MOXETUMOMAB PASUDOTOX-TDFK IN HEAVILY PRETREATED PATIENTS WITH RELAPSED/REFRACTORY HAIRY CELL LEUKEMIA: LONG-TERM FOLLOW-UP FROM THE PIVOTAL PHASE 3 TRIAL

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Introduction

1. Hairy cell leukemia (HCL) is a rare B-cell malignancy, diagnosed in approximately 1000 patients each year in the USA.[1]
2. Purine nucleoside analogs (PNAs) are the recommended first-line treatment for HCL. However, many patients relapse, PNAs may become less effective over time[2] and previously there was no agreed standard of care for third-line treatment. Additionally, PNA treatment is associated with cumulative toxicity.[3]
3. Moxetumomab pasudotox-tdfk is a first-in-class recombinant CD22-directed cytotoxin, which was approved in the USA in 2018 for the treatment of adult patients with relapsed/refractory HCL,[4] based on the pivotal, multicenter, open-label, single-arm, phase 3 trial (Study 1053; NCT01829711).[5]

Objective

To report the long-term follow-up of the efficacy and safety of moxetumomab pasudotox-tdfk monotherapy in patients with HCL who participated in Study 1053.

Methods

- This study was conducted at **32 sites** in **14 countries**.
- Patients were eligible if they had histologically confirmed HCL, an Eastern Cooperative Oncology Group performance status of 0–2, and had received ≥ 2 prior systemic therapies, including ≥ 2 courses of a PNA, or 1 course of a PNA and ≥ 1 course of rituximab or a BRAF inhibitor.
- Patients received moxetumomab pasudotox-tdfk **40 µg/kg intravenously** on days 1, 3, and 5 of each 28-day cycle for six cycles, or until minimal residual disease (MRD)-negative complete response (CR), disease progression, initiation of alternate therapy, or unacceptable toxicity.
- Disease response and immunohistochemistry MRD status were determined by blinded independent central review (BICR).
- The **primary endpoint was durable CR** (CR confirmed at ≥ 1 time point with hematologic remission [HR] lasting > 180 days). In addition, **CR with HR lasting ≥ 360 days** was measured in this final analysis. CR was defined based on BICR of pathology, imaging, and normalization of hematologic parameters (i.e. HR, defined as hemoglobin ≥ 11.0 g/dL, absolute neutrophil count ≥ 1.5 × 10^3/µL, and platelet count ≥ 100 × 10^3/µL, without receiving transfusions or growth factors during the preceding 4 weeks of assessment). Duration of HR from the time of CR was determined by complete blood counts.
- Adverse events (AEs) were recorded 4 weeks prior to treatment enrollment, throughout treatment, and 4–6 weeks after the end of treatment.

Table 1. Baseline characteristics (ITT population)

Parameter	Moxetumomab pasudotox-tdfk 40 µg/kg (N = 80)
Age, years, median (range)	60.0 (34–84)
Variant HCL, n (%)	3 (3.8)
Splenectomy, n (%)	5 (6.3)
Number of prior systemic therapies, median (range)	3.0 (2–11)
> 3 prior lines, n (%)	39 (48.8)
Baseline hemoglobin, g/dL, median (range)	11.1 (6.5–16.3)
Baseline neutrophil count, × 10^3/µL, median (range)	0.81 (0.1–6.2)
Baseline platelet count, × 10^3/µL, median (range)	68.0 (6.0–350.0)
Prior cancer therapy, n (%)	
PNA	80 (100)
Rituximab	60 (75)
BRAF inhibitor	14 (18)
Interferon-α	20 (25)
Other	8 (10)
Unfit for PNA re-treatment, n (%)	30 (37.5)
At risk of infection[a]	20 (25.0)
Active infection[b]	19 (23.8)
Patients refractory to PNA,[c] n (%)	39 (48.8)
PNA monotherapy[d]	29 (36.3)
PNA + rituximab[e]	15 (18.8)

[a]Patients whose baseline absolute neutrophil count was < 0.5 × 10^3/µL. [b]Patients whose medical history included a serious infection or febrile neutropenia marked as "ongoing" or ending after the first dose of moxetumomab pasudotox-tdfk. [c]Patients whose HCL was refractory to any line of PNA. Note: a patient was counted as having HCL refractory to PNA monotherapy and/or PNA + rituximab. [d]Patients who did not achieve an OR or who achieved an OR lasting < 1 year. [e]Patients who did not achieve an OR or who achieved an OR lasting < 2 years.
HCL, hairy cell leukemia; ITT, intention-to-treat; OR, overall response; PNA, purine nucleoside analog.

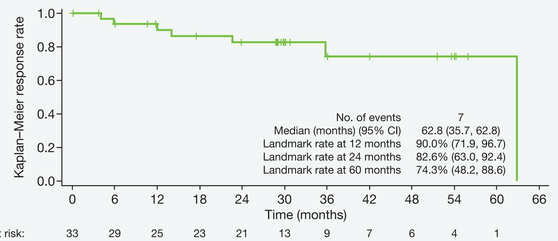
Results

- **Eighty patients** (63 males; median age 60.0 years) were enrolled and treated with moxetumomab pasudotox-tdfk (Table 1).
- The median number of prior systemic therapies was 3.0; 48.8% of patients were PNA-refractory, and 37.5% were unfit for PNA re-treatment (Table 1).
- The median number of treatment cycles administered was 6.

Efficacy

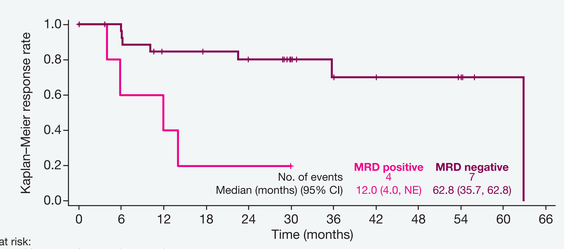
- Disease responses, as assessed by the BICR and the investigators for the intention-to-treat population, are presented in Table 2. Results described below are as assessed by the BICR.
- With a **median follow-up of 24.6 months** (range 1.2–71.7 months), **the durable CR rate was 36.3%**. Out of 29 patients who had a durable CR rate, 26 were found to be MRD-negative by immunohistochemistry. **CR rate with HR lasting ≥ 360 days was 32.5%**. The median **duration of HR from onset of CR was 62.8 months** (Figure 1).
- **The CR rate was 41.3%**. MRD negativity was achieved in 27 (81.8%) of the 33 patients in CR (Figure 2). **The median duration of CR was 62.8 months**. Landmark rates of CR duration at 6, 12, 18, 24, 36, 48, and 60 months were: 93.5%, 77.1%, 73.6%, 70.0%, 61.2%, 61.2%, and 61.2%, respectively.
- **The objective response rate (ORR) was 75%** (Table 2).
- **Median progression-free survival was 41.5 months** (Figure 3).

Figure 1. Duration of hematologic remission from complete response (median follow-up 24.6 months)



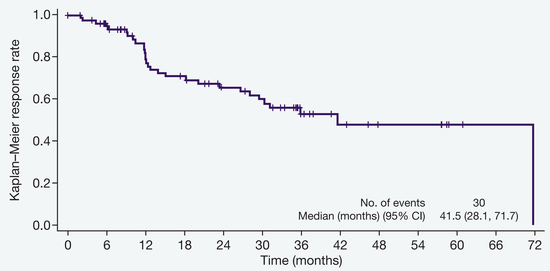
Data are for the patients with a complete response in the intention-to-treat population, as assessed by blinded independent central review (n = 33).
Hematologic remission: hemoglobin ≥ 11.0 g/dL, absolute neutrophil count ≥ 1.5 × 10^3/µL, and platelet count ≥ 100 × 10^3/µL, without receiving transfusions or growth factors within the preceding 4 weeks of assessment.
CI, confidence interval.

Figure 2. Duration of complete response by MRD status (median follow-up 24.6 months)



Data are for the patients with a complete response in the intention-to-treat population, as assessed by independent central review (n = 33).
CI, confidence interval; MRD, minimal residual disease; NA, not applicable; NE, not evaluable.

Figure 3. Progression-free survival



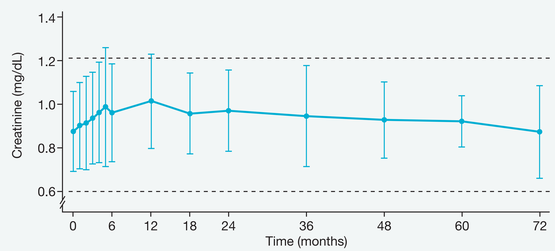
Data are for the intention-to-treat population, as assessed by independent central review (n = 80).
CI, confidence interval.

Table 2. Disease responses and immunohistochemistry MRD status (ITT population)

Parameter	Moxetumomab pasudotox-tdfk 40 µg/kg (N = 80) Final analysis (Median F/U = 24.6 mo)	
	BICR-assessed	Investigator-assessed
Durable CR > 180 days (primary endpoint), n (%)	29 (36.3)	39 (48.8)
95% CI[a]	25.8, 47.8	37.4, 60.2
CR ≥ 360 days, n (%)	26 (32.5)	36 (45.0)
95% CI[a]	22.4, 43.9	33.8, 56.5
Best overall response		
CR, n (%)	33 (41.3)	42 (52.5)
95% CI[a]	30.4, 52.8	41.0, 63.8
CR and MRD–, n (%)[b]	27 (33.8)	26 (32.5)
95% CI[a]	23.6, 45.2	22.4, 43.9
CR and MRD+, n (%)[b]	6 (7.5)	6 (7.5)
95% CI[a]	2.8, 15.6	2.8, 15.6
PR, n (%)	27 (33.8)	21 (26.3)
Objective response rate (CR or PR), n (%)	60 (75.0)	63 (78.8)
95% CI[a]	64.1, 84.0	68.2, 87.1
Duration of response, mo, median (range)	66.7 (0+ to 66.7)	42.1 (0.0+ to 69.0)
Duration of CR, mo, median (range)	62.8 (0.1+ to 62.8)	56.6 (0.0+ to 69.0)

CR was defined as clearing of the bone marrow of hairy cells by routine hematoxylin and eosin stain, radiologic resolution of pre-existing lymphadenopathy and/or organomegaly, and hematologic remission. PR was defined as ≥ 50% decrease or normalization (< 500/mm^3) in peripheral blood lymphocyte count, reduction of pre-existing lymphadenopathy and/or organomegaly, and HR.
[a]Two-sided CI was calculated using the exact probability method based on the binomial distribution. [b]Determined by immunohistochemistry.
BICR, blinded independent central review; CI, confidence interval; CR, complete response; F/U, follow-up; HR, hematologic remission; ITT, intention-to-treat; mo, months; MRD, minimal residual disease; NA, not available; NR, not reached; PR, partial response.

Figure 4. Mean serum creatinine over time



Data are mean ± SD. Intention-to-treat population; N = 80. The upper horizontal line corresponds to the mean of upper bounds of normal laboratory ranges and the lower horizontal line corresponds to the mean of the lower bounds of normal laboratory ranges.
SD, standard deviation.

Safety

- As per the primary analysis, the most frequent treatment-related AEs were **nausea** (**28%**), **peripheral edema** (**26%**), **headache** (**21%**), and **pyrexia** (**20%**).
- Treatment-related grade 3/4 AEs were reported in 24 patients (30.0%).
- Serious AEs were reported in 28 patients (35.0%), with hemolytic uremic syndrome (HUS, 7.5%), pyrexia (6.3%), and capillary leak syndrome (CLS, 5.0%) being the most frequent.
- Treatment-related AEs led to study **drug discontinuation** in eight patients (**10.0%**): HUS, n = 4 (5.0%); CLS, n = 2 (2.5%); and increased blood creatinine, n = 2 (2.5%).
- **Grade 3/4 CLS** occurred in two patients (**2.5%**) and **grade 3/4 HUS** in five patients[a] (**6.3%**). In general, CLS and HUS events were manageable and reversible with appropriate supportive care and monitoring.
- Based on the follow-up analyses of serum creatinine, there was **no decline in renal function** over time; 12 months post treatment, all mean (standard deviation) **serum creatinine laboratory values stayed within normal limits** (Figure 4), suggesting that current management strategies for HUS and CLS (oral hydration, intravenous fluid supplementation on the day of infusion, and use of dexamethasone) are adequate.
- Four deaths were reported; two were due to study disease progression and two were due to an AE (one each of pneumonia and septic shock, which were considered not related to study treatment).

[a]Includes one sponsor-adjudicated event of HUS.

Conclusions

1. **Moxetumomab pasudotox-tdfk achieved a high rate of deep and durable responses.**
   - **36.3% of patients achieved a durable CR > 180 days (primary endpoint).**
   - **32.5% of patients achieved a CR with HR lasting ≥ 360 days.**
2. **Moxetumomab pasudotox-tdfk treatment was associated with a manageable safety profile.**
   - **Proactive monitoring of patients, particularly for symptoms of CLS and HUS, is important in the management of these safety risks.**

References

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Conflicts of interest

RJK: coinventor on the National Institutes of Health patent for moxetumomab pasudotox-tdfk. CD: advisory board for MedImmune. PLZ: consultant for EUSA Pharma, Merck Sharp & Dohme, Sanofi, and Verastem; speaker bureaus/advisory boards for Bristol-Myers Squibb, Celgene, EUSA Pharma, Gilead, Immune Design, Janssen-Cilag, Kyowa Kirin, Merck Sharp & Dohme, Portola, Roche, Sandoz, Sanofi, Servier, and Verastem. TR: research grant from AstraZeneca/MedImmune. PDiC: consultant/advisory boards and speaker/honoraria for Bristol-Myers Squibb, Incyte, Novartis, and Pfizer. BTG: consultant/advisory boards for Astellas, BerGenBio, Daiichi Sankyo, Pfizer, and Seattle Genetics; ownership interests in ACTII AS and KinN Therapeutics AS; research funding from ERA PerMed, Helse Vest Regional Health Authority, Horizon 2020 (EU), Norwegian Cancer Society, and The Research Council of Norway. XT: consultant/advisory boards for AbbVie, Gilead, and Innate Pharma; research support from Roche and Sysmex. GJR: consultant/advisory boards or data/safety monitoring committee for AbbVie, Actinium, Agios, Amphivena, Argenx, Astex, Astellas, Bayer, Celgene, Celltrion, Daiichi Sankyo, Eisai, Janssen, Jazz, Novartis, MEI Pharma, Orsenix, Otsuka, Pfizer, Roche/Genentech, Sandoz, Takeda, and Trovagene; research support from Cellectis. LK: honoraria from AbbVie, Amgen, Celgene, Janssen, and Takeda; advisory boards for Amgen, Celgene, Janssen, and Takeda; travel support for international meetings from Amgen and Janssen. NKC: AstraZeneca employee/shareholder. SL and PP: Acerta Pharma (a member of the AstraZeneca group) employees/shareholders. JD, DEG, WHW, IP, and FG: none to declare.

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