# Tislelizumab, a PD-1 Inhibitor For Relapsed/refractory Mature (NK)/T-cell Neoplasms: Results From a Phase 2 Study

Abstract P1239

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## BACKGROUND

- Effective treatment choices are limited for patients with R/R mature NK/T-cell neoplasms after failure of standard therapies[1]
- Tislelizumab, a humanized anti–PD-1 monoclonal antibody, demonstrated outstanding efficacy and favorable safety in patients with R/R classic HL[2,3]
  - In a phase 2 study of tislelizumab in patients with HL, the ORR was 87.1% and the CR rate was 62.9%; median PFS was 31.5 months at median follow-up of 33.8 months[2,3]

## AIM

- We present safety and efficacy data of the phase 2 study of tislelizumab in patients with R/R mature NK/T-cell neoplasms

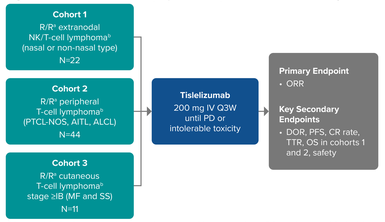
## METHODS

- This was a global, multicenter, single-arm, open-label, phase 2 study (NCT03493451)
- Patients were enrolled into 3 cohorts based on the type of NK/T-cell neoplasm and received tislelizumab 200 mg intravenously every 3 weeks until disease progression or intolerable toxicity (**Figure 1**)
- Eligible patients had ≥1 prior systemic therapy, disease progression during/after most recent therapy completion or refractory disease, ECOG PS ≤2, and life expectancy ≥6 months

## OBJECTIVES

- The primary endpoint was investigator-assessed ORR
- Secondary endpoints included DOR, CR rate, PFS, and OS in cohorts 1 and 2, and safety

**Figure 1: Global, Multicenter, Open-Label, Phase 2 Clinical Study**




[a]Relapse was defined as disease progression during or after completion of the most recent therapy. Refractory disease was defined as failure to achieve CR or PR to most recent therapy.
[b]All patients had previously received at least 1 appropriate systemic therapy (eg, a non-anthracycline–based regimen such as L-asparaginase–based therapy for patients in cohort 1; combination chemotherapy for patients in cohort 2).

## RESULTS

- A total of 77 patients received tislelizumab
  - Cohort 1: R/R ENKTL (n=22)
  - Cohort 2: R/R PTCL (n=44; 21 patients with PTCL-NOS, 11 with AITL, and 12 with ALCL)
  - Cohort 3: R/R cutaneous T-cell lymphomas (n=11; 8 patients with MF and 3 patients with SS; **Table 1**)
- Median number of treatment cycles for cohorts 1, 2, and 3 was 5 (range, 1-37), 4.5 (range, 1-38), and 17 (range, 3-25), respectively
- Efficacy was reported in cohort 1 at a median follow-up of 8.4 months; ORR was 31.8% with 18.2% of patients achieving CR (**Table 2**), and median DOR was not reached (95% CI: 2.7, NE). Median PFS was 2.7 months (95% CI: 1.5, 5.3), and median OS was 8.8 months (95% CI: 3.3, NE; **Figure 2**)
- Efficacy also was noted in cohort 2 at a median follow-up of 9.3 months; ORR was 20.5% with 9.1% of patients achieving CR (**Table 2**), and median DOR was 8.2 months (95% CI: 2.5, NE). Median PFS was 2.7 months (95% CI: 2.6, 4.8), and median OS was 13.3 months (95% CI: 7.7, 26.2; **Figure 2**)
- Cohort 3 demonstrated efficacy at a median follow-up of 16.6 months; ORR was 45.5% with 9.1% of patients achieving CR (**Table 2**); median DOR was 11.3 months (95% CI: 2.8, 11.3). Median PFS in cohort 3 was 16.8 months (95% CI: 2.6, 16.8), and median OS was not reached (95% CI: 4.9, NE; **Figure 2**)
- The most frequent TEAEs were pyrexia (32.5%), anemia (18.2%), arthralgia (18.2%), and diarrhea (15.6%)
- The most frequent grade ≥3 TEAEs were anemia (7.8%), pneumonia (6.5%), and neutropenia (5.2%)
- **Table 3** includes treatment-related and immune-mediated TEAEs
- No treatment-related AEs leading to death were reported

## RESULTS (cont.)

**Table 1: Patient Demographics and Baseline Disease Characteristics**

| | Cohort 1 (n=22) | Cohort 2 (n=44) | Cohort 3 (n=11) | Total (N=77) |
|---|---|---|---|---|
| **Age, years** | | | | |
| Median | 47.5 | 58.0 | 62.0 | 56.0 |
| Min, max | 24, 76 | 21, 84 | 35, 76 | 21, 84 |
| **Age group, n (%)** | | | | |
| <60 years | 13 (59.1) | 24 (54.5) | 5 (45.5) | 42 (54.5) |
| ≥60 years | 9 (40.9) | 20 (45.5) | 6 (54.5) | 35 (45.5) |
| **Sex, n (%)** | | | | |
| Male | 14 (63.6) | 29 (65.9) | 8 (72.7) | 51 (66.2) |
| Female | 8 (36.4) | 15 (34.1) | 3 (27.3) | 26 (33.8) |
| **Race, n (%)** | | | | |
| Asian | 19 (86.4) | 23 (52.3) | 2 (18.2) | 44 (57.1) |
| White | 2 (9.1) | 18 (40.9) | 8 (72.7) | 28 (36.4) |
| Not reported | 1 (4.5) | 3 (6.8) | 1 (9.1) | 5 (6.5) |
| **ECOG PS at baseline, n (%)** | | | | |
| 0 | 3 (13.6) | 21 (47.7) | 6 (54.5) | 30 (39.0) |
| 1 | 17 (77.3) | 21 (47.7) | 4 (36.4) | 42 (54.5) |
| 2 | 2 (9.1) | 2 (4.5) | 1 (9.1) | 5 (6.5) |
| **Disease status, n (%)** | | | | |
| Relapsed disease | 12 (54.5) | 21 (47.7) | 4 (36.4) | 37 (48.1) |
| Refractory disease | 10 (45.5) | 23 (52.3) | 7 (63.6) | 40 (51.9) |
| **Advanced-stage disease,[a,b] n (%)** | 14 (63.6) | 36 (81.8) | 9 (81.8) | 59 (76.6) |
| **Bone marrow involvement,[a] n (%)** | 2 (9.1) | 9 (20.5) | 3 (27.3) | 14 (18.2) |
| **B symptoms, n (%)** | 6 (27.3) | 11 (25.0) | 1 (9.1) | 18 (23.4) |
| **High[c] LDH at baseline, n (%)** | 13 (59.1) | 16 (36.4) | 3 (27.3) | 32 (41.6) |
| **Low[c] lymphocyte count at baseline,[b] n (%)** | 9 (40.9) | 23 (52.3) | 3 (27.3) | 35 (45.5) |
| **Number of prior regimens, median (range)** | 2.0 (1, 5) | 2.0 (1, 8) | 4.0 (2, 6) | 2.0 (1, 8) |
| **Number of prior regimens, n (%)** | | | | |
| <3 | 13 (59.1) | 24 (54.5) | 2 (18.2) | 39 (50.6) |
| ≥3 | 9 (40.9) | 20 (45.5) | 9 (81.8) | 38 (49.4) |
| **Prior autologous SCT, n (%)** | 0 (0.0) | 6 (13.6) | 0 (0.0) | 6 (7.8) |
| **Prior allogeneic SCT, n (%)** | 1 (4.5) | 0 (0.0) | 0 (0.0) | 1 (1.3) |
| **Prior radiation therapy, n (%)** | 16 (72.7) | 8 (18.2) | 4 (36.4) | 28 (36.4) |

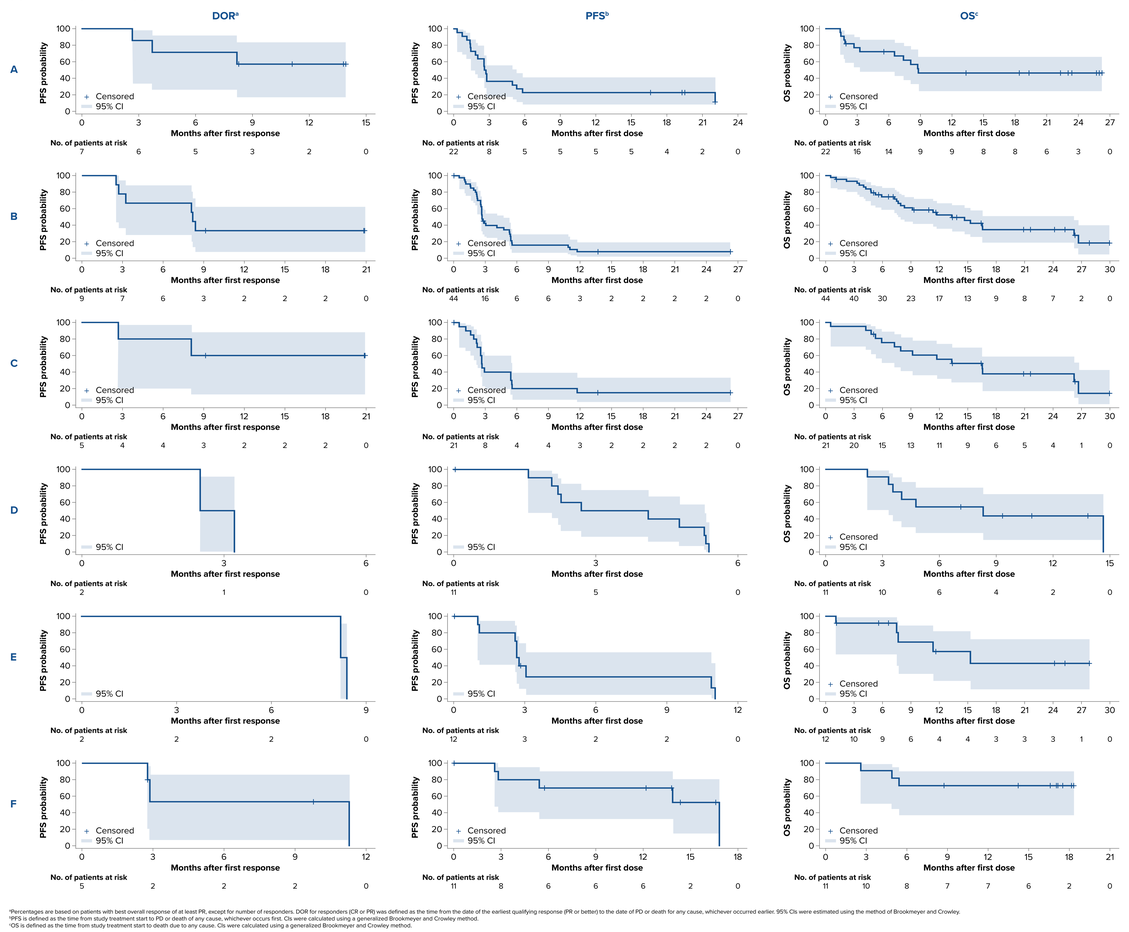
[a]Stage III-IV for cohorts 1 and 2; stage IIB or higher for cohort 3.
[b]Disease stage at study entry was missing for 1 patient in cohort 1. Bone marrow involvement at study entry was unknown for 3 patients in cohort 2 and 2 patients in cohort 3. B symptom data at study entry were missing for 1 patient in cohort 2 and 2 patients in cohort 3. Lymphocytes count at study entry was missing for 1 patient in cohort 2.
[c]Higher/lower than normal range provided by local laboratory.

**Table 2: Disease Response by Investigator Assessment**

| | Cohort 1 (N=22) | Cohort 2 PTCL-NOS (n=21) | Cohort 2 AITL (n=11) | Cohort 2 ALCL (n=12) | Cohort 2 Total (N=44) | Cohort 3 (N=11) |
|---|---|---|---|---|---|---|
| **ORR,[a] n (%)** | 7 (31.8) | 5 (23.8) | 2 (18.2) | 2 (16.7) | 9 (20.5) | 5 (45.5) |
| 95% CI[b] | (13.9, 54.9) | (8.2, 47.2) | (2.3, 51.8) | (2.1, 48.4) | (9.8, 35.3) | (16.7, 76.6) |
| **CR rate, n (%)** | 4 (18.2) | 3 (14.3) | 1 (9.1) | 0 (0.0) | 4 (9.1) | 1 (9.1) |
| 95% CI | (5.2, 40.3) | (3.0, 36.3) | (0.2, 41.3) | (0.0, 26.5) | (2.5, 21.7) | (0.2, 41.3) |
| **TTR, months[c]** | | | | | | |
| n | 7 | 5 | 2 | 2 | 9 | 5 |
| Median | 5.75 | 4.60 | 2.48 | 2.71 | 2.86 | 6.83 |
| Min, max | 2.1, 13.9 | 2.8, 5.5 | 2.1, 2.9 | 2.7, 2.7 | 2.1, 5.5 | 2.6, 11.1 |

[a]For patients in cohorts 1 and 2, responses were assessed by investigators per the Lugano criteria[4] with Lymphoma Response to Immunomodulatory Therapy criteria modification for immunomodulatory drugs.[5] For patients in cohort 3, responses were assessed by investigators per ISCL/EORTC guidelines.[6] ORR was defined as the proportion of patients achieving a best overall response of either CR or PR.
[b]Two-sided Clopper-Pearson 95% CI.
[c]TTR was defined as time from the first dose date to the date of earliest qualifying response (PR or CR). Only responders are included in the analysis for TTR.

**Figure 2: DOR, PFS, and OS by Investigator Assessment (A) Cohort 1 (ENKTL); (B) Cohort 2 (PTCL-NOS, AITL, ALCL); (C) Cohort 2a (PTCL-NOS); (D) Cohort 2b (AITL); (E) Cohort 2c (ALCL); and (F) Cohort 3 (MF or SS)**




[a]Percentages are based on patients with best overall response of at least PR, except for number of responders. DOR for responders (CR or PR) was defined as the time from the date of the earliest qualifying response (PR or better) to the date of PD or death for any cause, whichever occurred earlier. 95% CIs were estimated using the method of Brookmeyer and Crowley.
[b]PFS is defined as the time from study treatment start to PD or death of any cause, whichever occurs first. CIs were calculated using a generalized Brookmeyer and Crowley method.
[c]OS is defined as the time from study treatment start to death due to any cause. CIs were calculated using a generalized Brookmeyer and Crowley method.

**Table 3: Summary of TEAEs**

| TEAE[a] by MedDRA, n (%) | Cohort 1 (n=22) | Cohort 2 (n=44) | Cohort 3 (n=11) | Total (N=77) |
|---|---|---|---|---|
| **Patients with ≥1 TEAE** | 22 (100.0) | 41 (93.2) | 10 (90.9) | 73 (94.8) |
| Grade ≥3 TEAE | 13 (59.1) | 25 (56.8) | 8 (72.7) | 46 (59.7) |
| Grade ≥3 TEAE in ≥3 patients | | | | |
| Anemia | 3 (13.6) | 3 (6.8) | 0 (0.0) | 6 (7.8) |
| Pneumonia | 2 (9.1) | 3 (6.8) | 0 (0.0) | 5 (6.5) |
| Neutropenia | 0 (0.0) | 4 (9.1) | 0 (0.0) | 4 (5.2) |
| Neutrophil count decreased | 3 (13.6) | 0 (0.0) | 0 (0.0) | 3 (3.9) |
| Thrombocytopenia | 0 (0.0) | 3 (6.8) | 0 (0.0) | 3 (3.9) |
| White blood cell count decreased | 2 (9.1) | 1 (2.3) | 0 (0.0) | 3 (3.9) |
| **Patients with ≥1 treatment-related TEAE** | 17 (77.3) | 33 (75.0) | 7 (63.6) | 57 (74.0) |
| Treatment-related grade ≥3 | 7 (31.8) | 10 (22.7) | 0 (0.0) | 17 (22.1) |
| Treatment-related grade ≥3 TEAE in ≥2 patients | | | | |
| Anemia | 2 (9.1) | 1 (2.3) | 0 (0.0) | 3 (3.9) |
| Pneumonia | 2 (9.1) | 1 (2.3) | 0 (0.0) | 3 (3.9) |
| Neutrophil count decreased | 3 (13.6) | 0 (0.0) | 0 (0.0) | 3 (3.9) |
| White blood cell count decreased | 2 (9.1) | 1 (2.3) | 0 (0.0) | 3 (3.9) |
| Platelet count decreased | 1 (4.5) | 1 (2.3) | 0 (0.0) | 2 (2.6) |
| Pyrexia | 0 (0.0) | 2 (4.5) | 0 (0.0) | 2 (2.6) |
| **Immune-mediated TEAE** | 6 (27.3) | 13 (29.5) | 3 (27.3) | 22 (28.6) |
| Grade ≥3 TEAE | 2 (9.1) | 2 (4.5) | 0 (0.0) | 4 (5.2) |
| Grade ≥3 TEAE in ≥3 patients | | | | |
| Hepatitis | 0 (0.0) | 1 (2.3) | 0 (0.0) | 1 (1.3) |
| Hypothyroidism | 1 (4.5) | 0 (0.0) | 0 (0.0) | 1 (1.3) |
| Blood creatine phosphokinase increased | 1 (4.5) | 0 (0.0) | 0 (0.0) | 1 (1.3) |
| Rash | 0 (0.0) | 1 (2.3) | 0 (0.0) | 1 (1.3) |
| Urticaria | 0 (0.0) | 1 (2.3) | 0 (0.0) | 1 (1.3) |

Treatment-related TEAEs included those events considered by the investigator to be related to drug treatment or with missing assessment of the causal relationship.
Patients with multiple events for a given MedDRA preferred term are counted only once for each preferred term.
[a]TEAE was defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of a new anticancer therapy. TEAEs also included all immune-mediated AEs and drug-related serious AEs recorded up to 90 days after the last dose of study drug, regardless of whether the patient started a new anticancer therapy. The worsening of an AE to grade 5 beyond day 30 after the last dose of study treatment was also considered a TEAE (if it was prior to the start of a new anticancer therapy).

## CONCLUSIONS

- Tislelizumab was well tolerated, achieving modest efficacy in R/R mature NK/T-cell neoplasms, with some long-lasting remissions, particularly in cutaneous T-cell lymphomas
- Further studies are warranted to determine the biologic features associated with response and to explore optimal combination therapies

## ABBREVIATIONS

AE, adverse event; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; CI, confidence interval; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ENKTL, extranodal NK/T-cell lymphoma; EORTC, European Organisation for Research and Treatment of Cancer; HL, Hodgkin lymphoma; ISCL, International Society for Cutaneous Lymphomas; LDH, lactate dehydrogenase; MedDRA, Medical Dictionary for Regulatory Activities; MF, mycosis fungoides; min, minimum; NE, not evaluable; NK, natural killer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death-1; PFS, progression-free survival; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; Q3W, once every 3 weeks; R/R, relapsed/refractory; SCT, stem cell transplantation; SS, Sézary syndrome; TEAE, treatment-emergent adverse event; TTR, time to response.

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## DISCLOSURES

**EB:** honoraria from Roche, Gilead, Novartis; consulting role with Takeda, Roche, Gilead; research funding from Amgen; travel expenses from AbbVie, Incyte
**KJS:** consulting role with Seattle Genetics, Bristol Myers Squibb, Merck, Servier; travel expenses from Seattle Genetics; honoraria from Seattle Genetics, Bristol Myers Squibb, Merck, Kyowa Kirin, Novartis, Novartis Canada
**HHu:** consulting role with Bristol Myers Squibb, Roche, Bristol Myers Squibb; steering committee role with BeiGene; data monitoring committee role with Innovent
**GG:** consulting role with Takeda, Gilead Sciences, IQVIA, Clinigen Group, Roche, Italfarmaco; speakers' bureau for Amgen, Roche; travel expenses from Janssen, Gilead Sciences
**AML:** research funding from Novartis, Janssen, AbbVie, Roche, Amgen, Celgene, Bristol Myers Squibb, Takeda, Incyte, BeiGene, Oncopeptides AB, Verastem, Kenymharm, Archigen, Debiopharm International, Morphosys, Fibrogen, Oncorova Therapeutics, Inc.
**AJMF:** consulting role with Gilead, Juno, Novartis, PletsaPharm, Roche; speakers' bureau for Gilead, Roche; research funding from ADC Therapeutics, Bayer HealthCare Pharmaceuticals, BeiGene, Bristol Myers Squibb, Genmab, Gilead, Hutchison MediPharma, Incyte, Janssen Research & Development, MEI Pharma, Novartis, PentixaPharm, Pharmacyclics, Prothera, Roche, Takeda; inventor of patents on NGr-hTNF-ISCHOP in relapsed or refractory PCNSL and ENKTL and ENKIR-hTNF in brain tumors
**GLD:** consulting role with Takeda, Blueprint Medicines, Roche
**SHa:** employment and stock ownership with BeiGene
**XLi:** employment, stock ownership, honoraria, travel, accommodations, and expenses from BeiGene
**HY:** employment, stock ownership, patents with BeiGene
**JP:** employment and stock ownership with BeiGene
**WN:** employment and stock ownership with BeiGene
**WZho:** employment, stock ownership, and consulting role with BeiGene
**HJ:** employment and stock ownership with BeiGene
**JH:** employment, research funding and patents with BeiGene; leadership role with BeiGene, Protara; stock ownership with Aptevo, Roche
**PLZ:** honoraria from Roche, Gilead, Novartis, Servier, Incyte, Takeda, Janssen, Verastem, Eisai, BeiGene, Sanofi, Merck, Bristol Myers Squibb, Janssen; consulting role with Roche, Gilead, Novartis, Servier, Incyte, Takeda, ELISA Pharma, Kyowa Kirin, BeiGene, Sanofi, Merck, Bristol Myers Squibb, Janssen; speakers' bureau for Roche, Gilead, Novartis, Incyte, Takeda, Kyowa Kirin, Sanofi, Merck, Janssen
**HH, YLK, GZ, JC, HY, SHu, JH, KZ, FR, HZ, WS, JJ, HL, WZha, XK, CG:** nothing to disclose