Abstract #7574: A phase 2 study of HLX208, a BRAF^{V600E} inhibitor, in adult patients with Langerhans cell histiocytosis and/or Erdheim-Chester disease harboring *BRAF*^{V600E} mutation

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Background

- Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD) are rare disorders with no current standard treatments. Various chemotherapeutic options, such as cytarabine, vincristine + prednisone, cladribine, methotrexate + cytarabine[1-5] for LCH, and interferon-α and cladribine for ECD are commonly used in the clinics.
- Recent breakthrough in the understanding of LCH and ECD pathogenesis revealed the abnormal activation of MAPK (Mitogen Activating Protein Kinase) signaling pathway in these tumor cells. The most common cause is the *BRAF*^{V600E} mutation, with mutation frequency of 25%–75% in adult LCH[6], and 50%–70% in ECD[7].
- Currently, BRAF inhibitors are only used for ECD patients with *BRAF*^{V600} mutations in the United States. Other marketed BRAF inhibitors have no indication for LCH and ECD.
- HLX208 is a selective BRAF^{V600E} inhibitor that possessed a proprietary novel chemical structure that differs from other marketed BRAF inhibitors. Systematic preclinical studies have demonstrated a single crystal morph, high bioavailability, and excellent antitumor efficacy for HLX208.
- Here, we report the efficacy and safety results from this phase 2 study of HLX208 in adult LCH and/or ECD patients with *BRAF*^{V600E} mutations.

Methods

- This single-arm, open-label, multicenter, phase 2 study aimed to evaluate the efficacy, safety, and pharmacokinetics of HLX208 in adult patients with LCH and/or ECD harboring *BRAF*^{V600E} (Fig. 1).
- Patients received oral administration of HLX208 at 450 mg twice every day in 28-day cycles until disease progression, experiencing intolerable toxicity, withdrawal of consent, initiation of new antitumor therapy, or death (whichever occurred first).
- PET-CT scans were conducted at baseline, Q12W for 48 weeks, then Q24W until disease progression, initiation of new antitumor therapy, withdrawal of consent, loss to follow-up, death, or the end of this study (whichever occurred first).

Figure 1. Study design

Inclusion criteria:

- Age ≥18 years
- ECOG PS 0-2
- Histologically confirmed primary, relapsed, or refractory adult LCH and/or ECD
- Confirmation of harboring *BRAF*^{V600E} mutations
- At least one measurable lesion as assessed by IRRC per PERCIST v1.0

HLX208 450mg oral twice-a-day

Primary endpoint: ORR assessed by IRRC per PERCIST v1.0

Secondary endpoints:

- ORR*
- DCR**
- TTR**
- DOR**
- PK
- OS, 12-month OS rate
- PFS, 12-month PFS rate**
- Safety
- Quality of life

* Assessed by the investigators per PERCIST v1.0, and by the IRRC and investigators per RECIST v1.1

** Assessed by the IRRC and investigators per PERCIST v1.0, and RECIST v1.1

DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRRC, independent radiological review committee; ORR, objective response rate; OS, overall survival; PERCIST, PET Response Criteria in Solid Tumors; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

Results

- As of January 15, 2023, 22 patients have received at least one dose of HLX208 and were included in the safety set (SS). Among the whole population, 10 patients were efficacy evaluable and included in the response evaluable population.

References

1. Cao XX, *et al. Am J Hematol*. **2020**;95(9):E235–E238.
2. Goyal G, *et al. Am J Hematol*. **2021**;96(5):E146–E150.
3. Saven A, *et al. Blood*. **1999**;93(12): 4125–4130.
4. Miao HL, *et al. BMC cancer*. **2020**;20(1):911.
5. Cantu MA, *et al. PLoS One*. **2012**;7(8):e43257.
6. Selway JL, *et al. Oncol Lett*. **2017**;14(4):4449–4454.
7. Goyal G, *et al. Blood*. **2020**;135(22):1929–1945.

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HLX208 was safe, well tolerated, and showed promising efficacy in adult LCH and/or ECD patients with *BRAF*^{V600E} mutation

Efficacy

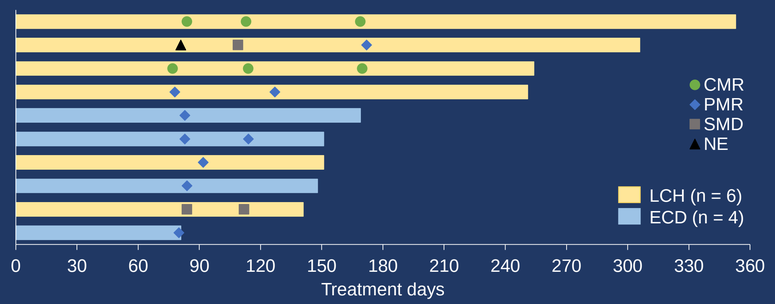
Table 2. Summary of response by IRRC and investigators per PERCIST v1.0

	IRRC-assessed (N = 10)	Investigators-assessed (N = 10)
ORR, % (95% CI)	**90.0** (55.5, 99.7)	**100.0** (69.2, 100.0)
DCR, % (95% CI)	100.0 (69.2, 100.0)	100.0 (69.2, 100.0)
CMR, n (%)	2 (20.0)	3 (30.0)
PMR, n (%)	7 (70.0)	7 (70.0)
SMD, n (%)	1 (10.0)	0

- The median follow-up duration was 4.8 months.
- ORR (unconfirmed) assessed by the IRRC and investigators per PERCIST v1.0 were **90.0%** and **100.0%**, respectively (Table 2).
- Disease control rate assessed by the IRRC and investigators per PERCIST v1.0 were 100% (95% CI 69.2–100%).
- Median DOR, PFS and OS were not reached.

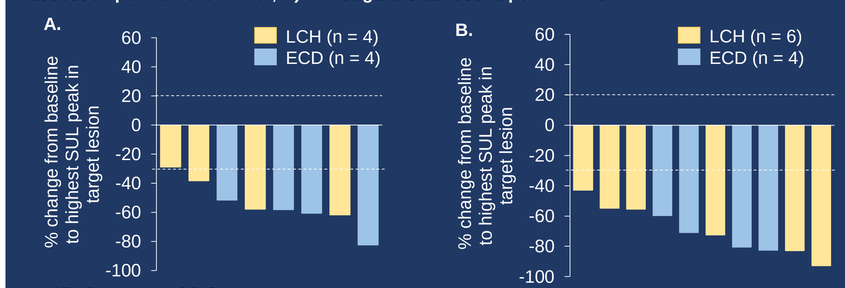
CI, confidence interval; CMR, complete metabolic response; PMR, partial metabolic response; SMD, stable metabolic disease.

Figure 2. Swimmer plot of patients' efficacy (IRRC-assessed per PERCIST v1.0)



CMR, complete metabolic response; PMR, partial metabolic response; SMD, stable metabolic disease; NE, non-evaluable.

Figure 3. Waterfall plot of change from baseline to highest SUL peak in target lesion. A) IRRC-assessed per PERCIST v1.0[a], B) investigators-assessed per PERCIST v1.0



[a] The SUL peaks of the 2 CMR patients dropped to background level, which are not recorded as values, and thus are not shown in Fig. 3A.

- Baseline demographics and characteristics of the patients are shown in Table 1.

Table 1. Patient demographics and baseline characteristics

	HLX208 (N = 22)		HLX208 (N = 22)
Median age (range), years	38.5 (18.0–69.0)	*BRAF*^{V600E} mutation, n (%)	
Male, n (%)	9 (40.9)	Positive	22 (100)
ECOG PS, n (%)		Negative	0
0	13 (59.1)	Prior lines of therapies, n (%)	
1	5 (22.7)	1	9 (40.9)
2	4 (18.2)	2	5 (22.7)
Tumor type, n (%)		3	3 (13.6)
LCH	12 (54.5)	4	1 (4.5)
ECD	9 (40.9)	Prior antitumor therapies, n (%)	
LCH and ECD	1 (4.5)	Chemotherapy	6 (27.3)
Classification, n (%)		Immunotherapy	3 (13.6)
Single-system multifocal	6 (27.3)	Targeted therapy	0
Multisystem	16 (72.7)	Others	4 (18.2)

Safety

- 17 (77.3%) patients in SS experienced treatment-emergent adverse events (TEAEs); 12 (54.4%) reported treatment-related adverse events (TRAEs) (Table 2).
- Most common TEAEs (≥10%) were alanine aminotransferase increased (36.4%), aspartate aminotransferase increased (22.7%), γ-glutamyltransferase increased (18.2%), and blood lactate dehydrogenase increased (18.2%) (Table 3).
- Most TEAEs were of grade 1 and 2 (n=15, 68.2%).
- 2 (9.1%) patients experienced grade ≥3 TRAEs and 1 (4.5%) experienced treatment-related serious adverse event (SAE).
- No AESIs were observed.
- No TEAEs that led to treatment discontinuation or death were observed.

Table 2. Safety summary

	HLX208 (N = 22)
Any TEAEs	17 (77.3)
Grade 1	8 (36.4)
Grade 2	7 (31.8)
Grade ≥3	2 (9.1)
Grade 5	0
Any TRAEs	12 (54.5)
Alanine aminotransferase increased	8 (36.4)
Aspartate aminotransferase increased	5 (22.7)
γ-glutamyltransferase increased	4 (18.2)
Blood lactate dehydrogenase increased	4 (18.2)
Any SAEs	1 (4.5)
Treatment-related	1 (4.5)

Table 3. TEAEs (≥10%) and grade ≥3 TEAEs (≥ 3%)

	HLX208 (N = 22)
Most common TEAEs (≥10%), n (%)	
Alanine aminotransferase increased	8 (36.4)
Aspartate aminotransferase increased	5 (22.7)
γ-glutamyltransferase increased	4 (18.2)
Blood lactate dehydrogenase increased	4 (18.2)
Most common grade ≥3 TEAEs (≥3%), n (%)	
Alanine aminotransferase increased	2 (9.1)
Aspartate aminotransferase increased	1 (4.5)
Blood alkaline phosphatase increased	1 (4.5)
Blood bilirubin increased	1 (4.5)
Drug-induced liver injury	1 (4.5)

AESI, adverse event of special interest; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; SAE, serious adverse event.

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