



# Moxetumomab Pasudotox: First Global Approval

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## Abstract

Moxetumomab pasudotox-tdfk (LUMOXITI™), an anti CD22 recombinant immunotoxin, has been developed by MedImmune and its parent company AstraZeneca for the treatment of hairy cell leukaemia. The product, discovered at the National Cancer Institute, is an optimised version of immunotoxin CAT-3888. Moxetumomab pasudotox is composed of the Fv fragment of an anti-CD22 monoclonal antibody fused to a 38 kDa fragment of *Pseudomonas* exotoxin A, PE38. The Fv portion of moxetumomab pasudotox binds to CD22, a cell surface receptor expressed on a variety of malignant B-cells, thereby delivering the toxin moiety PE38 directly to tumour cells. Once internalised, PE38 catalyses the ADP ribosylation of the diphthamide residue in elongation factor-2 (EF-2), resulting in the rapid fall in levels of the anti-apoptotic protein myeloid cell leukaemia 1 (Mcl-1), leading to apoptotic cell death. This article summarizes the milestones in the development of moxetumomab pasudotox leading to this first approval for the treatment of adults with relapsed or refractory hairy cell leukaemia who received at least two prior systemic therapies, including treatment with a purine nucleoside analogue. Development of moxetumomab pasudotox for non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and precursor cell lymphoblastic leukaemia/lymphoma was discontinued.

## 1 Introduction

Hairy cell leukaemia (HCL) is a chronic malignancy of mature neoplastic B cells with a characteristic serrated cytoplasmic border [1, 2]. HCL accounts for 2% of all leukaemias in the USA and is characterised by pancytopenia, and splenomegaly due to the infiltration of leukaemic cells positive for CD22, CD25, CD20, CD11c, CD19, CD103, CD123 tartrate-resistant acid phosphatase (TRAP), annexin A1 (ANXA1) and the BRAF V600E mutation [1]. Purine analogues (cladribine or pentostatin) are the standard of care for initial treatment and are associated with durable remissions that last for years; however, many patients relapse and require additional therapy [2]. Subsequent treatment is usually with purine analogues, although treatment efficacy is reduced, patients have shorter remissions and are ultimately

refractory to treatment [3]. Moreover, purine analogues have been associated with neurotoxicity [4] and are very immunosuppressive, which may increase the risk of opportunistic infections [2].

The unmet need for additional therapies led to the development of new agents, such as the recombinant CD22-targeted immunotoxin moxetumomab pasudotox-tdfk ((LUMOXITI™; hereafter moxetumomab pasudotox) developed by MedImmune and its parent company AstraZeneca. Moxetumomab pasudotox (CAT-8015) comprises the Fv fragment of a recombinant murine anti-CD22 monoclonal antibody fused to a 38 kDa fragment of *Pseudomonas* exotoxin A, PE38 [5]. Moxetumomab pasudotox was recently approved by the USA FDA for the treatment of adult patients with relapsed or refractory HCL who received at least two prior systemic therapies, including treatment with a purine nucleoside analogue [5, 6]. The recommended dosage of moxetumomab pasudotox is 0.04 mg/kg as an intravenous infusion over 30 min on days 1, 3 and 5 of each 28-day cycle for a maximum of 6 cycles. The US prescribing information for moxetumomab pasudotox carries boxed warnings regarding the risk of capillary leak syndrome (CLS) and haemolytic uraemic syndrome (HUS) in patients receiving moxetumomab pasudotox. This article summarizes the milestones in the development of moxetumomab pasudotox leading to this first approval for patients with relapsed or

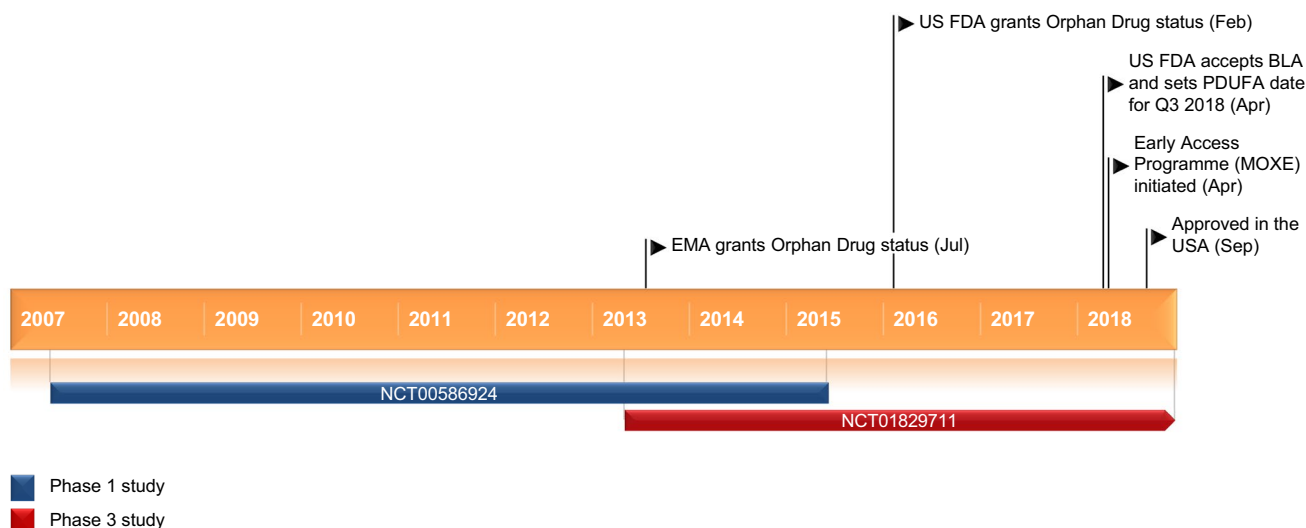
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Key milestones in the development of moxetumomab pasudotox for the treatment of adults with relapsed or refractory hairy cell leukaemia who received at least two prior systemic therapies, including

treatment with a purine nucleoside analogue. *BLA* biologics license application, *PDUFA* Prescription Drug User Fee Act, *Q3* quarter three

refractory HCL. The development of moxetumomab pasudotox for precursor cell lymphoblastic leukaemia/lymphoma, and non-Hodgkin's lymphoma and chronic lymphocytic leukaemia has been discontinued.

## 1.1 Company Agreements

Moxetumomab pasudotox was originated and initially developed by the National Cancer Institute, part of the US National Institutes of Health (NIH). Genencor licensed the candidates for haematological malignancies and entered into a co-operative research and development agreement (CRADA) with the NIH. Cambridge Antibody Technology (a subsidiary of AstraZeneca) acquired the intellectual property rights to moxetumomab pasudotox from Genencor in December 2004. Under the original license agreement with the NIH, Cambridge Antibody Technology gained the rights to a portfolio of intellectual property associated with the programme and was to pay future royalties to the NIH. A payment of up to \$US16 million was also made to Genencor upon closing of the deal. In October 2007, Cambridge Antibody Technology was integrated into MedImmune by its parent company AstraZeneca. The combined company is operating as MedImmune.

## 2 Scientific Summary

### 2.1 Pharmacodynamics

Moxetumomab pasudotox is an optimised version of the immunotoxin CAT-3888 (BL-22), with higher affinity for CD22 than the parent compound [7]. The affinity of CAT-3888 was increased and its off-rate decreased by hotspot mutagenesis, leading to the development of moxetumomab pasudotox which has threonine-histidine-tryptophan instead of serine-serine-tyrosine in the antigen-binding site of the heavy chain [8]. The Fv portion of moxetumomab pasudotox binds to CD22, a cell surface receptor expressed on a variety of malignant B-cells, thereby delivering the toxin moiety PE38 directly to tumour cells. Once internalised, PE38 catalyses the ADP ribosylation of the diphthamide residue in elongation factor-2 (EF-2), resulting in the rapid fall in levels of the anti-apoptotic protein myeloid cell leukaemia 1 (Mcl-1), leading to apoptotic cell death [9]. In a Burkitt's lymphoma subcutaneous xenograft tumor model, treatment with moxetumomab pasudotox was associated with rapid reduction in tumour volume and, in some cases, complete remission of tumours [7].

In the pivotal phase 3 study in patients with relapsed/refractory HCL (NCT01829711), treatment with moxetumomab pasudotox resulted in the rapid and sustained depletion of circulating CD19+ B cells [10]. At day 8, a 90% reduction in the median peripheral blood CD19+ B cell count was seen with moxetumomab pasudotox, with the counts remaining low until the end of treatment; in patients with partial or complete response, median CD19+ B cell counts returned to approximately normal levels at 6 months after therapy [10].

On day 8 after moxetumomab pasudotox treatment, median total CD3+ T cell, CD4+ T cell, CD8+ T cell and CD16+/CD56 Natural Killer cell counts were reduced 20–47% from baseline levels, and returned to or were above baseline levels on day 29 onwards [5]. Immunoglobulin (Ig) A, IgG and IgM levels remained generally unchanged at the end of treatment [5].

## 2.2 Pharmacokinetics

In patients with HCL, moxetumomab pasudotox concentrations increased dose-proportionally across a dose range of 0.005–0.05 mg/kg (0.1–1.3 times the approved dose) administered intravenously over 30 min on days 1, 3 and 5 of a 28-day cycle, according to pooled data from a phase 1 (NCT00586924;  $n = 49$ ) and a phase 3 (NCT01829711;  $n = 80$ ) study [5, 11]. Following treatment with moxetumomab pasudotox at the approved dosage, the steady-state mean peak plasma concentration ( $C_{max}$ ) of moxetumomab

pasudotox was 379 ng/mL and the mean area under the concentration-time curve from 0 to last was 626 ng·h/mL [5]. There was no systemic accumulation of moxetumomab pasudotox. The mean volume of distribution of moxetumomab pasudotox was estimated to be 6.5 L in a population pharmacokinetic model [5]. High exposure to moxetumomab pasudotox was significantly associated with low baseline CD19+ B cell levels ( $p < 0.001$ ), and in patients with high antidrug antibody (ADA) titres, the presence of ADA post-baseline was significantly ( $p < 0.05$ ) associated with lower  $C_{max}$  at cycle 3 and beyond [5, 12].

The metabolic pathway of moxetumomab pasudotox is unknown. However, it is thought that like other protein therapeutics, moxetumomab pasudotox undergoes proteolytic degradation into small peptides and amino acids via catalytic pathways [5]. In a population pharmacokinetic model, the estimated mean systemic clearance of moxetumomab pasudotox after the first dose of the first cycle was 25 L/h and after subsequent dosing was 4 L/h, as a result of depletion in CD22+ B cells after repeated dosing [5, 11]. The mean elimination half-life of moxetumomab pasudotox was 1.4 h [5].

The pharmacokinetic properties of moxetumomab pasudotox are not significantly affected by age, gender, race, bodyweight, mild hepatic impairment, or mild or moderate renal impairment, according to a pharmacokinetic analysis [5]. The pharmacokinetics of moxetumomab pasudotox in patients with moderate to severe hepatic impairment or severe renal impairment are unknown [5].

### Features and properties of moxetumomab pasudotox

Alternative names	CAT-8015; GCR-8015; HA22; LUMOXITI™
Class	Antineoplastics, immunoconjugates; immunotoxins; monoclonal antibodies
Mechanism of action	Binds to CD22 on the cell surface of B-cells and is internalized, resulting in ADP-ribosylation of elongation factor 2, inhibition of protein synthesis and apoptotic cell death
Route of administration	Intravenous
Pharmacodynamics	Treatment resulted in rapid and sustained depletion of circulating CD19+ cells
Pharmacokinetics	Mean elimination half-life 1.4 h Mean systemic clearance after the first dose of cycle 1 is 25 L/h and after subsequent dosing is 4 L/h
Adverse events in patients with HCL	
Most frequent any-grade TEAEs	Peripheral oedema, nausea, fatigue, headache and pyrexia
Most frequent grade 3 or 4 TRAEs	Decreased lymphocyte count and haemolytic uremic syndrome
Most frequent SAEs	Haemolytic uremic syndrome, pyrexia and capillary leak syndrome
ATC codes	
WHO ATC code	L01X-X (other antineoplastic agents)
EphMRA ATC code	L1X9 (all other antineoplastics)
Chemical name	Recombinant, murine immunoglobulin variable domain genetically fused to a truncated form of Pseudomonas exotoxin, PE38

SAEs serious adverse events, TEAEs treatment-emergent adverse events, TRAEs treatment-related adverse events

## 2.3 Therapeutic Trials

Intravenous moxetumomab pasudotox (0.04 mg/kg on days 1, 3 and 5 every 28 days for  $\leq 6$  cycles) was associated with high rates of independently-assessed durable complete responses in heavily pretreated adults with relapsed/refractory HCL in a pivotal, multicentre, open-label, phase 3 study (NCT01829711;  $n = 80$ ) [10]. Eligible patients had an indication for treatment (i.e. at least one of the following: neutrophils  $< 1.0 \times 10^9/L$ , platelets  $< 100 \times 10^9/L$ , haemoglobin  $< 10$  g/dL or symptomatic splenomegaly) and must have received at least two previous systemic therapies (including two courses of a purine nucleoside analogue or one course of rituximab or a *BRAF* inhibitor following a single prior purine nucleoside analogue course). At a median follow-up of 16.7 months, 30% of patients who received moxetumomab pasudotox had durable complete responses (primary endpoint), i.e. complete response as assessed by blinded independent central review with maintenance of hematologic remission for  $> 180$  days. The objective response rate in moxetumomab pasudotox recipients was 75% and the complete response rate was 41%. The median durations of complete response, progression-free survival (PFS) and haematological remission from complete response were not reached. Of the patients achieving complete responses, the majority (28/33) had achieved the responses by the end-of-treatment assessment. Twenty-seven patients with complete response achieved minimal residual disease (MRD) negativity [as assessed by immunohistochemistry (IHC)], and six patients had relapsed as of data cutoff (four patients had asymptomatic bone marrow relapse and two had loss of haematological remission). The median duration of complete response for the MRD-negative patients was not reached and for MRD-positive patients was 5.9 months [10].

An earlier phase 1, dose-escalation study (NCT00586924) in 28 patients with relapsed/refractory HCL showed that dose-limiting toxicity was not reached with moxetumomab

pasudotox doses of 0.005–0.05 mg/kg every other day for three doses at  $\geq 4$ -week intervals for  $\leq 16$  cycles [13]. Subsequently the 0.05 mg/kg cohort of patients ( $n = 12$ ) was expanded to include 21 additional patients [14]. Patients in the combined 0.05 mg/kg cohort ( $n = 33$ ) received 143 cycles of moxetumomab pasudotox without any dose-limiting toxicity [14]. Complete remission was achieved by 64% of patients in this cohort, with a median duration of remission of 42 months; the overall response rate was 88% [14]. In the 32 patients assessed for MRD by the most sensitive measure of bone marrow aspirate flow cytometry, moxetumomab pasudotox therapy eradicated MRD in  $> 50\%$  (11/21) of patients with complete remission. The median duration of remission in MRD-negative patients was 42 months compared with 14 months in MRD-positive patients ( $p < 0.001$ ) [14]. A retrospective analysis was conducted of data from all patients who received moxetumomab pasudotox 0.005–0.05 mg/kg in this study and were evaluable for blinded independent central pathologist-reviewed MRD response (as assessed by bone marrow IHC;  $n = 37$ ) [15]. Results suggested that a MRD-negative response was associated with a longer duration of complete response (not estimable vs. 13 months;  $p = 0.0002$ ) and longer PFS (not reached vs. 82 months;  $p = 0.0031$ ) than a MRD-positive response (median follow-up 84 and 82 months in patients with MRD-negative and -positive responses) [15].

Another study (NCT00462189) evaluated the MRD response with moxetumomab pasudotox, as assessed by IHC of bone marrow biopsy and flow cytometry of blood and bone marrow aspirate in the expanded cohort of the phase 1 study (NCT00586924) [16]. Of the 46 evaluable patients, 13 achieved elimination of MRD (i.e. 12 of 33 patients who received the 0.05 mg/kg dose and one of three patients who received the 0.04 mg/kg). Resolution of MRD was achieved in a median of 84 days (just prior to cycle 4), and 11 of 13 (85%) patients remained MRD-free for a median of 45 months, with all 13 remaining MRD-free in blood [16].

### Key clinical trials of moxetumomab pasudotox

Drug(s)	Indication	Phase	Status	Location(s)	Identifier	
Moxetumomab pasudotox	Advanced HCL	3	Ongoing (not recruiting)	Multinational	NCT01829711; 130106; 13-C-0106; CD-ON-CAT-8015-1053	MedImmune LLC
Moxetumomab pasudotox	R/R HCL	EAP	Ongoing	NA	NCT03501615; D3143R00002; MOXE	AstraZeneca
Moxetumomab pasudotox	HCL	1	Completed	Poland, USA	NCT00586924; CAT-8015-1001	MedImmune LLC, Cambridge Antibody Technology

EAP early access programme, NA not available

## 2.4 Adverse Events

Moxetumomab pasudotox had a generally acceptable tolerability profile in the pivotal, multicentre, open-label, phase 3 study (NCT01829711;  $n=80$ ) in heavily pretreated adults with relapsed/refractory HCL [10]. The most common (incidence >30%) treatment-emergent adverse events (AEs) with moxetumomab pasudotox were peripheral oedema (39%), nausea (35%), fatigue (34%), headache (33%) and pyrexia (31%). The most common grade 3 or 4 treatment-related AEs with moxetumomab pasudotox were decreased lymphocyte count (8%) and haemolytic uremic syndrome (HUS; 5%); grade 3 or 4 infections were reported in 13 (16%) patients, with infections in two patients considered to be treatment related. Serious AEs occurring at an incidence of  $\geq 5\%$  with moxetumomab pasudotox were HUS (8%), pyrexia (6%) and capillary leak syndrome (CLS; 5%). HUS (four patients), capillary leak syndrome (two patients) and HUS-associated increase in blood creatinine (two patients) were the most common treatment-related AEs that led to discontinuation of therapy. Three deaths reported in the study (pneumonia, septic shock, and sepsis syndrome and underlying HCL) were considered unrelated to therapy. All HUS and capillary leak syndrome events with moxetumomab pasudotox were reversible. Of the 76 evaluable patients, 59% (45/76) of patients receiving moxetumomab pasudotox had ADA at baseline, with the frequency of neutralizing antibodies and ADA titres increasing after repeated treatment cycles. Patients with high ADA titres (>10,000) had reduced exposure to moxetumomab pasudotox [10].

## 2.5 Ongoing Clinical Trials

Ongoing studies of moxetumomab pasudotox include the long-term follow up of the pivotal, multicentre, open-label, phase 3 study (NCT01829711) in heavily pretreated adults with relapsed/refractory HCL and an 'Early Access Programme' to provide access to moxetumomab pasudotox for patients with relapsed/refractory HCL (NCT03501615).

## 3 Current Status

Moxetumomab pasudotox received its first global approval in the USA on 13 September 2018 for the treatment of adults with relapsed or refractory HCL who received at least two prior systemic therapies, including treatment with a purine nucleoside analogue.

## Compliance with Ethical Standards

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**Conflict of interest** During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made

by the author on the basis of scientific completeness and accuracy. Sohita Dhillon is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

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## References

- Kreitman RJ, Arons E. Update on hairy cell leukemia. *Clin Adv Hematol Oncol*. 2018;16(3):205–15.
- Grever MR, Abdel-Wahab O, Andritsos LA, et al. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. *Blood*. 2017;129(5):553–60.
- Getta BM, Park JH, Tallman MS. Hairy cell leukemia: past, present and future. *Best Pract Res Clin Haematol*. 2015;28(4):269–72.
- Kreitman RJ. Immunoconjugates and new molecular targets in hairy cell leukemia. *Hematology*. 2012;2012:660–6.
- AstraZeneca. LUMOXITT™ (moxetumomab pasudotox-tdfk): US prescribing information. 2018. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/761104s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761104s0001bl.pdf). Accessed 4 Oct 2018.
- FDA. FDA approves moxetumomab pasudotox-tdfk for hairy cell leukemia [media release]. 13 Sept 2018. <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm620473.htm>.
- Alderson RF, Kreitman RJ, Chen T, et al. CAT-8015: a second-generation pseudomonas exotoxin A-based immunotherapy targeting CD22-expressing hematologic malignancies. *Clin Cancer Res*. 2009;15(3):832–9.
- Salvatore G, Beers R, Margulies I, et al. Improved cytotoxic activity toward cell lines and fresh leukemia cells of a mutant anti-CD22 immunotoxin obtained by antibody phage display. *Clin Cancer Res*. 2002;8(4):995–1002.
- Kreitman RJ, Pastan I. Antibody fusion proteins: anti-CD22 recombinant immunotoxin moxetumomab pasudotox. *Clin Cancer Res*. 2011;17(20):6398–405.
- Kreitman RJ, Dearden C, Zinzani PL, et al. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. *Leukemia*. 2018;32(8):1768–77.
- Kuruville D, Chia YL, Santiago L, et al. Efficacy and safety of moxetumomab pasudotox (moxe) in adult patients (pts) with relapsed/refractory Hairy Cell Leukemia (HCL) in relation to drug exposure, baseline disease burden, and immunogenicity [abstract no. 7060]. *J Clin Oncol*. 2018;36(15 Suppl).
- Balic K, Standifer N, Santiago L, et al. Pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of Moxetumomab pasudotox (Moxe), an immunotoxin targeting CD22, in adult patients (Pts) with relapsed or refractory Hairy Cell Leukemia (HCL) [abstract no. 7061]. In: 54th annual meeting of the American Society of Clinical Oncology. 2018.
- Kreitman RJ, Tallman MS, Robak T, et al. Phase I trial of anti-CD22 recombinant immunotoxin moxetumomab pasudotox (CAT-8015 or HA22) in patients with hairy cell leukemia. *J Clin Oncol*. 2012;30(15):1822–8.
- Kreitman RJ, Tallman MS, Robak T, et al. Minimal residual hairy cell leukemia eradication with moxetumomab pasudotox: phase 1 results and long-term follow-up. *Blood*. 2018;131(21):2331–4.
- Kreitman R, Tallman MS, Robak T, et al. Negative minimal residual disease associated with extended response to moxetumomab pasudotox in patients with relapsed/refractory hairy cell leukemia: long-term follow-up of bone marrow immunohistochemistry analyses from a phase 1 study [abstract no. 2765]. *Blood*. 2017;130(Suppl 1).
- Kreitman RJ, Arons E, Still K, et al. Moxetumomab pasudotox and minimal residual disease in hairy cell leukemia [abstract no. 7079]. *J Clin Oncol*. 2015;33(15 Suppl).