



## The 65th ASH Annual Meeting Abstracts

## POSTER ABSTRACTS

**616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES****Efficacy and Safety of Clifutinib, a Novel, Highly Selective, Oral FLT3 Inhibitor, in Patients with FLT3-Mutated Relapsed or Refractory Acute Myeloid Leukemia: Updated Results from a Phase I Study**

Jie Jin<sup>1</sup>, Huafeng Wang<sup>1</sup>, Wen-Juan Yu<sup>1</sup>, Zheng Ge<sup>2</sup>, Xudong Wei<sup>3</sup>, Yuhua Li<sup>4</sup>, Zhongxing Jiang<sup>5</sup>, Yiqing Li<sup>6</sup>, Xin Du<sup>7</sup>, Linhua Yang<sup>8</sup>, Lie Lin<sup>9</sup>, Jishi Wang, PhD<sup>10</sup>, Yazhou Yao<sup>11</sup>, Xiaoping Hu<sup>12</sup>, Jianping Lan<sup>13</sup>, Xiuzhi Deng<sup>14</sup>, Tong Chen<sup>15</sup>, Xianqi Feng<sup>16</sup>, Dengju Li<sup>17</sup>, Ming Hou<sup>18</sup>, Rong Fu<sup>19</sup>, Siyong Huang<sup>20</sup>, Jingbo Wang<sup>21</sup>, Xin Du<sup>22</sup>, Hui Yang<sup>23</sup>, Haiping Yang<sup>24</sup>, Yingzhi Jiang<sup>25</sup>, Zhijie Wang<sup>25</sup>, Deng Li<sup>25</sup>, Bing Liu<sup>25</sup>, Ning Kang<sup>25</sup>, Yulei Zhuang<sup>25</sup>, Yingjun Zhang<sup>25</sup>

<sup>1</sup> The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

<sup>2</sup> Zhongda Hospital, Southeast University, Nanjing, China

<sup>3</sup> Department of Hematology, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China

<sup>4</sup> Department of Hematology, Zhujiang Hospital, Southern Medical University, Guangzhou, China

<sup>5</sup> Department of Hematology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

<sup>6</sup> Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China

<sup>7</sup> Guangdong Provincial People's Hospital, Guangzhou, China

<sup>8</sup> The Second Hospital of Shanxi Medical University, Taiyuan, China

<sup>9</sup> Hainan General Hospital, Haikou, China

<sup>10</sup> Affiliated Hospital of Guizhou Medical University, Guiyang City, China

<sup>11</sup> Baoji Central Hospital, Baoji, China

<sup>12</sup> PKU Care Luzhong Hospital, Zibo, China

<sup>13</sup> Department of Hematology, Zhejiang Provincial People's Hospital, Hangzhou, China

<sup>14</sup> Weihai Municipal Hospital, Weihai, China

<sup>15</sup> Department of Hematology, Huashan Hospital, Fudan University, Shanghai, China

<sup>16</sup> Affiliated Hospital of Qingdao University, Qingdao, China

<sup>17</sup> Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science & Technology, Wuhan, China

<sup>18</sup> Qilu Hospital of Shandong University, Jinan, China

<sup>19</sup> Tianjin Medical University General Hospital, Tianjin, China

<sup>20</sup> Xi'an Gaoxin Hospital, Xi'an, China

<sup>21</sup> Aerospace Center Hospital, Beijing, China

<sup>22</sup> The Second People's Hospital of Shenzhen, Shenzhen, China

<sup>23</sup> Shunde Hospital of Southern Medical University, Foshan, China

<sup>24</sup> The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China

<sup>25</sup> Sunshine Lake Pharma Co., Ltd, Dongguan, China

**Background:** Patients with relapsed/ refractory (R/R) FLT3-internal tandem duplication positive (FLT3-ITD+) acute myeloid leukemia (AML) have limited treatment options and poor prognosis. Clifutinib is a novel, highly selective, oral FLT-3 inhibitor with potent activity against FLT3-ITD(+) leukemic models both *in vitro* and *in vivo*. This study is a first-in-human study of clifutinib, with the purpose of evaluating the safety, tolerability, efficacy, and pharmacokinetic (PK) profile in Chinese patients with R/R FLT3-mutated AML (NCT04827069).

**Methods:** Patients aged  $\geq 18$  years with AML who were refractory to  $\geq 2$  cycles of standard induction chemotherapy or relapsed after achieving remission from previous treatments were enrolled. Previous use of FLT3 inhibitors were allowed. The study included two parts, a dose-escalation part (10 to 100 mg/day cohorts) and a dose-expansion part (40 and 70 mg/day cohorts). The primary endpoints were safety and tolerability, and the secondary endpoints were efficacy [CR(complete remission)/CRh (complete remission with partial hematologic recovery) rate, composite complete remission (CRc: CR+CRh+CRi,

CRi defined as complete remission with incomplete hematological recovery) rate, TTR (time to remission), duration of remission (DOR), and overall survival (OS)] and pharmacokinetics (PK).

**Results:** As of May 2023, 75 patients (pts) were enrolled (Figure 1), with a median age of 55 years (range:18-80), and 96.0% pts were FLT3-ITD(+) or TKD(+) [80.0% with ITD(+)/TKD(-), 9.3% with ITD(+)/TKD(UK), 5.3% with ITD(+)/TKD(+), 1.3% with ITD(-)/TKD(+)], 58.7% pts had received  $\geq 2$  lines of previous treatment, and 32.0% pts exposed to FLT3 inhibitors. 3 pts experienced dose-limiting toxicities (DLT): one out of 6 pts in the 55 mg/day cohort (Grade 3 QTcF prolongation with  $\Delta$ QTcF =71 ms) and 2 out of 6 pts in the 100 mg/day cohort (Grade 3 nausea and Grade 3 atrial fibrillation). Therefore, the maximum tolerated dose of clifutinib was 70 mg/day. The most common (rate  $\geq 20\%$ ) treatment-related adverse events (TRAEs) included leukopenia (70.7%), thrombocytopenia (68%), neutropenia (64%), anemia (48%), lymphopenia (26.7%), pneumonia (26.7%), hypokalemia (26.7%), aspartate aminotransferase increased (22.7%), alkaline phosphatase increased (21.3%) and alanine aminotransferase increased (20.0%). Grade  $\geq 3$  TRAEs occurring in  $\geq 20\%$  pts were leukopenia, thrombocytopenia, neutropenia, anemia, lymphopenia, and pneumonia. Approximately dose-proportional PK parameters were observed across 40-100 mg/day dose range for both single and repeat dosing (the parent drug might approach saturation at 100 mg/day), and median  $t_{max}$  ranged from 2 to 6 hours.

For efficacy, responses occurred in 28 (40.6%) of 69 FLT3-ITD(+) or TKD(+) efficacy evaluable pts, including 5 (7.2%) CR, 5(7.2%) CRh, 17 (24.6%) CRi, 1 (1.4%) MLFS, and the median TTR was 32 days (range: 26-149 days). The efficacy was better in the 40 mg/day group compared to 70 mg/day and 40-100 mg/day groups, with CR/CRh rate of 21.2% (7/33) vs 8.3% (2/24) vs 14.5% (10/69), CRc rate of 48.5% (16/33) vs 33.3% (8/24) vs 39.1% (27/69), and median DOR of CR/CRh was 3.2 months (95% CI:1.9, NA) vs 0.9 months (95% CI: NA, NA ) vs 3.2 months (95% CI: 0.9, 7.4 ), the median OS was 6.5 months vs 5.4 months vs 6.3 months, respectively. Among FLT3-ITD(+)/TKD(-) subjects administered with clifutinib 40 mg/day, the CR/CRh rate was 23.1% (6/26) with 3 patients achieved CR, median DOR of CR/CRh was 3.7 months, the CRc rate was 53.8% (14/26), and median OS was 7.4 months. Compared to FLT3-ITD(+) or TKD(+) pts, 40 mg dose group exhibited better efficacy in FLT3-ITD(+)/TKD(-) pts. In addition, clifutinib exhibited more potent anti-leukaemic activity in patients received only one line of previous treatment. Among patients experienced only one line treatment of 40 mg dose group, the CR/CRh rate was 30.8% (4/13), the CRc rate was 53.8% (7/13), and the median OS was 7.9 months (Table 1) .

**Conclusion:** This phase 1 study has demonstrated an acceptable safety profile and a significant anti-leukaemic activity of clifutinib in FLT3 mutant R/R AML, with the best response at the dose of 40 mg/day in FLT3-ITD(+)/TKD(-) AML. A confirmatory phase 3 study is currently ongoing to further evaluate the efficacy and safety of clifutinib dosed at 40 mg/day in R/R AML pts after first-line therapy with FLT3-ITD(+)/TKD(-) (NCT05586074).

**Keywords:** Acute myeloid leukemia, FLT3 inhibitor, Clifutinib

**Disclosures** No relevant conflicts of interest to declare.

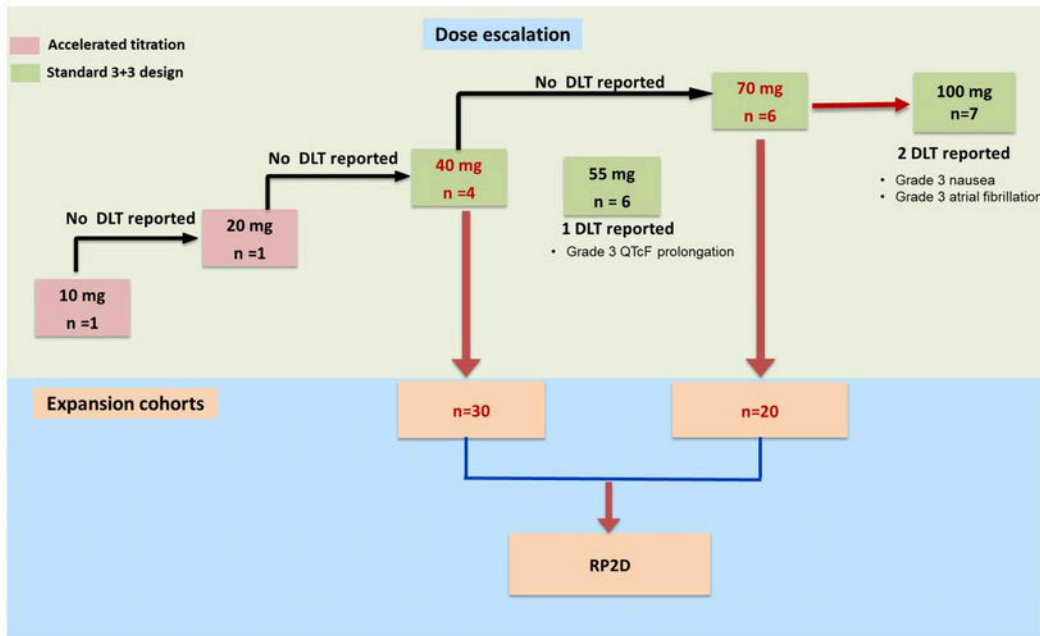


Figure 1 Study Design

Table 1 Efficacy of Clifutinib in Patients with FLT3-mutated Relapsed or Refractory Acute Myeloid Leukemia

Response	FLT3-ITD(+) or TKD(+)						FLT3-ITD(+)/TKD(-)	
	≥ one line of previous treatment			only one line of previous treatment			40 mg (n=26)	40-100 mg (n=58)
	40 mg (n=33)	70 mg (n=24)	40-100 mg (n=69)	40 mg (n=13)	70 mg (n=10)	40-100 mg (n=28)		
CR, n (%)	3 (9.1)	1(4.2)	5 (7.2)	1 (7.7)	1 (10.0)	3 (10.7)	3 (11.5)	3 (5.2)
CRh, n (%)	4 (12.1)	1(4.2)	5 (7.2)	3 (23.1)	1 (10.0)	4 (14.3)	3 (11.5)	4 (6.9)
CRi, n (%)	9 (27.3)	6(25)	17 (24.6)	3 (23.1)	2 (20.0)	6 (21.4)	8 (30.8)	16 (27.6)
MLFS	0	0	1 (1.4)	0	0	0	0	0
CR/CRh, n (%)	7 (21.2)	2(8.3)	10 (14.5)	4 (30.8)	2 (20.0)	7 (25.0)	6 (23.1)	7 (12.1)
CRc, n (%)	16 (48.5)	8 (33.3)	27 (39.1)	7 (53.8)	4 (40.0)	13 (46.4)	14 (53.8)	23 (39.7)
DOR of CR/CRh (months), Median (95% CI)	3.2(1.9,NA)	0.9(NA,NA)	3.2(0.9,7.4)	3.7 (1.9, NA)	0.9 (NA, NA)	3.7(0.9, NA)	3.7(1.9, NA)	3.2(0.9, NA)
TTR (days), Median (range)	29(26,134)	42.5 (26,149)	32(26,149)	32(26,84)	42.5(27,149)	32(26,149)	32(26,134)	32(26,149)

CR, complete remission (CR); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; CRc, Composite CR (CR+CRh+CRi); DOR, duration of remission; TTR, time to remission.

Figure 1

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