	Yes	
	Total	
SAE	Yes	
	No	
	Total	

1.2.1. MOST FREQUENT ADVERSE EVENTS AND TOXICITIES

The following table shows the most frequent Adverse events taking a threshold of 5% and in overall and also taking into account the treatment phase at the date that the AEs first appeared.

Table 101. Most frequent AEs with 5% threshold

	Induction	Maintenance	Start day missing	Total
	N (%)	N (%)	N (%)	N (%)
Example: Platelet count decreased, Neutrophil count decreased…				

The following table shows the most frequent ***Toxicities*** taking a threshold of 5% and in overall and also taking into account the treatment phase at the date that the AEs first appeared.

Table 102. Most frequent Toxicities with 5% threshold

	Induction	Maintenance	Start day missing	Total
	N (%)	N (%)	N (%)	N (%)
Example: Diarrhea, Anemia…				

The following table shows the most frequent ***Toxicities*** taking a threshold of 5%, according to their maximum grade in overall:

Table 103. Grades of most frequent Toxicities with 5% threshold. Overall

	No	G-UK	G-1	G-2	G-3	G-4	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Example: Nausea, Anemia…							

Table 104. Grades of most frequent Toxicities (5% threshold). Induction phase.

	No	G-UK	G-1	G-2	G-3	G-4	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Example: Nausea, Anemia…							

Table 105. Grades of most frequent Toxicities (5% threshold).Maintenance phase.

	No	G-UK	G-1	G-2	G-3	G-4	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Example: Nausea, Anemia…							

1.1.1. HEMATOLOGICAL AND NON-HEMTOLOGICAL TOXICITIES

The following table shows all the hematological toxicities (with maximum grade) taking into account the treatment phase at the date that the AEs first appeared.

Table 106. List of all hematological toxicities

	Induction	Maintenance	Total
	N (%)	N (%)	N (%)
Example: Anemia - Grade 1, Lymphocyte count decreased - Grade 2…			

The following table shows all the non-haematological toxicities with maximum grade ≥3, taking into account the treatment phase at the date that the AEs first appeared.

Table 107. List of non-hematological toxicities G≥3

	Induction	Maintenance	Total
	N (%)	N (%)	N (%)
Example: Cefalea - Grade 3, Diarrhea - Grade 3…			

The following table shows all the non-haematological toxicities with their maximum grades, taking into account the treatment phase at the date that the AE first appeared.

Table 108. List of non-hematological toxicities any grade

	Induction	Maintenance	AE start day missing	Total
	N (%)	N (%)	N (%)	N (%)
Example: Abdominal pain - Grade 2, Anorexia - Grade 2…				

1.1.1. SAES

Table 109. List of non-hematological toxicities G≥3

	Induction	Maintenance	Total
	N (%)	N (%)	N (%)
Example: Abdominal pain - Grade 3, Anemia - Grade 3, Vomiting - Grade 3…			

Table 110. List of all adverse events reported as SAEs

Study Subject ID	Hospital	AE with grade	Date AE start	Date AE end	Continuing at the end of study	AE related with treatment (possible /probable/ definitely)	Status	AEs according to treatment

2. ANNEXES

2.1. ANNEX 1: RELEVANT PREVIOUS EVENTS

Table 111. List of all relevant previous events

		N
Relevant previous events	Example: Arterial hypertension, Acute cholecystitis, Dyslipidemia…	

2.2. ANNEX 2: PREVIOUS MEDICATION

Table 112. List of all previous medication

		N
Previous medication	Example: Acetylsalicylic acid, Omeprazole, Trimethoprim/sulfamethoxazole…	

2.3. ANNEX 3: ALL TOXICITIES

Table 113. List of all toxicities

Study Subject ID	Hospital	AE with grade	Date AE start	Date AE end	Continuing at the end of study	SAE	Status	Hematological AE	AEs according to treatment