New Drugs in Hematology

Golidocitinib

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Disclosure

- I have the following relevant financial relationships to disclose:

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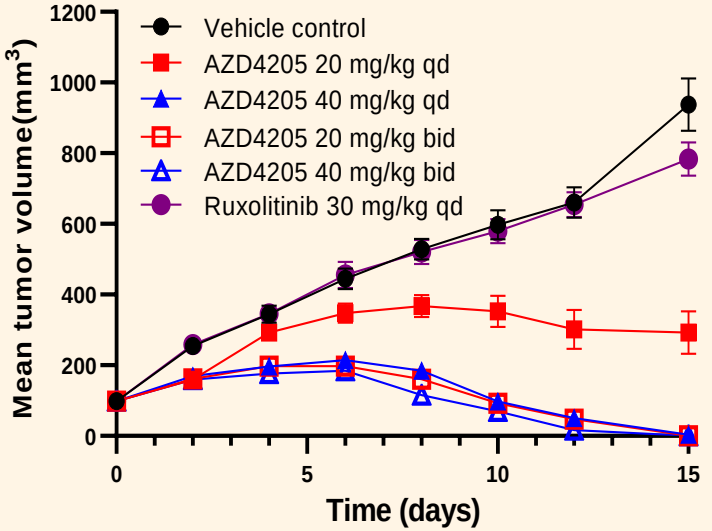
Background

- **Peripheral T Cell Lymphomas (PTCLs)** are a group of heterogenous and rare non-Hodgkin's lymphomas originating from mature T cells. Due to lack of standard treatment for relapsed/refractory PTCLs (r/r PTCLs) [1], the clinical prognosis is poor with a 5-year survival rate of lower than 30% [2].

- **Golidocitinib** (AZD4205) is a rationally designed JAK1 selective inhibitor:
  - Orally available (capsules)
  - **High-selectivity to JAK1:** > 200-fold selectivity over JAK2, JAK3, and TYK2
  - Favorable PK properties
  - Effective anti-tumor activity in T cell lymphoma cell lines and animal models
  - The first JAK1 selective inhibitor developed for T cell lymphomas entering into pivotal study



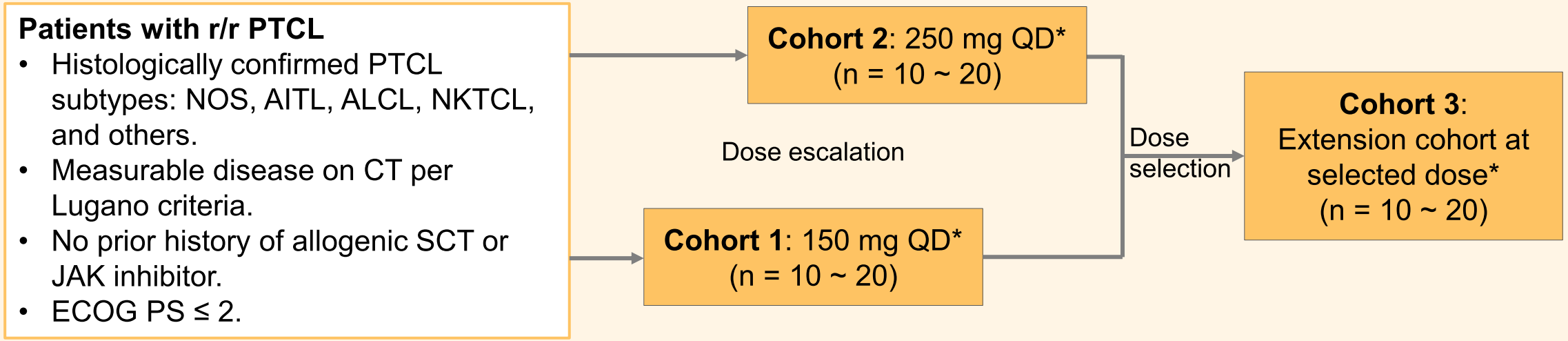
Abbreviations: JAK, Janus kinase; PK, pharmacokinetics; PTCL, peripheral T cell lymphoma; r/r, relapsed/refractory; TYK2, tyrosine kinase 2.

1. NCCN Guidelines, Version 1.2023; 2. Bellei M, et al, Haematologica, 2018; 3. Song Y, et al., Annals of Onco, 2023

Overall Design of JACKPOT8 Study

- JACKPOT8 study (NCT04105010): a single arm, open label, phase I/II study to assess the safety, tolerability, PK, and anti-tumor efficacy of golidocitinib treating patients with r/r PTCL

Figure 3. JACKPOT8 Study Design (Phase I part)

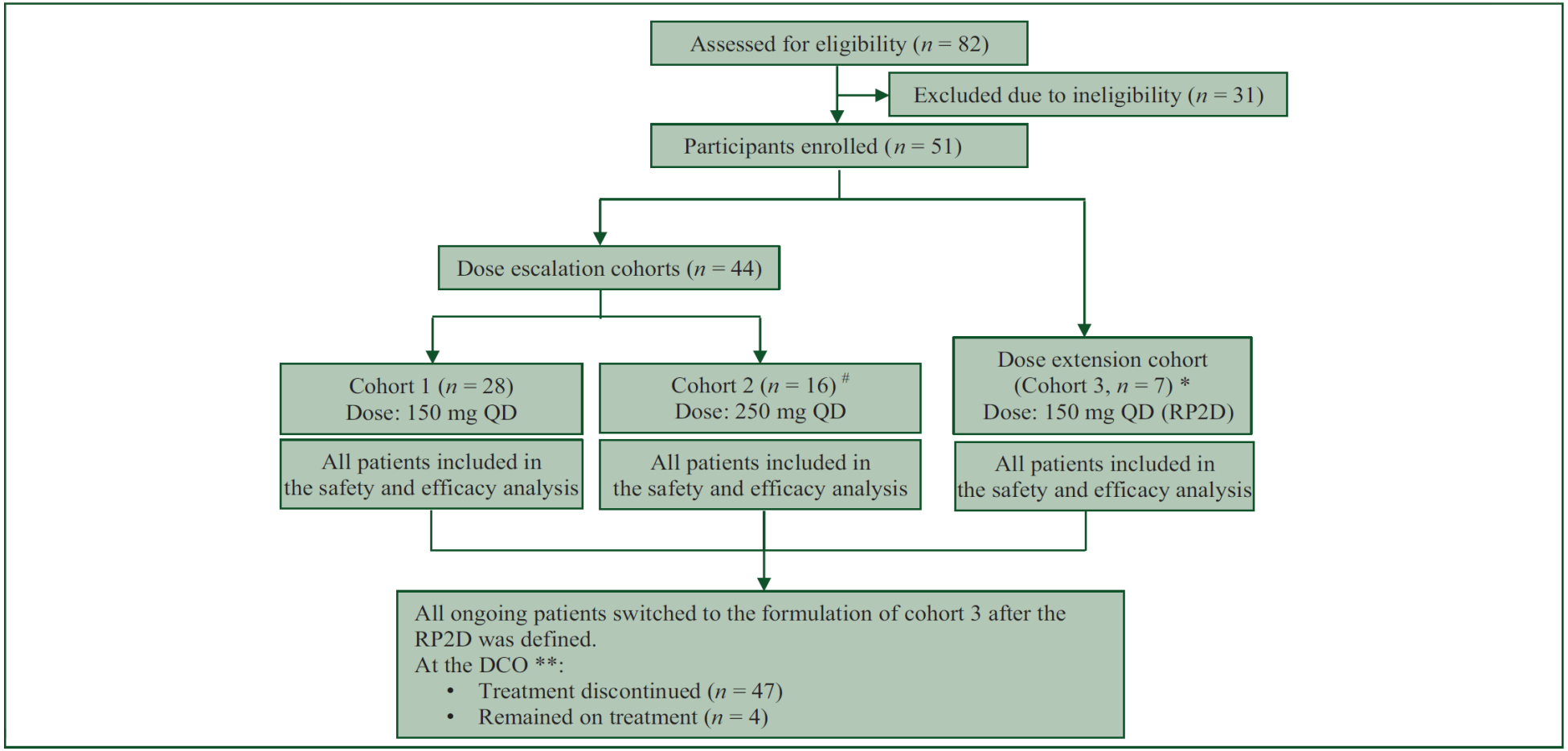


* Golidocitinib continued being administrated on a 21-day dosing cycle till disease progression or intolerance.

- Primary endpoints
  - The adverse events of golidocitinib treating r/r PTCL
- Secondary endpoints
  - Investigator-assessed ORR, DoR, and PFS
  - The PK profile of golidocitinib in r/r PTCL

Kim WS et al EHA 2022

Phase I trail of Golidocitinib



Song Y et al. Ann Oncol 2023

Patient Enrolment & Baseline Characteristics

As of 31 May 2021, a total of 51 subjects with r/r PTCL were enrolled and received at least one dose of golidocitinib.

Table 1. Baseline Characteristics of All Subjects

Category \ Dose level	150 mg	250 mg	Total
n	35	16	51
Age, years			
Median (range)	61.0 (33, 78)	61.5 (29, 79)	61.0 (29, 79)
Sex			
Female/Male	14/21	3/13	17/34
ECOG PS, n (%)			
0/1	34 (97.1%)	16 (100.0%)	50 (98.0%)
No. of prior therapies, n (%)			
Median (range)	2.0 (1, 8)	2.5 (1, 8)	2.0 (1, 8)
≥ 3 lines	13 (37.1%)	8 (50.0%)	21 (41.2%)
Chemotherapy	35 (100.0%)	16 (100.0%)	51 (100.0%)
HDAC inhibitor	8 (22.9%)	6 (37.5%)	14 (27.5%)
CD30 targeting therapy	2 (5.7%)	0 (0%)	2 (3.9%)

Category \ Dose level	150 mg	250 mg	Total
n	35	16	51
PTCL subtype based on local diagnosis, n (%)			
PTCL-NOS	15 (42.9%)	6 (37.5%)	21 (41.2%)
AITL	14 (40.0%)	6 (37.5%)	20 (39.2%)
NKTCL	2 (5.7%)	2 (12.5%)	4 (7.8%)
ALCL ALK-negative	3 (8.6%)	1 (6.3%)	4 (7.8%)
MEITL	1 (2.9%)	1 (6.3%)	2 (3.9%)
Baseline BM involved, n (%)	10 (28.6%)	5 (31.3%)	15 (29.4%)
History of SCT, n (%)	7 (20.0%)	3 (18.8%)	10 (19.6%)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HDAC, histone deacetylase; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; NKTCL, natural-killer/T cell lymphoma; MEITL, monomorphic epitheliotropic intestinal T cell lymphoma; BM, bone marrow; SCT, stem cell transplantation.

Anti-tumor Efficacy of Golidocitinib Treating r/r PTCL

At the DCO, 49 subjects completed at least one tumor assessment after dose with golidocitinib (n = 34 at 150 mg, n = 15 at 250 mg), and the other 2 subjects discontinued without any tumor assessments.

Table 2. Best Overall Response by Dose Level

Dose level	150 mg	250 mg	Total
n	34	15	49
Best overall response			
Complete response, n (%)	8 (23.5%)	3 (20.0%)	11 (22.4%)
Partial response, n (%)	6 (17.6%)	4 (26.7%)	10 (20.4%)
Stable disease, n (%)	7 (20.6%)	2 (13.3%)	9 (18.4%)
ORR [95% Confidence interval]	41.2% [24.6, 59.3]	46.7% [21.3, 73.4]	42.9% [28.8, 57.8]

n includes all subjects who completed at least one post-treatment anti-tumor efficacy assessment at the data cut-off.
The tumor response was assessed by local investigators per Lugano criteria.
Tumor responses were observed in various subtypes, including AITL, PTCL-NOS, ALCL ALK- and extra-nodal nasal NK/TCL.

Anti-tumor Efficacy of Golidocitinib in Treating r/r PTCL

Profound Reduction in Tumor Burden and Durable Response with Golidocitinib Treatment

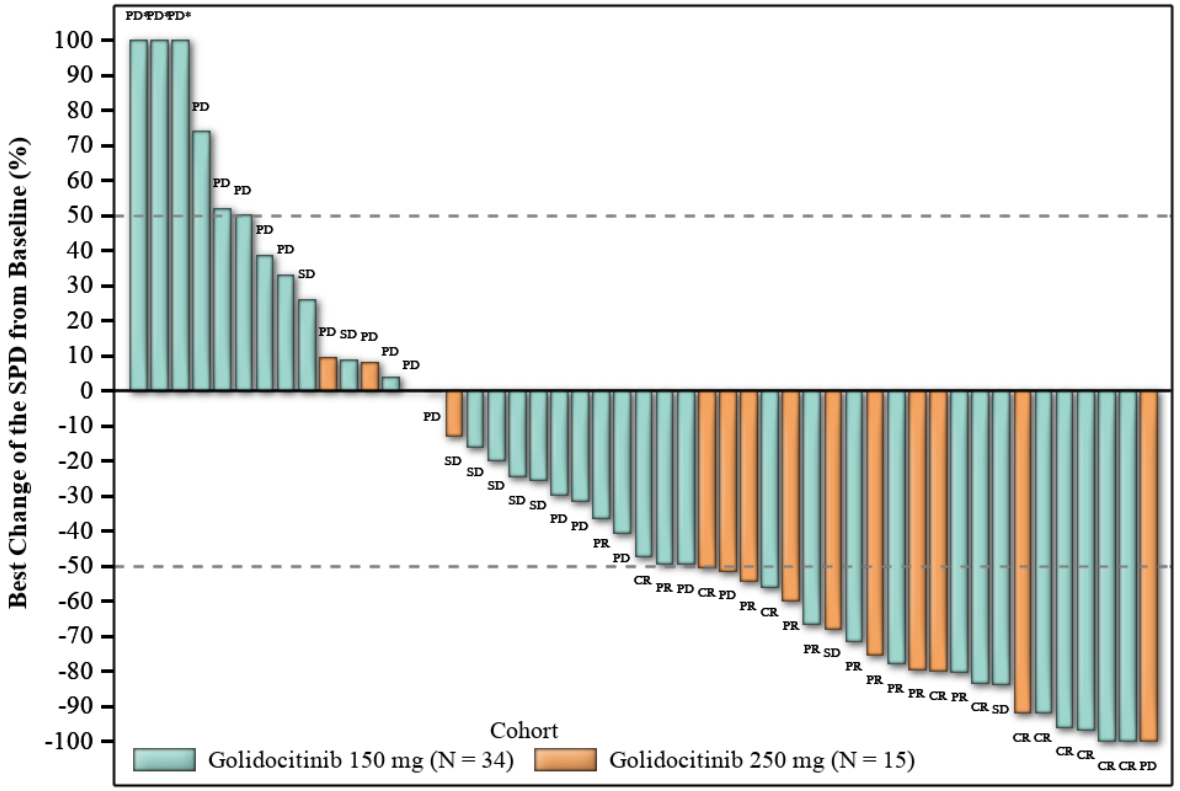


Figure 4. Maximum percentage reduction from baseline in target lesions

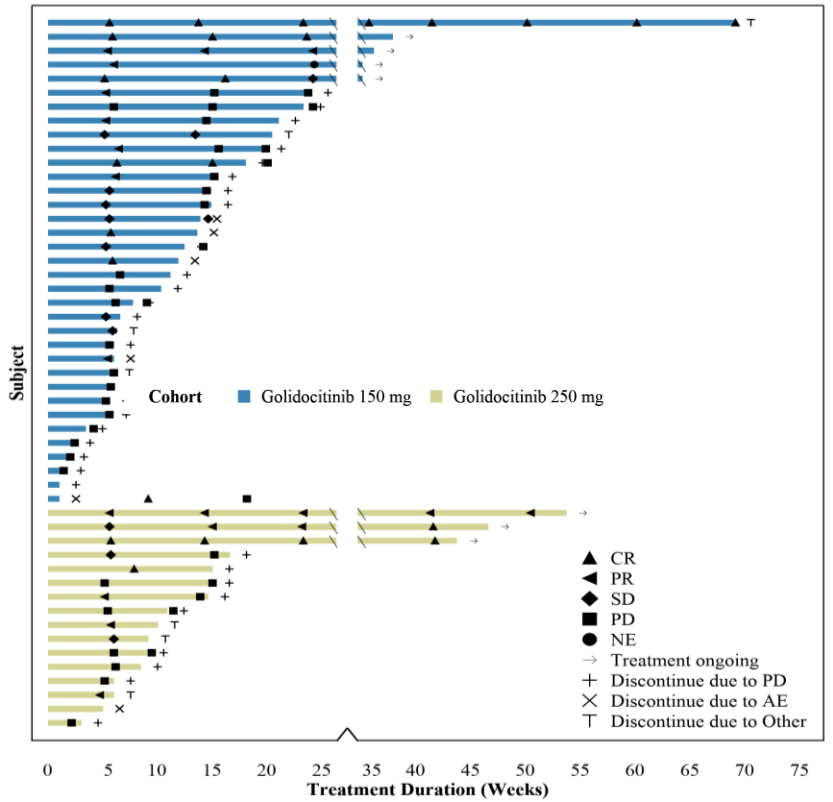


Figure 5. Duration on treatment of all subjects

Footnote: The median duration of response (DoR) was not reached at the data cut-off (31 May 2021), and the longest DoR was > 14 months.

Anti-tumor Efficacy of Golidocitinib in Treating r/r PTCL

Table 3. Best Overall Response by Histology (All Dose Levels)

Histological subtypes	PTCL-NOS	AITL	ALCL ALK-	Extra-nodal Nasal NK/TCL	MEITL	Total
n	19	20	4	4	2	49
Best overall response, n (%)						
Complete response, n (%)	2 (10.5%)	7 (35.0%)	1 (25.0%)	1 (25.0%)	0	11 (22.4%)
Partial response, n (%)	3 (15.8%)	6 (30.0%)	1 (25.0%)	0	0	10 (20.4%)
ORR	26.3%	65.0%	50.0%	25.0%	0	42.9%

- n includes all subjects who completed at least one post-treatment anti-tumor efficacy assessment at the data cut-off.
- The diagnosis of histological subtypes were based on local investigational sites' assessment.
- The tumor response assessment was performed by local investigators per Lugano criteria.

Safety and Tolerability of Golidocitinib Treating r/r PTCL

At the DCO, a total of 51 subjects with r/r PTCL were enrolled and dosed with golidocitinib (n = 35 at 150 mg, n = 16 at 250 mg).

Table 4. Overall AEs by Dose Level

Category, n (%)	Golidocitinib Dose Level		Total n = 51
	150 mg (n = 35)	250 mg (n = 16)	
Subject with at least one AE	32 (91.4)	16 (100.0)	48 (94.1)
Subjects with at least one G3+ AE	21 (60.0)	9 (56.3)	30 (58.8)
Subjects with at least one SAE	12 (34.3)	8 (50.0)	20 (39.2)
Subjects with at least one AE leading to dose reduction	5 (14.3)	6 (37.5)	11 (21.6)
Subjects with at least one AE leading to dose discontinuation	5 (14.3)	1 (6.3)	6 (11.8)

Abbreviation: AE, adverse event; SAE, serious adverse event.
Footnote: This table summarizes the treatment emergent adverse events (irrespective of relatedness) per investigators' assessment by data cut-off date (31 May 2021). n includes all subjects who had received at least one dose of golidocitinib at the cut-off.

Safety and Tolerability of Golidocitinib Treating r/r PTCL

Table 5. CTCAE G3+ AEs by Dose Level

CTCAE G3+ AEs ≥ 3 subjects MedDRA Preferred Term, n (%)	Golidocitinib Dose Level		Total n = 51
	150 mg (n = 35)	250 mg (n = 16)	
Neutropenia	12 (34.3)	3 (18.8)	15 (29.4)
Thrombocytopenia	4 (11.4)	4 (25.0)	8 (15.7)
Pneumonia	4 (11.4)	2 (12.5)	6 (11.8)
Anemia	4 (11.4)	0	4 (7.8)
Hepatic enzyme increased	4 (11.4)	0	4 (7.8)
WBC decreased	2 (5.7)	1 (6.3)	3 (5.9)

Footnote: This table summarizes the CTCAE grade 3 or higher AEs (irrespective of relatedness) per inv estigators' assessment, which were observed in ≥ 3 subjects by data cut-off date (31 May 2021). n inclu des all subjects who had received at least one dose of golidocitinib at the data cut-off.

- The preliminary data demonstrated a comparable safety and tolerability profile of golidocitinib in r/r PTCL, with the approved therapies.
- The most common (incidence > 10%) G3+ AEs included thrombocytopenia, neutropenia and pneumonia.
- The majority AEs were reversible, or clinically manageable with dose modifications.

Study Design

Key eligibility criteria

Patients with r/r PTCLs

- PTCLs diagnosed locally
- Had relapsed from or been refractory/intolerant to prior systemic therapy[1]
- Measurable disease
- Age ≥ 18 y (for Korean ≥ 19 y)
- ECOG PS ≤ 2
- Adequate bone marrow reserve and organ/system functions

Golidocitinib 150 mg QD[2]

1 cycle = 21 days

Tumor assessment

Day 1 of Cycle 3, and then every 3 cycles until disease progression or withdrawal from the study

Primary endpoint: IRC assessed ORR based on CT images per Lugano 2014 criteria

Secondary endpoints: other efficacy endpoints, e.g., IRC assessed CRR, DoR PFS and TTR, investigator assessed ORR, CRR, DoR, PFS, TTR and safety

1. Eligible patients must have relapsed from or been refractory/intolerant to prior systemic therapy(ies) for PTCLs and now require further treatment. In patients with CD30 positive ALCL, the prior systemic treatment should include CD30-targeted therapy (brentuximab vedotin).

2. Golidocitinib is administered orally at the recommended phase 2 dose (150 mg QD) on a 21-day dosing cycle until disease progression, intolerance or other discontinuation criteria are met.

Abbreviations: ALCL, anaplastic large-cell lymphoma; CD, cluster of differentiation; CT, computed tomography; CRR, complete response rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IRC, independent review committee; ORR, objective response rate; PFS, progression free survival; PTCL, peripheral T cell lymphoma; QD, once daily; r/r, relapsed/refractory; TTR, time to response.

Demographics and Baseline Characteristics

Demographics & Characteristics	n = 104
Median age, y (range)	58 (20 - 78)
Female/Male, n (%)	37 (35.6)/67 (64.4)
ECOG PS, n (%)	
0/≥1	46 (44.2)/58 (55.8)
Median lines of prior systemic therapies (range)	2 (1 - 3)
Types of prior systemic therapies, n (%)	
Chemotherapy	104 (100.0)
Pralatrexate	1 (1.0)
Mitoxantrone liposome	3 (2.9)
HDAC inhibitor	50 (48.1)
Brentuximab vedotin	13 (12.5)
ALK inhibitor	1 (1.0)
Prior autologous HSCT, n (%)	2 (1.9)
Bone marrow involvement at baseline, n (%)	20 (19.2)
LDH elevation at baseline, n (%)	52 (50.0)

Demographics & Characteristics	n = 104
Histology subtypes by central review, n (%)	
PTCL, NOS	51 (49.0)
AITL	16 (15.4)
ALCL	11 (10.6)
NK/TCL	4 (3.8)
Others*	9 (8.7)
Central confirmed non-PTCL	4 (3.8)
Unable to confirm	9 (8.7)

Data cut-off date: August 31, 2023

- Between Feb 26, 2021 to Oct 12, 2022, a total of 104 subjects with r/r PTCLs were enrolled.
- All subjects received at least one dose of golidocitinib at 150 mg QD.

Note: * 'Others' including 1 centrally diagnosed as T cell prolymphocytic leukemia and 8 centrally diagnosed as PTCLs with unconfirmable histology subtypes.
Abbreviations: AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HDAC, histone deacetylase; HSCT, hematopoietic stem cell transplant; LDH, lactate dehydrogenase; NK/TCL, natural-killer/T cell lymphoma; PTCL, NOS, peripheral T cell lymphoma, not otherwise specified; r/r, relapsed/refractory; QD, once daily.

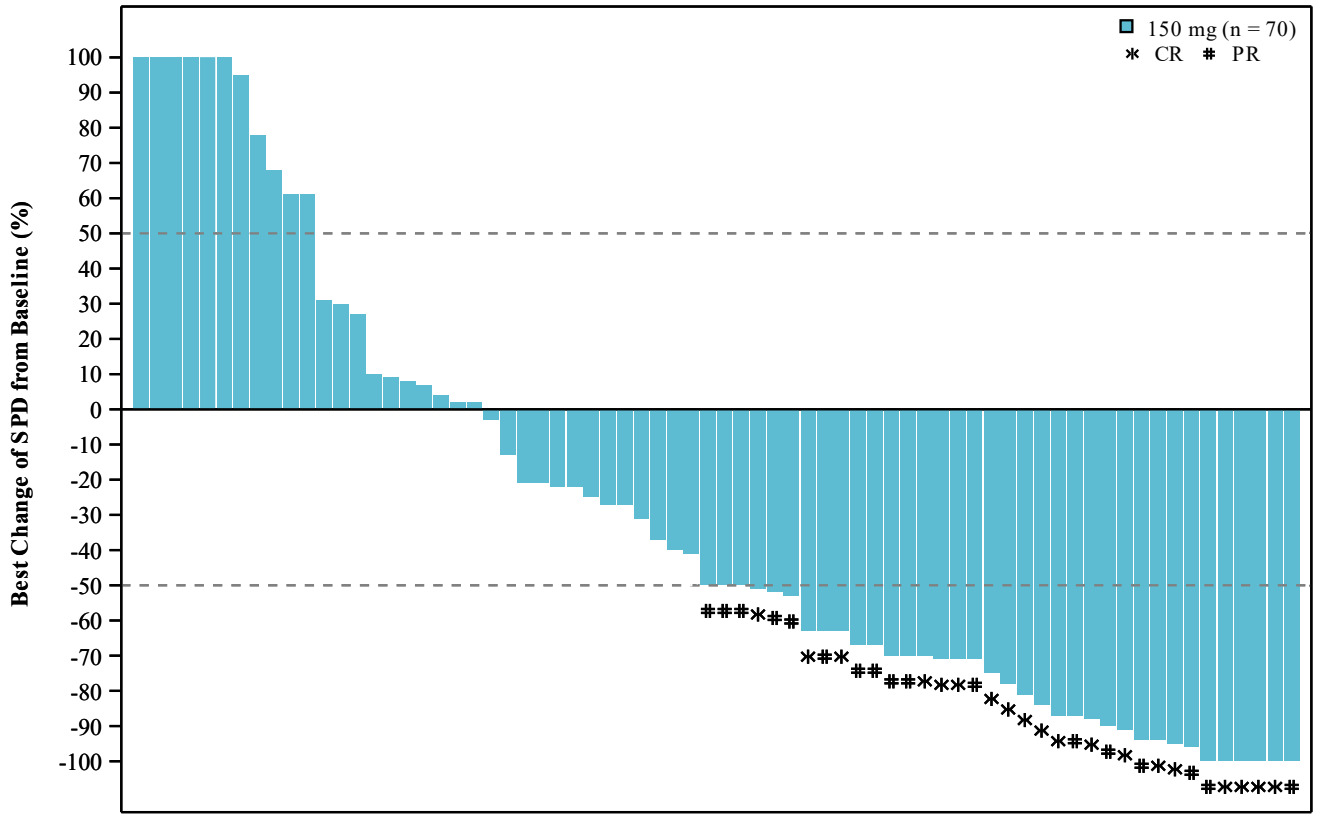
Tumor Response

Tumor Response	n = 88	
	By IRC	By Investigator
ORR, n (%)	39 (44.3)	35 (39.8)
Overall response, n (%)		
Complete response	21 (23.9)	10 (11.4)
Partial response	18 (20.5)	25 (28.4)
Stable disease	17 (19.3)	15 (17.0)
Progressive disease	20 (22.7)	26 (29.5)
Not evaluable	12 (13.6)	12 (13.6)

- Subjects were included in the efficacy analysis if they:
  - ✓ Had received at least one dose of golidocitinib
  - ✓ Had confirmed PTCLs per central pathology review
  - ✓ Had at least one baseline measurable lesion per IRC review
- Subjects without any post-baseline assessment were also included in the efficacy analysis if they met the above criteria.
- Per IRC assessment, 26 (29.5%) subjects achieved radiological CR, but 5 of which downgraded to PRs due to no post-treatment bone marrow confirmation, resulting in CR rate to 23.9%.

The following subjects were **not** included in the efficacy analysis set: 4 confirmed as non-PTCL by central pathology review, 9 not providing sufficient tumor tissue for central pathology confirmation, and 3 no baseline measurable lesions by IRC assessment.
Abbreviations: CR, complete response; IRC, independent review committee; ORR, objective response rate; PR, partial response; PTCL, peripheral T cell lymphoma.

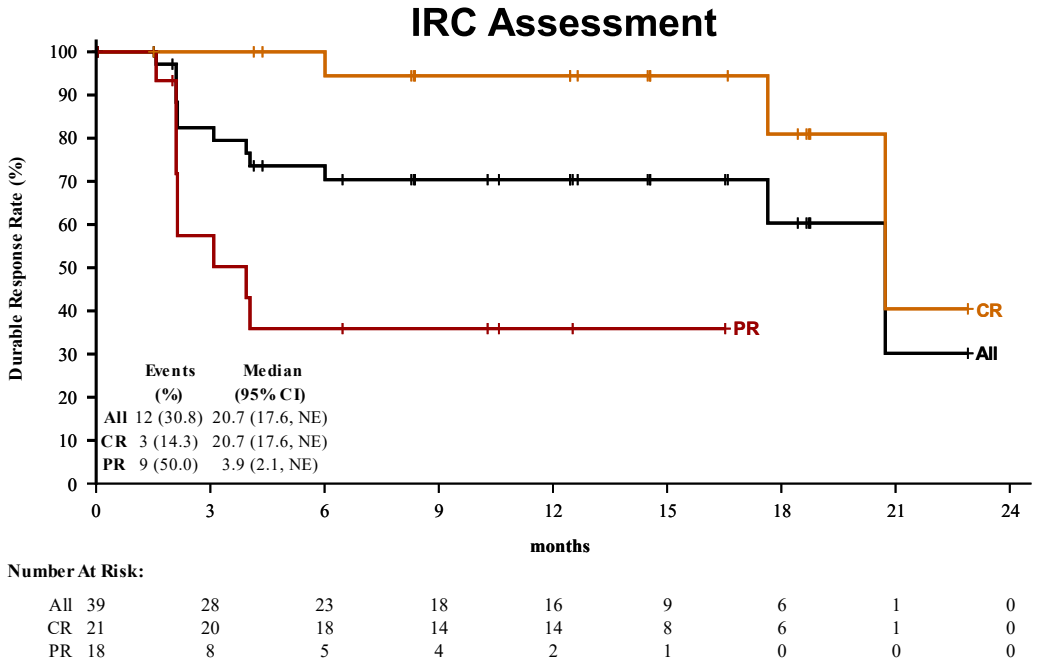
Tumor Size Change after Treatment

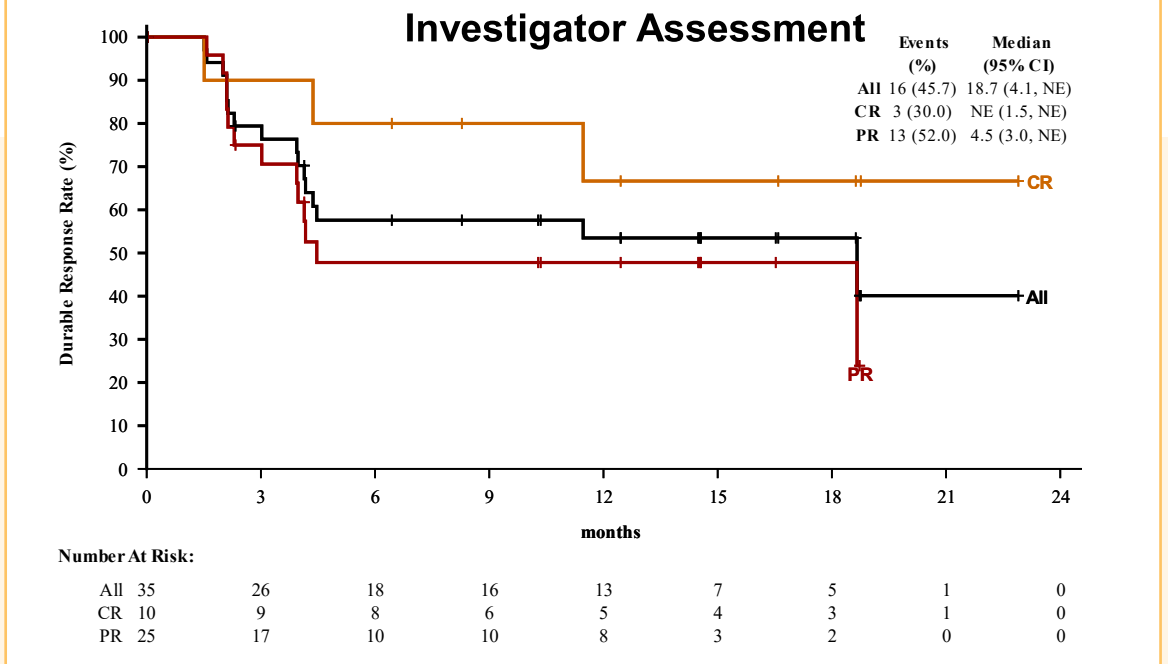


The majority (70.0%) of subjects achieved target lesion size reduction by IRC assessment

Note: Subjects with both baseline and post-baseline tumor assessment results available were included in the waterfall plot. SPD increase more than 100% was presented as 100%. Tumor response was assessed by IRC per Lugano 2014 criteria.
Abbreviations: CR, complete response; IRC, independent review committee; PR, partial response; SPD, sum of products of perpendicular diameters.

Duration of Response by IRC and Investigator





DoR

- By IRC assessment, with a median follow-up of 12.5 months, the median DoR was 20.7 months.
- By investigator assessment, with a median follow-up of 14.5 months, the median DoR was 18.7 months.
- Subjects with CRs achieved longer DoR compared with those with PRs.

PFS

- By IRC assessment, with a median follow-up of 11.9 months, the median PFS was 5.6 months.
- By investigator assessment, with a median follow-up of 15.9 months, the median PFS was 3.4 months.

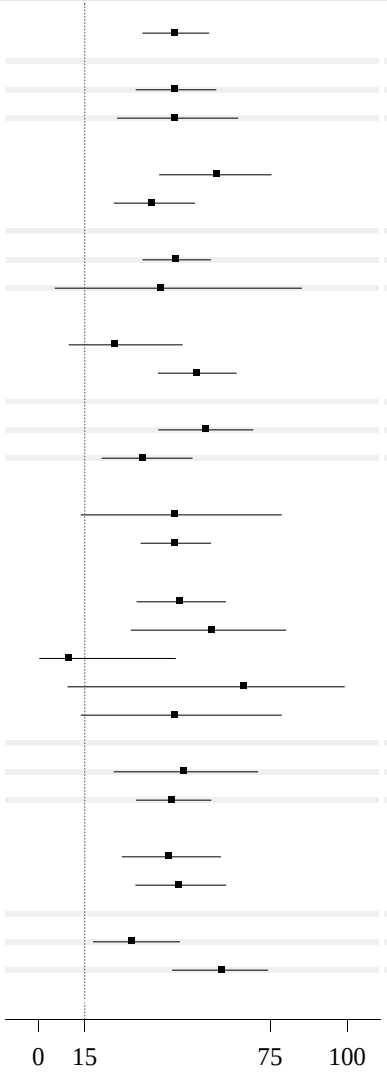
OS

- with a median follow-up of 17.5 months, the median OS was 19.4 months.

Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; NE, not estimable; IRC, independent review committee; OS, overall survival; PFS, progression free survival; PR, partial response.

Subgroup Analysis

Subgroup	ORR n/N (%)	95% CI [a]
Overall	39/88 (44.3)	(33.7, 55.3)
Age Group		
<65	27/61 (44.3)	(31.5, 57.6)
≥65	12/27 (44.4)	(25.5, 64.7)
Sex		
Female	18/31 (58.1)	(39.1, 75.5)
Male	21/57 (36.8)	(24.4, 50.7)
Geographical Region		
Asia: China and S. Korea	37/83 (44.6)	(33.7, 55.9)
Non-Asia: United States and Australia	2/5 (40.0)	(5.3, 85.3)
Prior Systemic Therapy		
<2	6/24 (25.0)	(9.8, 46.7)
≥2	33/64 (51.6)	(38.7, 64.2)
Prior HDAC Inhibitor Therapy		
Yes	24/44 (54.5)	(38.8, 69.6)
No	15/44 (34.1)	(20.5, 49.9)
Prior CD30 Targeted Therapy		
Yes	4/9 (44.4)	(13.7, 78.8)
No	35/79 (44.3)	(33.1, 55.9)
Histology Subtype by Central Pathology Review		
PTCL-not otherwise specified (PTCL, NOS)	23/50 (46.0)	(31.8, 60.7)
Angioimmunoblastic T-cell lymphoma (AITL)	9/16 (56.3)	(29.9, 80.2)
Anaplastic large-cell lymphoma (ALCL)	1/10 (10.0)	(0.3, 44.5)
Natural killer/T-cell lymphoma (NK/TCL)	2/3 (66.7)	(9.4, 99.2)
Others	4/9 (44.4)	(13.7, 78.8)
Bone Marrow Involvement at Baseline by Biopsy		
Yes	9/19 (47.4)	(24.4, 71.1)
No	30/69 (43.5)	(31.6, 56.0)
ECOG Performance Status at Baseline		
0	17/40 (42.5)	(27.0, 59.1)
≥1	22/48 (45.8)	(31.4, 60.8)
LDH Elevation at Baseline		
Yes	14/46 (30.4)	(17.7, 45.8)
No	25/42 (59.5)	(43.3, 74.4)

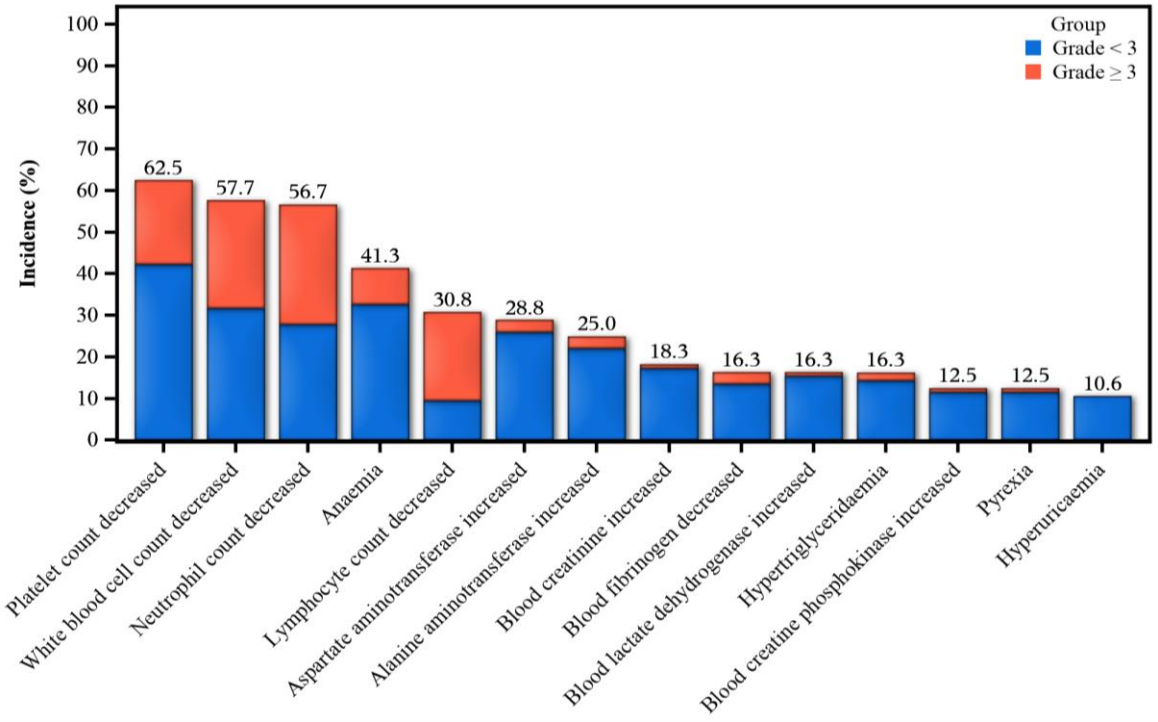


- Tumor response observed across various PTCL subtypes
- Tumor response observed irrespective of age, gender, baseline ECOG performance status, bone marrow involvement and serum LDH elevation, and types of prior anti-lymphoma therapies

[a] The 95% CI of rate was estimated based on the Clopper-Pearson method.
Abbreviations: AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large cell lymphoma; CD, cluster of differentiation; CI, confidence interval; CRR, complete response rate; ECOG, Eastern Cooperative Oncology Group; HDAC, histone deacetylase; IRC, independent review committee; LDH, lactate dehydrogenase; NK/TCL, natural-killer/T cell lymphoma; ORR, objective response rate; PTCL, NOS, peripheral T cell lymphoma, not otherwise specified.

Summary of Safety

TRAE, n (%)	n = 104
Any TRAE	96 (92.3)
Any TRAE with Grade ≥ 3	62 (59.6)
Any TRSAE	25 (24.0)
Any TRAE leading to dose interruption	40 (38.5)
Any TRAE leading to dose reduction	8 (7.7)
Any TRAE leading to drug discontinuation	9 (8.7)
Any TRAE with fatal outcome	1 (1.0)



The most common (incidence > 10%) Grade 3+ TRAEs included platelet count decreased, white blood cell count decreased, neutrophil count decreased and lymphocyte count decreased.

Abbreviations: TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event
Note: Adverse events were coded using MedDRA version 25.1. Adverse event grades were evaluated based on NCI-CTCAE Version 5.0.
TRAEs with incidence ≥ 10% were presented in the figure.

Conclusion

Golidocitinib is an effective therapy for treating r/r PTCLs with acceptable safety profile:

Remarkable anti-tumor efficacy

- Per IRC assessment, ORR 44.3%, and CRR 23.9%
- Median DoR 20.7 months; median PFS 5.6 months and median OS 19.4 months
- Tumor response across various PTCL subtypes, irrespective of age, gender, baseline ECOG PS, bone marrow involvement, serum LDH elevation, and types of prior anti-lymphoma therapies

Safety

- Acceptable safety profile of golidocitinib in treating subjects with r/r PTCLs
- Majority of TRAEs: hematological in nature, reversible or clinically manageable

Abbreviations: CRR, complete response rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IRC, independent review committee; LDH, lactate dehydrogenase; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PTCL, peripheral T cell lymphoma; r/r, relapsed/refractory; TRAE, treatment-related adverse event.

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- *Study investigators and their study teams*
- *Dizal Pharmaceutical*

- *The full article with more detailed data is now available on Lancet Oncology.*

For more information about the study, please contact: publication@dizalpharma.com

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Thank You

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