High-selective JAK1 inhibitor, golidocitinib, demonstrates targeting JAK/STAT pathway to treat r/r PTCL

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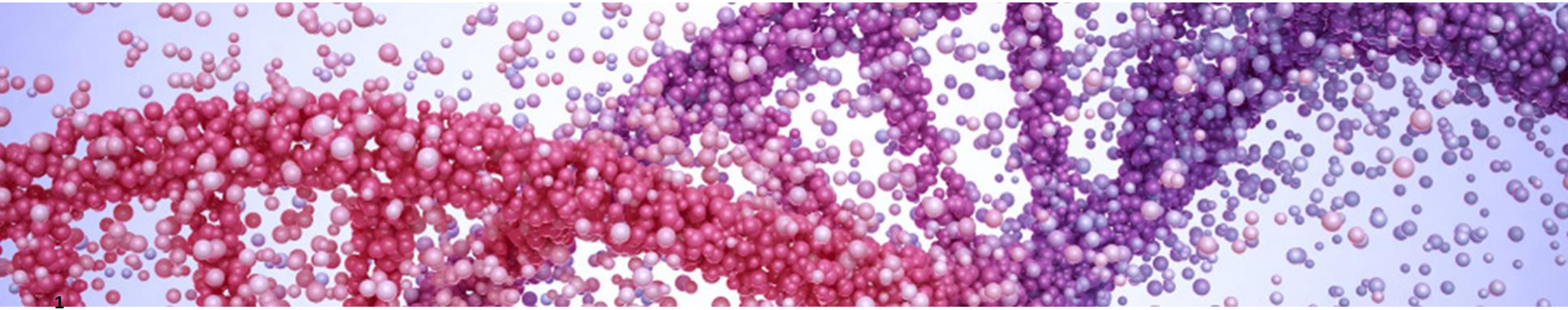

Disclosures

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Disease Background

- Genomic profiling of **T-cell neoplasms** reveals **frequent genomic aberrations in the JAK/STAT pathway** with clonal evasion from targeted therapies. [1]

- **JAK enzymes maybe rational therapeutic targets for T-cell leukemias and lymphomas**.

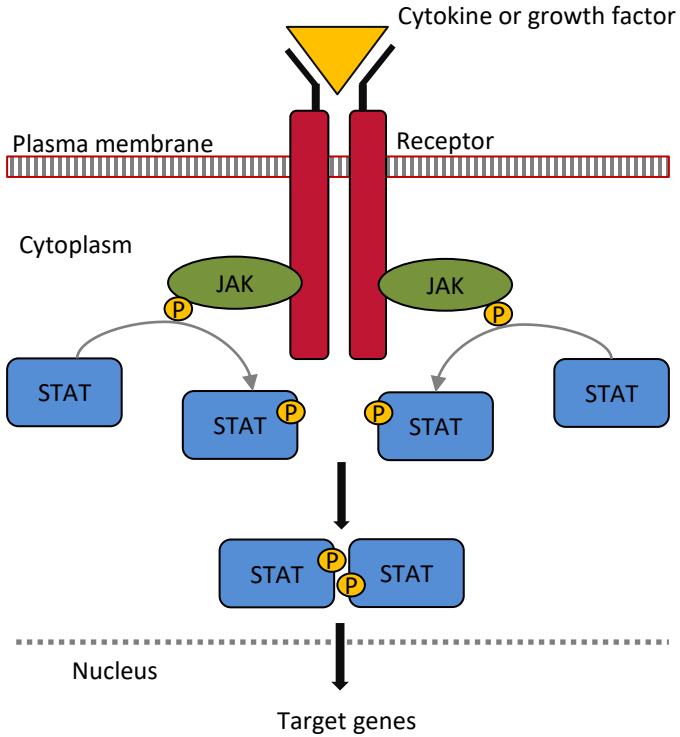


Figure 1. JAK/STAT signaling pathway

1. A Greenplate, et al, JCO Precis Oncol, 2018

Targeting JAK-STAT for T-cell Malignancies

- **Golidocitinib:**
  - An orally available, **high-selective JAK1 inhibitor**.
  - **Favorable PK properties:** once daily dosing regimen can maintain efficacious blood concentration during dosing interval.
  - Preclinical study showed the profound **dose-dependent anti-tumor activities of golidocitinib in T-lymphoma** cell lines and xenograft models with good correlations between exposure and pSTAT3 modulations.

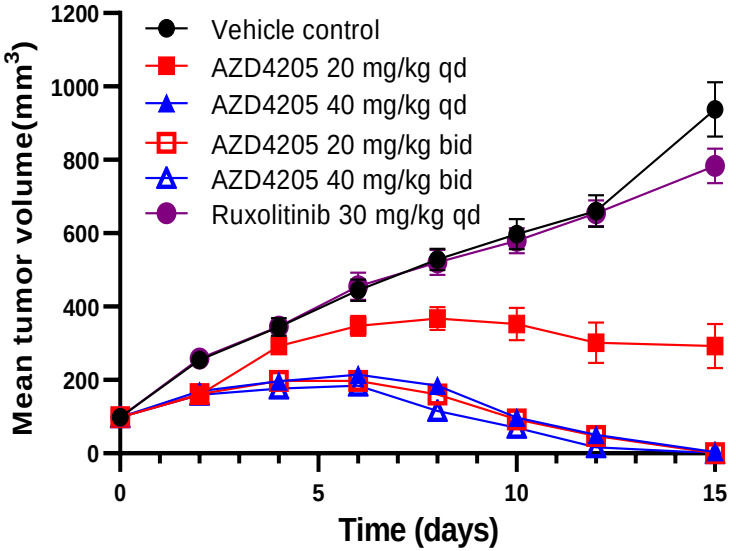
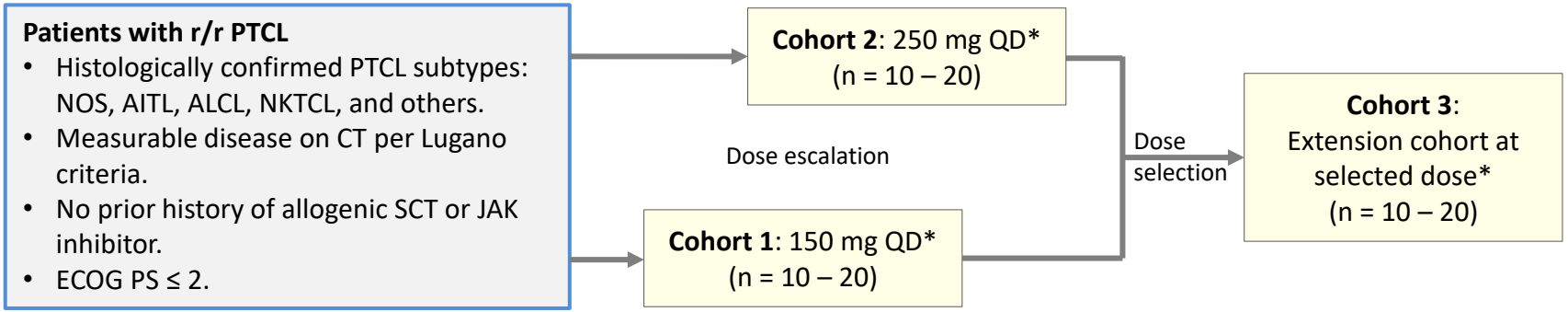


Figure 2. Golidocitinib (AZD4205) shows dose-dependent anti-tumor efficacy in Hut-102 xenograft model

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.

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

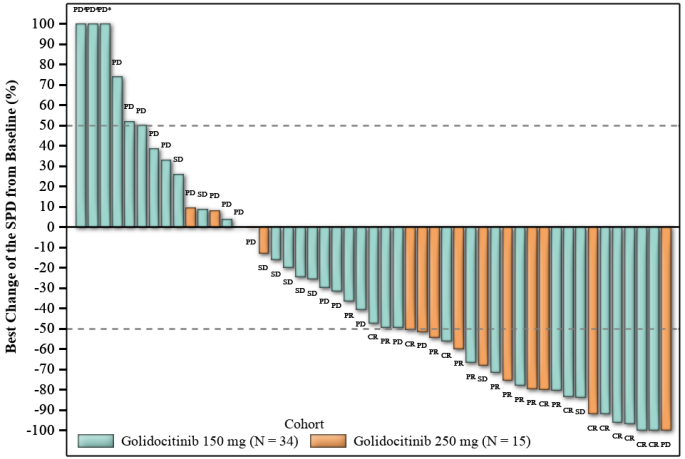
- At the DCO, 49 subjects completed at least one tumor assessment after dose with golidocitinib (n = 34 at 150 mg, n = 15 at 250 mg), and the other 2 subjects discontinued without any tumor assessments.

Table 2. Best Overall Response by Dose Level

Dose level	150 mg	250 mg	Total
n	34	15	49
Best response			
CR, n (%)	**8 (23.5%)**	**3 (20.0%)**	**11 (22.4%)**
PR, n (%)	**6 (17.6%)**	**4 (26.7%)**	**10 (20.4%)**
SD, n (%)	**7 (20.6%)**	**2 (13.3%)**	**9 (18.4%)**
ORR [95% CI]	**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.

Figure 4. Water-fall Plot



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 3. Overall AEs by Dose Level

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

- 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.

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 investigators' assessment, which were observed in ≥ 3 subjects by data cut-off date (31 May 2021). n includes 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.

Exploratory Biomarker Studies

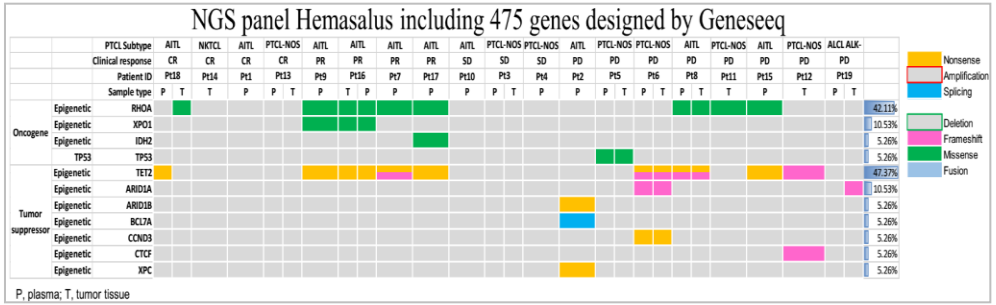
- Tumor samples from 20 subjects were determined suitable for pSTAT3 IHC analysis. A positive trend between clinical activity and high level of pSTAT3 was observed (Table 4).
- Targeted genomic sequencing was carried out with samples from 19 subjects. No genetic mutations associated with JAK/STAT pathway (including JAK1/2/3, STAT3/5A/5B/6) were identified in the tested samples.

Table 4. pSTAT3 expression level and efficacy

	pSTAT3 expression level [1]		Total n = 20
	Low (n = 13)	High (n = 7) [2]	
ORR (r/n)	30.8% (4/13)	57.1% (4/7)	40.0% (8/20)

Note: 1. pSTAT3 expression assay was conducted with pSTAT3 IHC based on archived tumor tissues, which were collected from 20 subjects at baseline; 2. pSTAT3 high was defined as pSTAT3 stained in ≥ 60% of tumor cells.

Figure 5. Genomic profiling



Note: Genomic profile was analyzed with NGS designed by Geneseeq based on archived tumor tissue/plasma collected from 19 subjects at baseline.

Summary

- **Efficacy**
  - Promising anti-tumor activity of golidocitinib was observed in patients with r/r PTCL.
- **Safety**
  - Golidocitinib was well tolerated, with comparable safety profiles with currently approved therapies.
  - The most common (incidence > 10%) grade 3 or higher AEs included thrombocytopenia, neutropenia, and pneumonia.
  - The majority of AEs were reversible, or clinically manageable with dose modifications.
- **Exploratory biomarker**
  - No apparent correlation between genetic mutations in JAK/STAT pathway and clinical response was observed, while baseline high pSTAT level seems to correlate (Larger sample size is needed to confirm the findings).

Acknowledgements

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