Tislelizumab, an Anti–PD-1 Antibody, in Patients With Relapsed/Refractory Classical Hodgkin Lymphoma:

Final Analysis From the LYSA Phase 2 TIRHOL Study BGB-A317-210

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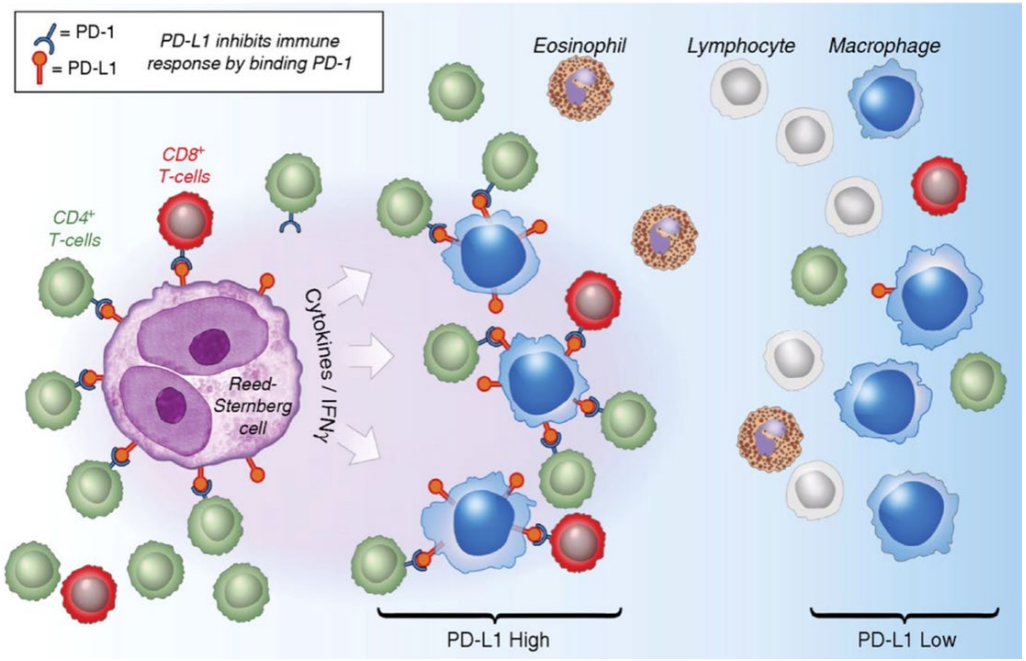
Consultancy: Roche, BMS, Takeda

Honoraria: Gilead, Roche, BMS, AbbVie, Takeda

Immune Escape in Classical Hodgkin Lymphoma



PD-1 inhibitors:

Pembrolizumab, nivolumab

Objective response: 64-74%
Complete response: 16-25%

PD1 blockers are now used in combination with CT in 2nd and 1st line therapy

CT, chemotherapy; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.

Carey CD et al. Blood. 2017;130 (22):2420-2430.

Tislelizumab in Classical Hodgkin Lymphoma

- **Tislelizumab**
  - An anti-PD-1 antibody with minimized FcγR binding on macrophages leads to reduced clearance
  - High binding affinity with PD-1
  - Binding surface of tislelizumab on PD-1 overlaps largely with that of the PD-L1
  - Slow dissociation rate of tislelizumab from PD-1

Hong Y et al. FEBS Open Bio. 2021;11(3):782-792.

- **Clinical activity of tislelizumab in R/R cHL**
  - Phase 2 study with 70 Chinese patients with R/R cHL
  - ORR: 87%
  - CRR: 63%
  - 3-year PFS: 40%

Song Y, et al. Clin Cancer Res. 2022;28(6):1147-1156.

Song Y, et al. Leukemia. 2020;34(2):533-542.

→ **These results need further evaluation in a broader population with different standards of care, including more frequent use of autologous stem cell transplantation and targeted agents**

cHL, classical Hodgkin lymphoma; CRR, complete response rate; ORR, overall response rate; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; R/R, relapsed/refractory.

TIRHOL Study Design and Objectives

- **Phase 2, multicenter, single-arm study of tislelizumab in patients with R/R cHL (NCT04318080)**
- **Recruitment**: France, Belgium, US and Australia

Cohort 1: R/R cHL with prior ASCT and BV

Cohort 2: R/R cHL with prior BV; not candidate for ASCT; ≥2 prior lines of therapy

Primary endpoint:
ORR by investigator
PET-CT International Lugano 2014 criteria

Key Secondary endpoints:
DOR, TTR, CR rate

Exploratory endpoints:
PFS, OS, PRO, PK, biomarkers

- **Amendments**
  - Possibility to include patients in cohort 2 after ≥1 prior systemic regimen for cHL
  - Possibility to include patients without previous therapy with BV in cohorts 1 & 2 (October 2021)
- **Statistics**
  - **Alternative ORR of 65%** compared to 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 1-sided alpha of 0.05 is greater than 80%

ASCT, autologous stem cell transplant; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; CR, complete response; DOR, duration of response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; R/R, relapsed/refractory; TTR, time to response.

Clinical Characteristics

- Between August 2020 and September 2022, 45 patients were enrolled and dosed

	Cohort 1 (n=14)	Cohort 2 (n=31)	Overall (n=45)
Age, median (range), years	49 (24-69)	69 (18-87)	64 (18-87)
Age ≥45 years, n (%)	8 (57.1)	23 (74.2)	31 (68.9)
Male sex, n (%)	10 (71.4)	20 (64.5)	30 (66.7)
Time since initial diagnosis, median (range), in months	40.2 (22-29)	14.1 (6-326)	24.7 (6-326)
ECOG PS 1, n (%)	4 (28.6)	13 (41.9)	17 (37.8)
IPS ≥3, n (%)	5 (35.7)	17 (56.7)	22 (50.0)
Refractory status at enrollment, n (%)	0	13 (41.9)	13 (28.9)
No. of prior lines, median (range)	2 (2-4)	2 (1-4)	2 (1-4)
Prior monoclonal antibody therapy[a], n (%)	11 (78.6)	23 (74.2)	34 (75.6)
Chemotherapy, n (%)	14 (100)	31 (100)	45 (100)
Radiotherapy, n (%)	6 (43)	4 (13)	10 (22)
ASCT, n (%)	14 (100)	0 (0)	14 (31)
Other anticancer therapy, n (%)	0 (0)	2 (7)	2 (4)

[a]33 (73%) received prior BV.
ASCT, autologous stem cell transplant; BV, brentuximab vedotin; ECOG, Eastern Cooperative Oncology Group performance status; IPS, International Prognostic Score.

Primary Endpoint: Overall Response Rate by Investigator

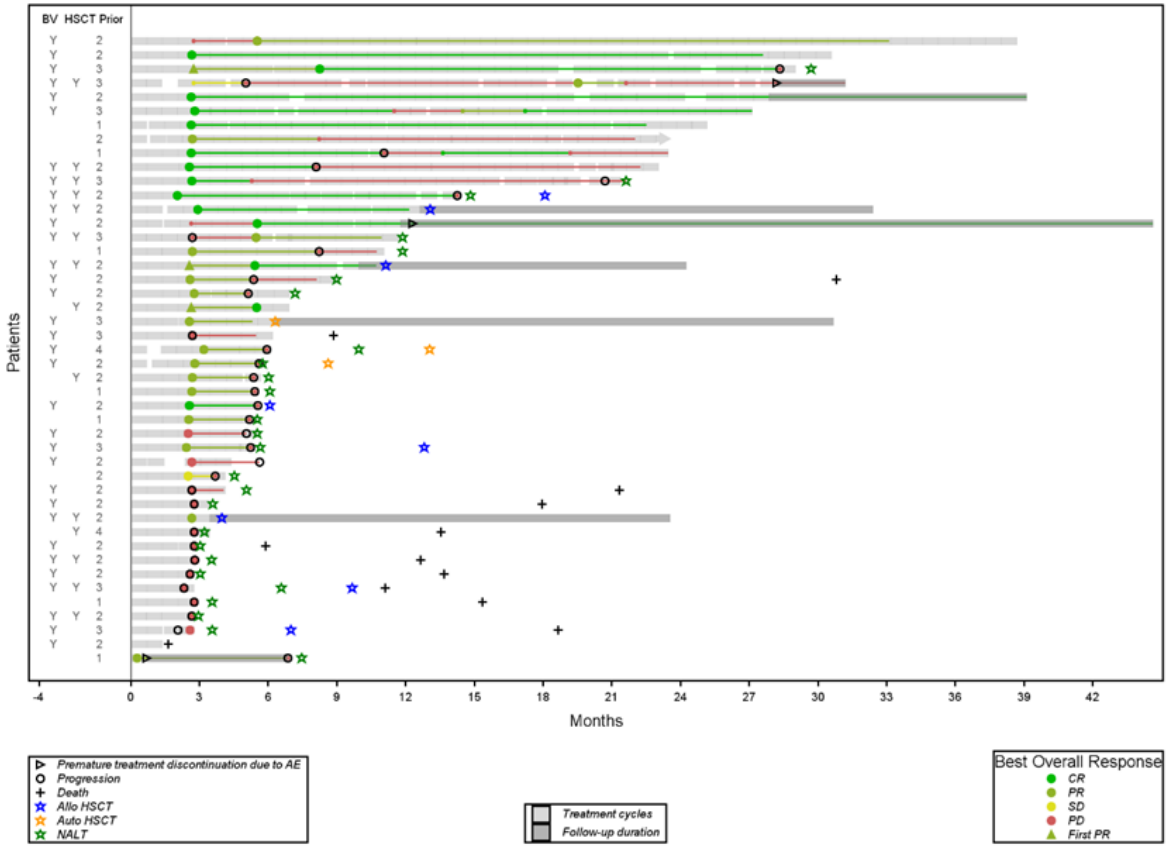
- According to PET-CT International Lugano 2014

Best overall response, n (%)	Cohort 1 (n=14)	Cohort 2 (n=31)	Overall (N=45)
Complete response	**6 (42.9)**	**8 (25.8)**	**14 (31.1)**
Partial response	4 (28.6)	12 (38.7)	16 (35.6)
Stable disease	0	1 (3.2)	1 (2.2)
Progressive disease	4 (28.6)	9 (29.0)	13 (28.9)
Not evaluated	0	1 (3.2)	1 (2.2)
ORR, n (%) [95% CI]	**10 (71.4)** [41.9-91.6]	**20 (64.5)** [45.4-80.8]	**30 (66.7)** [51.0-80.0]
Z test value, one-sided *P*-value			2.92, *P*=.0017

ORR, overall response rate; PET-CT, positron emission tomography-computed tomography.

Swimmer Plot for Response

- **Median TTR was 2.69 months** (range, 0.3-19.5 months)
- **Median DOR was 12.3 months** (95% CI, 3 months-NR)
  - Cohort 1: 18 months
  - Cohort 2: 7 months
  - CMR patients: 25.6 months
- Four patients underwent subsequent SCT



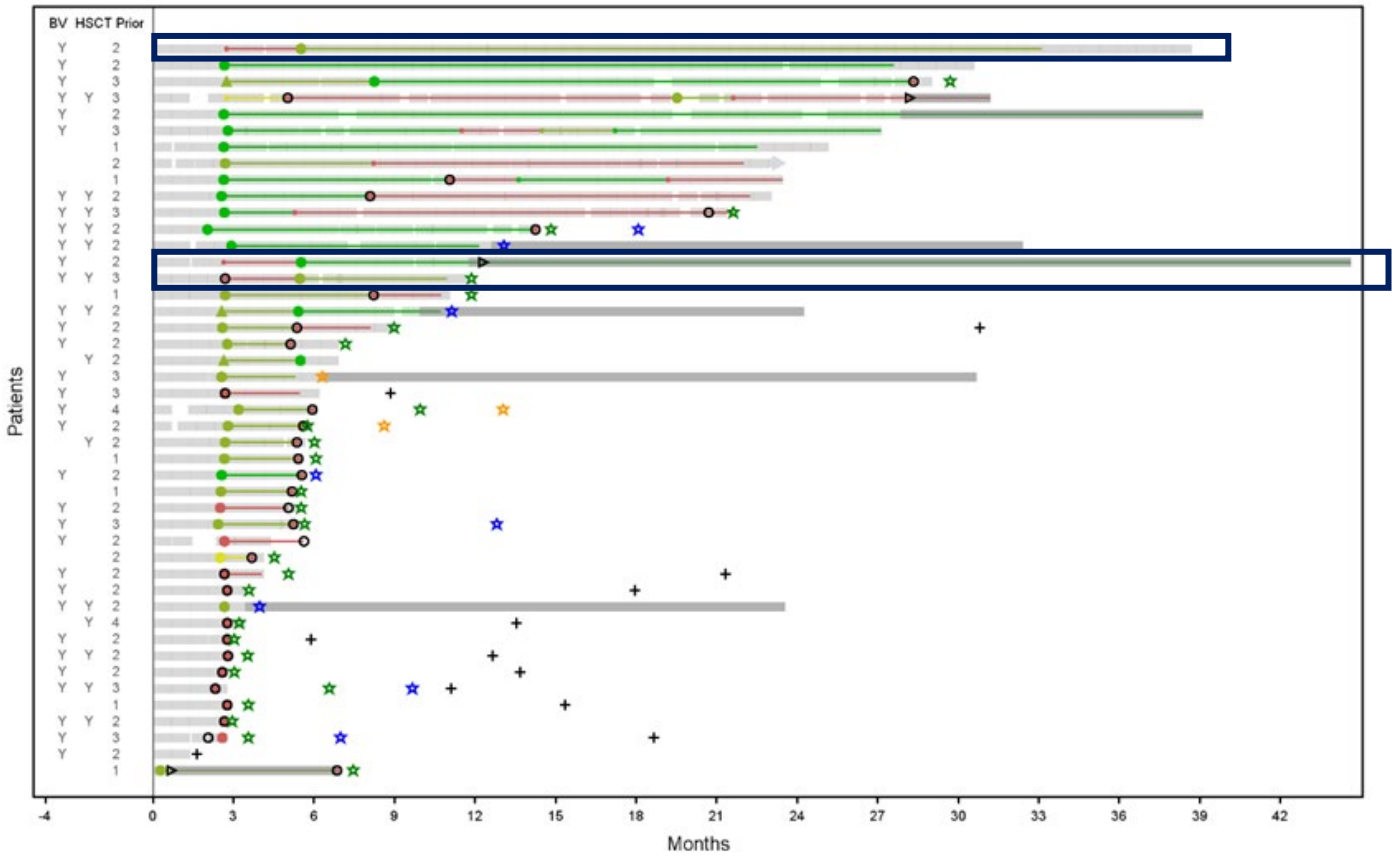
CMR, complete metabolic response; CR, complete response; DOR, duration of response; HSCT, hematopoietic stem cell transplant; NALT, new anti-leukemia treatment; NR, not reached; PD, progressive disease; PR, partial response; SCT, stem cell transplant; SD, stable disease; TTR, time to response.

Different Patterns of Responses

3 patients

PD and then response

IR(1) according to LYRIC



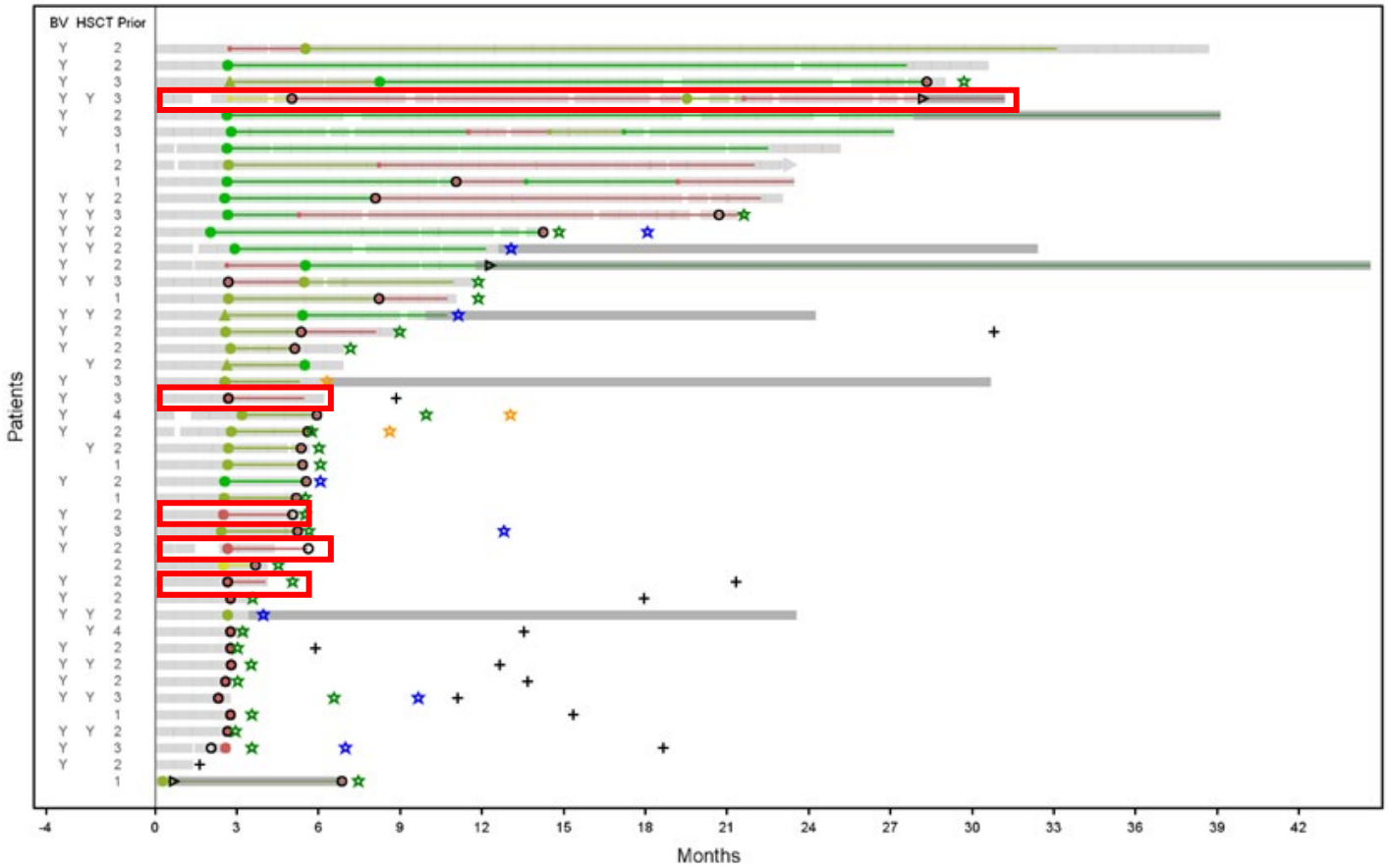
PD, progressive disease; HSCT, hematopoietic stem cell transplant; IR, indeterminate response; LYRIC, lymphoma response to immunomodulatory therapy criteria.

Different Patterns of Responses

5 patients

No initial response

but clinical benefit



HSCT, hematopoietic stem cell transplant.

Different Patterns of Responses

8 patients

Initial response

Loss of response

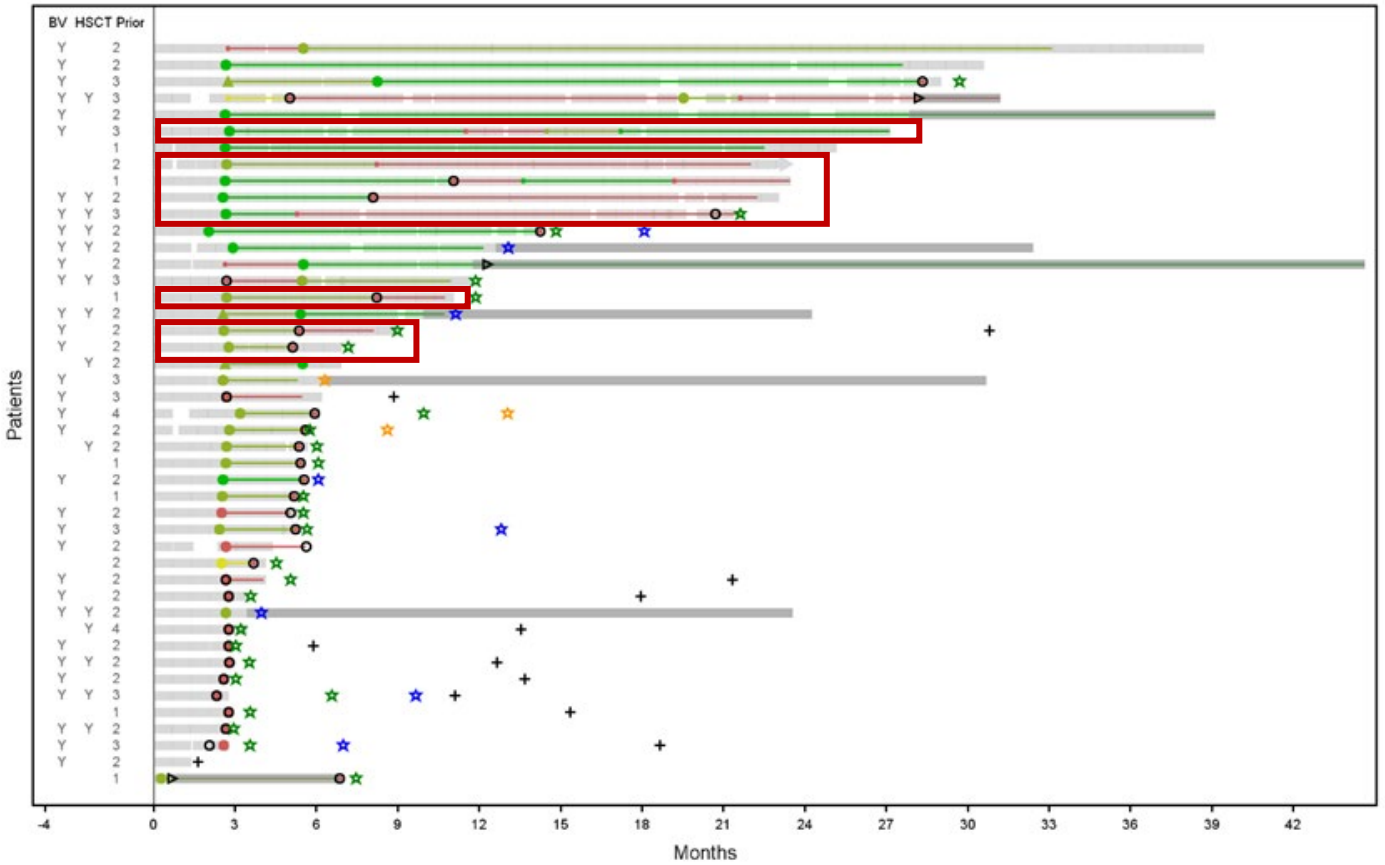
Then alternative loss/gain response

Continue tislelizumab for clinical benefit

IR(2) and IR(3) according to LYRIC

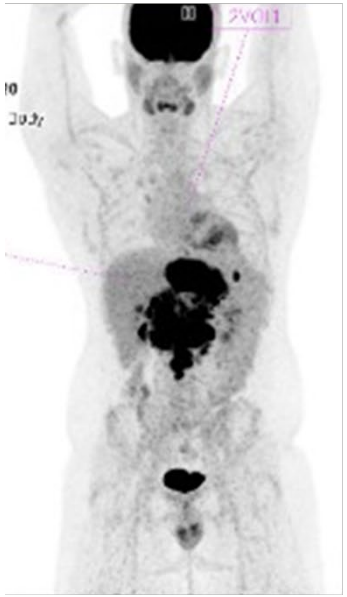
In total

Sixteen patients with PD continued tislelizumab treatment for a **median of 9.1 months** (range, 1.4-35.3) after PD

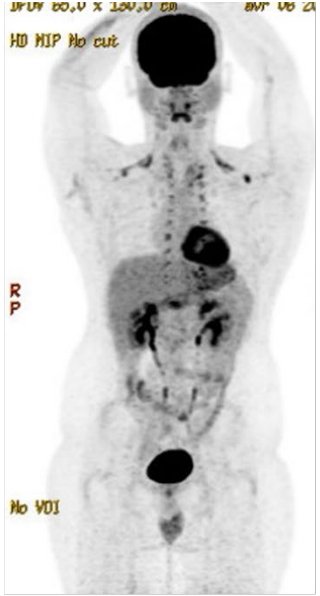


PD, progressive disease; HSCT, hematopoietic stem cell transplant; IR, indeterminate response; LYRIC, lymphoma response to immunomodulatory therapy criteria.

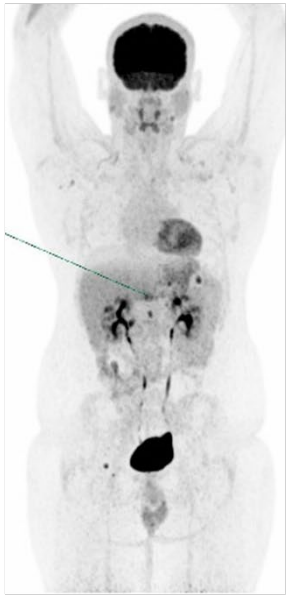
Example of PET/CT Imaging



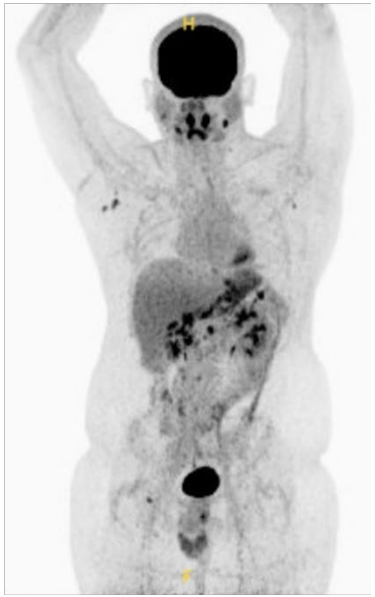
Baseline



> 4 cycles
CMR



> 20 cycles
DS5



> 32 cycles
DS5

PET-CT, positron emission tomography-computed tomography.

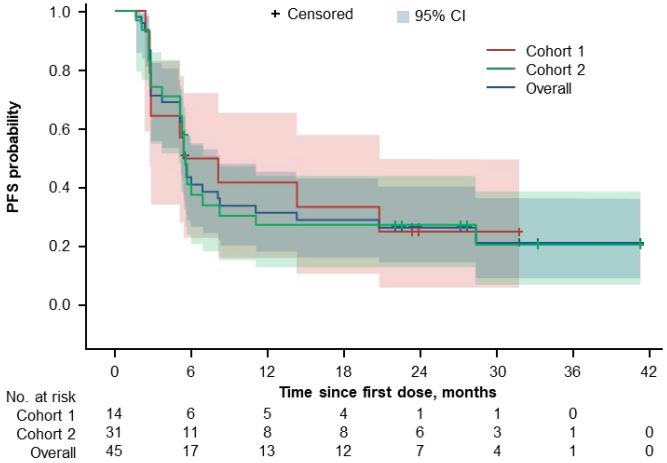
Outcomes With a Median Follow-up of 30 Months

Progression-free survival

Median PFS: 5.60 months (95% CI, 5-8)

Cohort 1: 5.75 months

Cohort 2: 5.60 months



Overall survival

2-year OS rate: 75% (95% CI, 59-85)

Cohort 1: 77% (3 deaths)

Cohort 2: 74% (9 deaths)

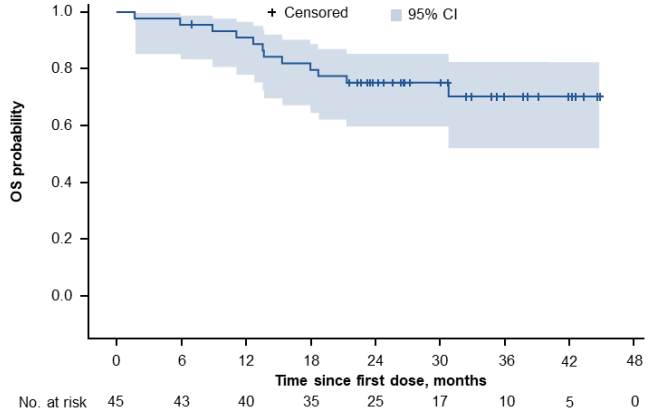
Causes of death (n=12)

8 lymphoma

2 toxicity of additional treatment

1 peritonitis > cycle 2 (unrelated AE)

1 septic shock after treatment period



AE, adverse event; OS, overall survival; PFS, progression-free survival.

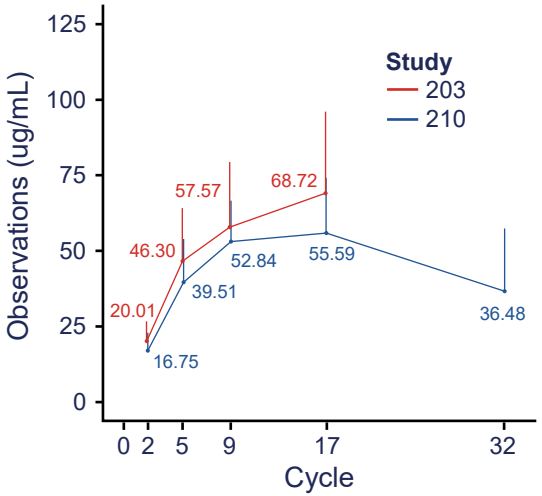
Toxicities

Patients with TEAEs, n (%)	Cohort 1 (n=14)	Cohort 2 (n=31)	Overall (N=45)
≥1 TEAE of any grade	12 (85.7)	30 (96.8)	42 (93.3)
Grade ≥3 TEAE	4 (28.6)	12 (38.7)	**16 (35.6)**
Serious TEAE	4 (28.6)	9 (29.0)	**13 (28.9)**
TEAE leading to tislelizumab discontinuation or interruption	3 (21.4)	10 (32.3)	13 (28.9)
Fatal TEAE	0	1 (3.2)	**1 (2.2)**
Immune-related AE	6 (42.9)	11 (35.5)	**17 (37.8)**
Grade ≥3 immune-related AE	1 (7.1)	2 (6.5)	**3 (6.7)**

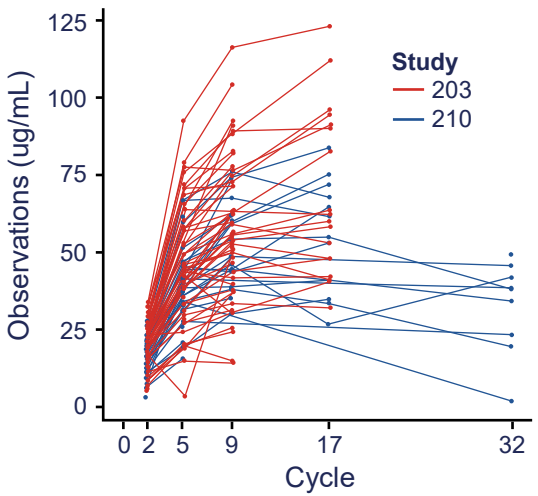
- Grade ≥3 immune-related AEs: maculopapular rash, hepatitis, hemolytic anemia (n=1 each)

AE, adverse event; TEAE, treatment-emergent adverse event.

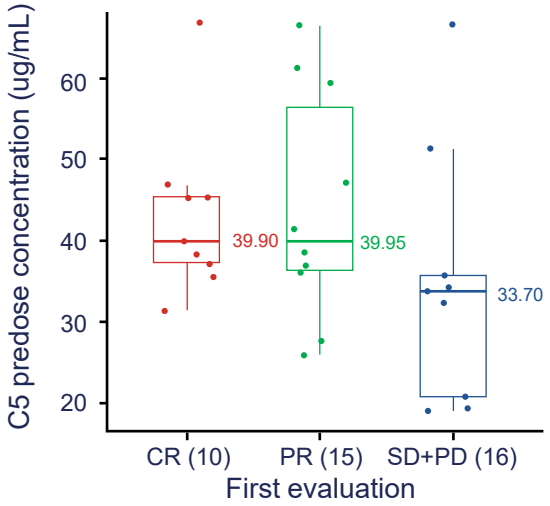
Pharmacokinetic analyses: 42 patients, 120 predoses



Mean



Individuals



C5 predose

- 6 patients (13.64%) had transient ADA (no persistance)

ADA, anti-drug antibodies; C, cycle; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Conclusions

- **TIRHOL met its primary endpoint, with an acceptable safety profile**
  - ORR of 64% (90% CI, 51.1-76.3) and a CRR of 31%
  - CRR of 43% in cohort 1 and 26% in cohort 2
  - Durable responses have been observed, especially in CMR patients (median of 25.6 months)
- **Complexity of response evaluation during anti-PD-1 therapy**
  - PFS is short using strict definition for PD but did not reflect clinical benefit with tislelizumab
  - 12/45 (27%) of patients had indeterminate response
  - Specific works are ongoing on PET/CT
- **This study confirmed that tislelizumab is a promising treatment option in cHL**

cHL, classical Hodgkin lymphoma; CRR, complete response rate; ORR, overall response rate; PD-1, programmed cell death-1; PD, progressive disease; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival.

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