Tislelizumab, an Anti–PD-1 Antibody, in Patients With Relapsed/Refractory Classical Hodgkin Lymphoma in TIRHOL BGB-A317-210: A Prospective, Multicenter, Phase 2 LYSA Study Conducted in Western Countries

Hervé Ghesquières,[1] Krimo Bouabdallah,[2] Marc André,[3] Philippe Quittet,[4] Cécile Borel,[5] Aspasia Stamatoullas Bastard,[6] Michael Gilbertson,[7] Fabien Le Bras,[8] Catherine Thieblemont,[9] Baptiste Delapierre,[10] Mohamed Touati,[11] Pierre Feugier,[12] Julien Lazarovici,[13] Nadine Morineau,[14] Thomas Gastinne,[15] Isabelle Chaillol,[16] Rod Ramchandren,[17] Harsh Shah,[18] Dipenkumar Modi,[19] Heather Allewelt,[20] Pierre Fustier,[21] Jianfeng Xu,[20] Amit Agarwal,[20] Franck Morschhauser,[22] Cédric Rossi[23]

[1]Lyon Sud Hospital, Pierre Benite, France; [2]CHU Bordeaux Pessac, Bordeaux, France; [3]CHU UCL Namur, Yvoir, Belgium; [4]CHU Montpellier, Montpellier, France; [5]IUCT Oncopole, Toulouse, France; [6]Centre Henri Becquerel, Rouen, France; [7]Monash Health, Melbourne, Australia; [8]CHU Mondor, Creteil, France; [9]Hopital Saint-Louis, Paris, France; [10]Caen University Hospital, Caen, France; [11]CHU Limoges, Limoges, France; [12]CHU Nancy, Nancy, France; [13]Gustave Roussy Institute, Villejuif, France; [14]CHD de Vendee, La Roche Sur Yon, France; [15]CHU deNantes, Nantes, France; [16]Lymphoma Academic Research Organisation, Lyon, France; [17]University of Tennessee Medical Center, Knoxville, TN, USA; [18]University of Utah, Salt Lake City, UT, USA; [19]Karmanos Cancer Institute, Detroit, MI, USA; [20]BeiGene, San Mateo, CA, USA; [21]BeiGene, Basel, Switzerland; [22]CHU de Lille, Lille, France; [23]CHU Dijon, Dijon, France

BACKGROUND

- Programmed cell death protein-1 (PD-1) blockade is commonly used to treat relapsed/refractory (RR) classical Hodgkin lymphoma (cHL), but the overall response rates (ORRs) and complete response rates (CRRs) of approved anti–PD-1 antibodies remain suboptimal
- Tislelizumab blocks PD-1 with a high specificity and affinity, and minimized FcγR binding on macrophages leads to reduced clearance[1]
- Results of the initial phase 2 study of tislelizumab in Chinese patients with RR cHL were impressive, with an ORR and a CRR of 87% and 63%, respectively, and 3-year progression-free survival (PFS) of 40%[2,3]
- These results need further evaluation in a broader population with different standards of care, including more frequent use of autologous stem cell transplantation (ASCT) and targeted agents

METHODS

Inclusion Criteria

- TIRHOL (NCT04318080) is an international, prospective, phase 2 study for patients with RR cHL, conducted in France, Belgium, the USA, and Australia
- Histologically confirmed cHL
- Patients must have relapsed or refractory cHL
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Measurable disease defined as ≥1 F-fluorodeoxyglucose-avid lesion
- Cohort 1 included patients who previously underwent ASCT
- Cohort 2 included patients who were ineligible for ASCT
- Prior therapy with brentuximab vedotin was required in initial design
  - The protocol was amended to remove this criterion for both cohorts in October 2021

Statistics

- The primary endpoint was ORR (best overall response of complete response [CR] or partial response), as assessed by investigator, according to positron emission tomography-computed tomography (PET-CT) International Lugano 2014 criteria
- Null hypothesis is ORR=45%, based on previous clinical trials, and alternative hypothesis is ORR >45%
- Assuming an alternative ORR of 65% compared with the null ORR of 45% in cohort 1 and cohort 2 combined, using a binomial exact test, the power to reject the null hypothesis with 42 patients at a one-sided alpha of 0.05 is greater than 80%
- Secondary endpoints were the CRR, time to response, duration of response, and safety and tolerability of tislelizumab
- PFS and overall survival were the main exploratory endpoints

Study Design

- From August 2020 to September 2022, 45 patients were enrolled and dosed
  - Cohort 1, N=14
  - Cohort 2, N=31
- Tislelizumab 200 mg was given intravenously every 3 weeks until progressive disease (PD), unacceptable toxicity, or study withdrawal
- Tumor assessments were performed every 12 weeks by PET-CT
- The data cut-off date for this primary analysis was December 12, 2022

RESULTS

Table 1. Clinical Characteristics

	Cohort 1 N=14	Cohort 2 N=31	Total N=45
Age (years)			
Median (range)	49 (24–69)	69 (18–87)	64 (18–87)
≥45 years, n (%)	8 (57)	23 (74)	31 (69)
Sex			
Male	10 (71)	20 (65)	30 (67)
Female	4 (29)	11 (35)	15 (33)
Time since initial diagnosis, months			
N	11	28	39
Median (range)	40.2 (22–229)	14.1 (6–326)	24.7 (6–326)
Pathological diagnosis, n (%)			
Nodular sclerosis cHL	5 (36)	13 (42)	18 (40)
cHL + unclassified	4 (29)	13 (42)	17 (38)
Lymphocyte-rich cHL	2 (14)	1 (3)	3 (7)
Mixed cellularity cHL	0 (0)	1 (3)	1 (2)
Insufficient material for review	3 (21)	3 (10)	6 (13)
Patient status at time of enrollment, n (%)			
Refractory	0 (0)	13 (42)	13 (29)
Relapse/progression	14 (100)	18 (58)	32 (71)
Ann Arbor stage, n (%)			
II	4 (29)	5 (16)	9 (20)
III	5 (36)	12 (39)	17 (38)
IV	5 (36)	14 (45)	19 (42)
Performance status (ECOG), n (%)			
0	10 (71)	18 (58)	28 (62)
1	4 (29)	13 (42)	19 (38)
B symptoms, Yes, n (%)	3 (21)	5 (16)	8 (18)
International prognostic score, n (%)			
0–2	9 (64)	13 (43)	22 (50)
≥3	5 (36)	17 (57)	22 (50)
Missing	0	1	1
Bulky disease, Yes, n (%)	3 (21)	2 (7)	5 (11)
Number of prior lines of therapy for cHL, n (%)			
1	0 (0)	7 (23)	7 (16)
2	9 (64)	17 (55)	26 (58)
3	4 (29)	6 (19)	10 (22)
4	1 (7)	1 (3)	2 (4)
Median (range)	2 (2–4)	2 (1–4)	2 (1–4)
Prior therapies for cHL, n (%)			
Monoclonal antibody[a]	11 (79)	23 (74)	34 (76)
Chemotherapy	14 (100)	31 (100)	45 (100)
Radiotherapy	6 (43)	4 (13)	10 (22)
Autologous transplant	14 (100)	0 (0)	14 (31)
Other anticancer therapy	0 (0)	2 (7)	2 (4)

[a]33 (73%) received prior BV.
BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; ECOG, Eastern Cooperative Oncology Group.

Table 2. Response to Treatment

	N=45
Best response according to Lugano classification, n (%)	
Complete remission	14 (31.1)
Partial remission	15 (33.3)
Stable disease	2 (4.4)
Progressive disease	13 (28.9)
Not evaluated	1 (2.2)
ORR according to Lugano classification, n (%)	29 (64.4)
90% CI for ORR rate	51.1–76.3
Binomial test for analyses of primary endpoint	
Z test value	2.62
One-sided *P* value	.0044

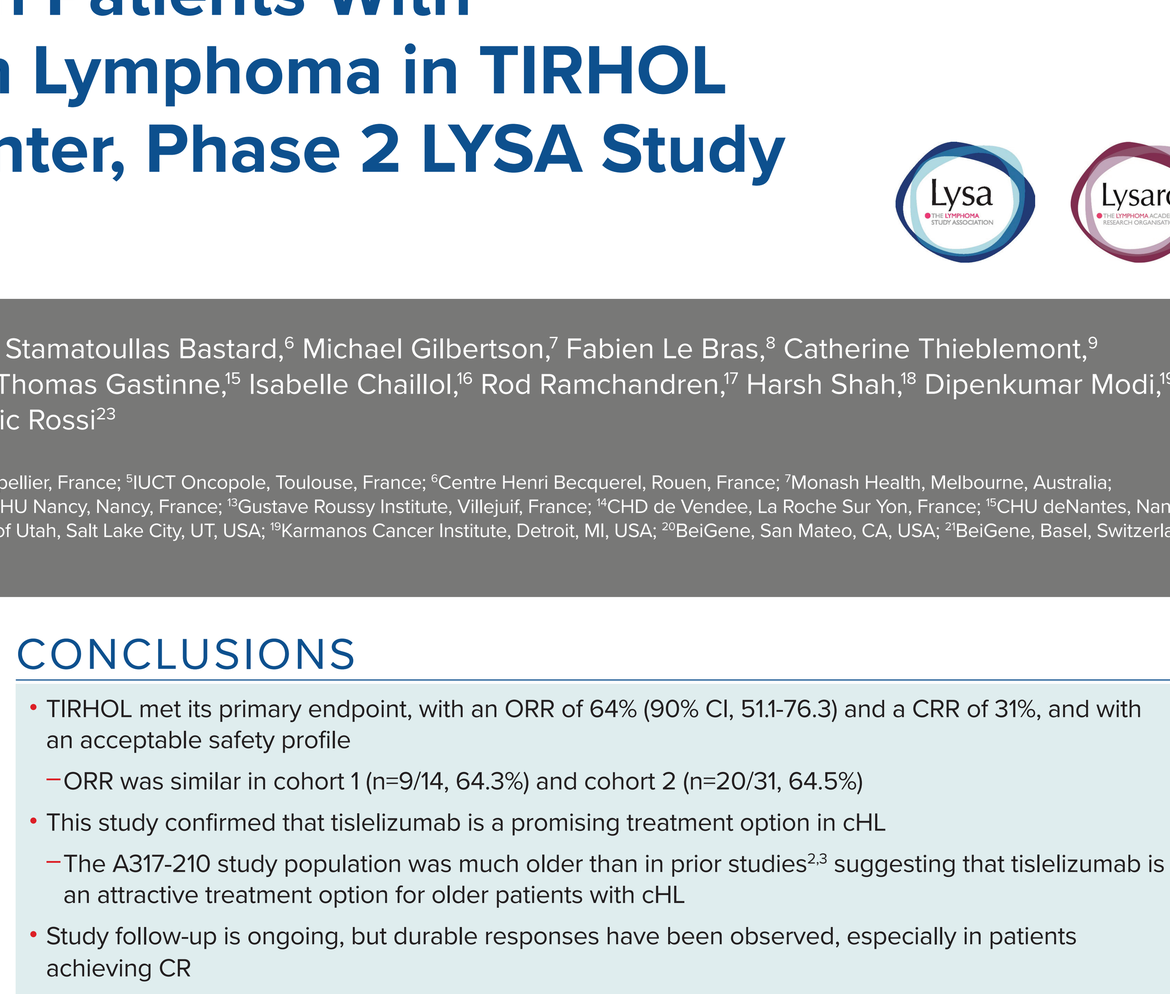
CI, confidence interval; ORR, overall response rate.

- ORR in cohort 1 was 64.3% (n=9/14) and in cohort 2 was 64.5% (n=20/31)
- Median number of tislelizumab doses (cycles) was 8 (range, 1-33)
- Median duration of treatment was 24 weeks (range, 3-105)
- Three patients with objective response underwent subsequent ASCT (1) or allogeneic SCT (2)

CONCLUSIONS

- TIRHOL met its primary endpoint, with an ORR of 64% (90% CI, 51.1-76.3) and a CRR of 31%, and with an acceptable safety profile
  - ORR was similar in cohort 1 (n=9/14, 64.3%) and cohort 2 (n=20/31, 64.5%)
- This study confirmed that tislelizumab is a promising treatment option in cHL
  - The A317-210 study population was much older than in prior studies[2,3] suggesting that tislelizumab is an attractive treatment option for older patients with cHL
- Study follow-up is ongoing, but durable responses have been observed, especially in patients achieving CR

Figure 1. Swimmer Plot for Response

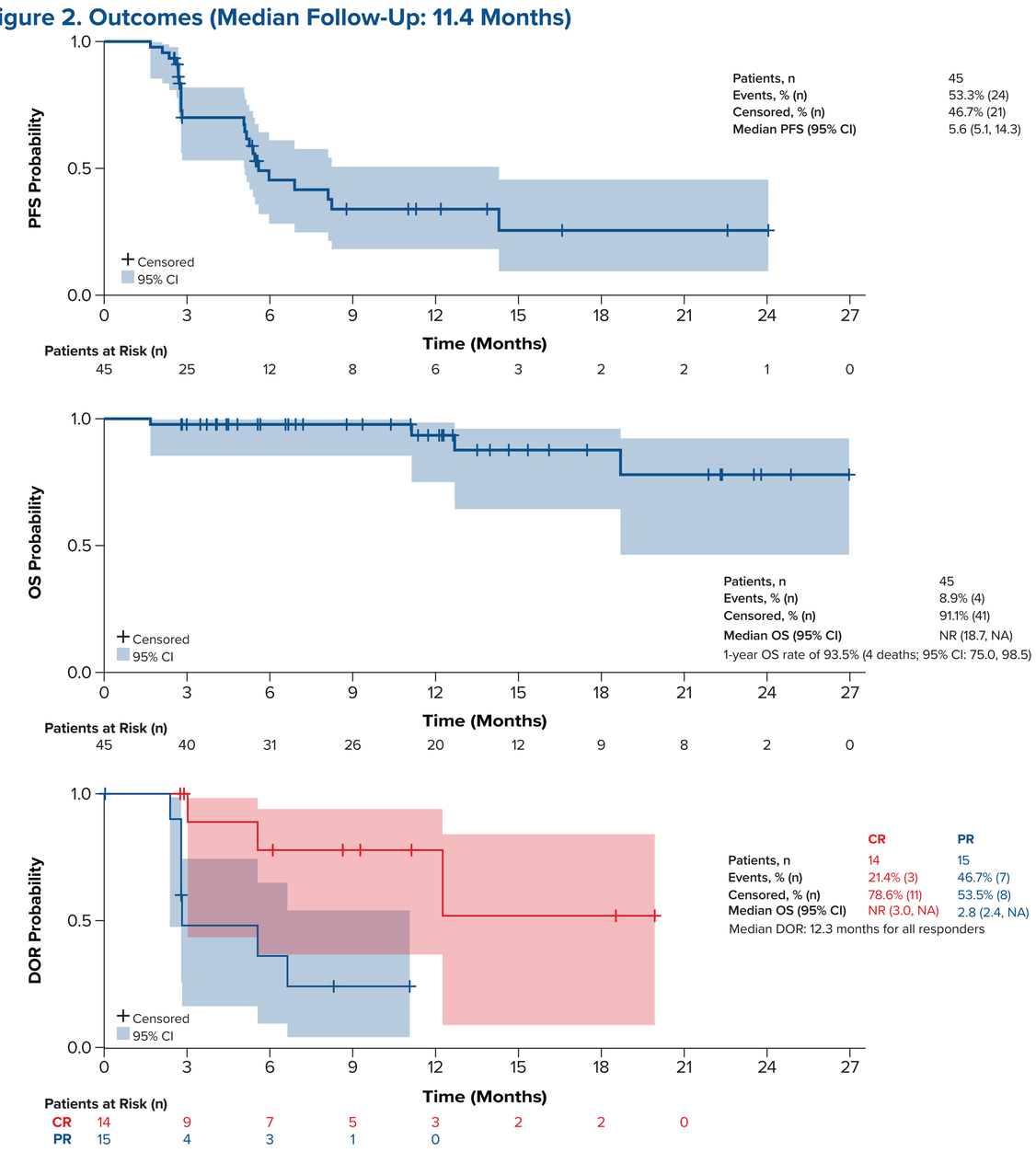


- As of the data cut-off date of December 12, 2022:
  - 19 patients remain on tislelizumab
  - 11 (24%) have continued treatment for >1 year
- 13 patients with SUV increase meeting PD criteria but continued clinical benefit continued tislelizumab for a median of 3.6 months (range Q1: 1.8-Q3: 9.5) after PD

Toxicity

- No treatment-emergent AEs leading to death
- Grade ≥3 treatment-emergent AEs: 15 (33%) patients
- Discontinuation (n=9) or interruption (n=2) of tislelizumab
- Immune-related (ir) AEs: 15 (33%) patients
  - Three patients had grade ≥3 irAEs: maculopapular rash, hepatitis, hemolytic anemia (n=1 each)

Figure 2. Outcomes (Median Follow-Up: 11.4 Months)



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ACKNOWLEDGMENTS

The authors would like acknowledge the LYSARC and BEIGENE TIRHOL team, every research team and site support staff, and especially the patients for participating in this study. This study was sponsored by BeiGene, Ltd. Editorial assistance was provided by Nucleus Global, an Inizio Company, and funded by BeiGene.

CORRESPONDENCE: Hervé Ghesquières, herve.ghesquieres@chu-lyon.fr

Presented at the 44th SFH Annual Meeting; March 27-29, 2024; Paris, France.
Data originally presented at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA. Abstract 1717