Tislelizumab, an Anti-PD1 Antibody, in Patients with Relapsed/Refractory Classical Hodgkin Lymphoma in TIRHOL BGB-A317-210: A Prospective Multicenter Lysa Phase 2 Study Conducted in Western Countries

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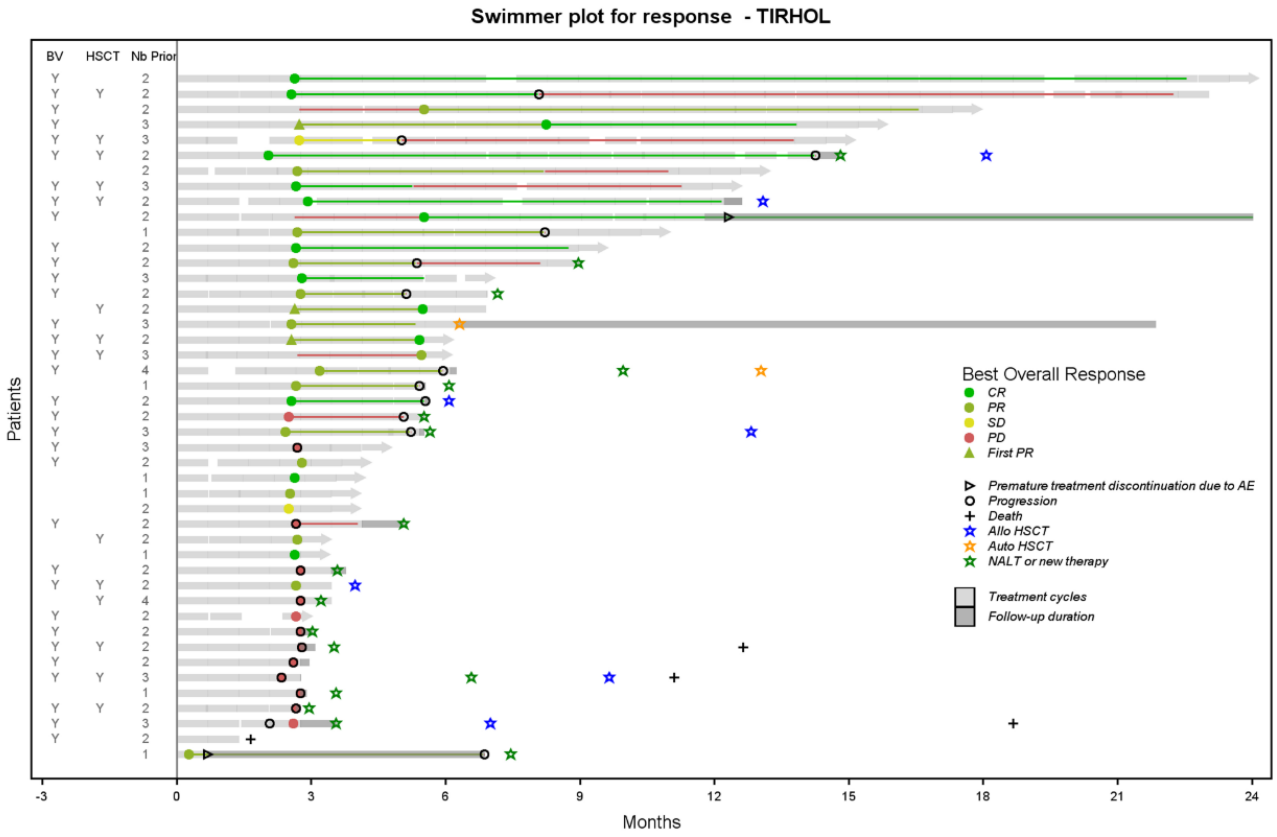
Background: Programmed cell death protein 1 (PD-1) blockade is commonly used to treat relapsed/refractory (RR) classical Hodgkin lymphoma (cHL) but the overall response rates (ORR) and complete response rates (CRR) of approved anti-PD1 antibodies remain suboptimal. Tislelizumab blocks PD-1 with a high specificity and affinity and minimized FcγR binding on macrophages leads to reduced clearance. Results of the initial phase 2 study of tislelizumab in Chinese patients with RR cHL were impressive, with ORR and CRR of 87% and 63%, respectively, and 3-year progression free survival (PFS) of 40%, warranting further evaluation in a Western population with different standard of care, including more frequent use of autologous stem cell transplantation (ASCT) and targeted agents.

Methods: TIRHOL (NCT04318080) is an international, prospective phase 2 study for patients with RR cHL conducted in France, Belgium, USA and Australia. Cohort 1 includes patients who previously underwent ASCT; cohort 2 includes patients who were ineligible for ASCT. Prior therapy with brentuximab vedotin (BV) was required in initial design; the protocol was amended to remove this criterion for both cohorts in October 2021. Tislelizumab 200 mg is given intravenously every 3 weeks until progressive disease (PD), unacceptable toxicity, or study withdrawal; tumor assessments are performed every 12 weeks. The primary endpoint is the ORR (best overall response of CR or partial response [PR]), as assessed by investigator, according to PET-CT International Lugano 2014 criteria. Null hypothesis is ORR = 45 % based on previous clinical trials and alternative hypothesis is ORR > 45%. Assuming the observed ORR = 65%, a sample size of 42 patients provides ≥ 80% power of at the one-sided 5% significance level. Secondary endpoints are CRR,

time to response (TTR), duration of response (DOR), safety and tolerability of tislelizumab. Main exploratory endpoints are PFS and overall survival (OS).

Results: Patients who received at least 1 dose of tislelizumab were included in the analysis. Between August 2020 and September 2022, 45 patients (14 in cohort 1 and 31 in cohort 2) were enrolled and dosed. At inclusion, the median age was 64 years (range 18-87), 67% were male and all had ECOG performance status 0-1; most patients had advanced stage disease (38% III, 42% IV), 11% had bulky disease, 18% had B symptoms and 29% had disease refractory to last therapy. The median prior lines of therapy received was 2 (1 – 4); 12 patients (27%) received ≥3 prior lines of therapy and 33 (73%) received prior BV. At last follow-up, the median number of tislelizumab doses (cycles) was 8 (1 – 33), corresponding to a median duration of treatment 24 weeks (range 3-105). The ORR was 64.4% (90% CI, 51% - 76%) with 14 (31%) patients achieving CR and 15 (33%) patients achieving PR (Figure 1). Remaining patients had stable disease (n=2, 4%), PD (n=13, 29%), or were not evaluated (n=1, 2%). The ORR was similar in cohort 1 (n=9/14, 64.3%) and cohort 2 (20/31, 64.5%). The median TTR was 2.69 months (range 0.3-5.6). The median DOR was 12.3 months (95% CI, 3 – NR) and was not reached for patients achieving CR. Three patients with objective response underwent subsequent ASCT (1) or allogeneic SCT (2). With a median follow-up of 11.4 months (95% CI, 6.7-13.5), the median PFS was 5.6 (95% CI, 5 – 14), 8, and 5 months for both cohorts combined, cohort 1, and 2, respectively. Thirteen 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. At last follow-up, 19 patients remain on tislelizumab and 11 (24%) have continued treatment for >1 year. The median OS was not reached with a 1-year OS rate of 93.5% (4 deaths; 95%CI, 75.0-98.5) and no treatment-related deaths. Grade ≥ 3 treatment emergent adverse events (TEAE) occurred in 15 (33%) patients, leading to discontinuation or interruption of tislelizumab in 9 and 2 patients, respectively. Immune-related (ir) AEs were observed in 15 (33%) patients and 3 patients had grade ≥ 3 irAEs (maculo-papular rash, hepatitis, hemolytic anemia).

Conclusions: TIRHOL met its primary endpoint with an ORR of 64% and a CRR of 31% with an acceptable safety profile. This study confirmed that tislelizumab is a promising treatment option in cHL. Study follow-up is ongoing, but durable responses have been observed, especially in patients achieving CR.


Swimmer plot for response - TIRHOL
BV
HSCT
Nb Prior
Patients
Months
-3
0
3
6
9
12
15
18
21
24
Best Overall Response
CR
PR
SD
PD
First PR
Premature treatment discontinuation due to AE
Progression
Death
Allo HSCT
Auto HSCT
NALT or new therapy
Treatment cycles
Follow-up duration