Research Article

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Cost–utility analysis of mogamulizumab in advanced mycosis fungoides and Sézary syndrome cutaneous T-cell lymphoma

Noemi Muszbek*[,1], Edit Remak[2], Qian Xin[1], Linda McNamara[3] & Trefor Jones[3]

[1]Visible Analytics, Oxford, UK
[2]Visible Analytics, Budapest, Hungary
[3]Kyowa Kirin, Marlow, UK
*Author for correspondence: noemi.muszbek@visibleanalytics.co.uk

Aim: This study assessed the cost–utility of mogamulizumab, a novel monoclonal antibody, versus established clinical management (ECM) in UK patients in previously treated advanced mycosis fungoides (MF)/Sézary syndrome (SS). **Materials & methods:** Lifetime partitioned survival model based on overall survival, next treatment-free survival and the use of allogeneic stem cell transplant was developed. Inputs were from the pivotal MAVORIC trial, real-world evidence and published literature. Extensive sensitivity analyses were conducted. **Results:** Discounted incremental quality-adjusted life years (QALYs), costs and incremental cost–effectiveness ratio were 3.08, £86,998 and £28,233. Results were most sensitive to the survival extrapolations, utilities and costs after loss of disease control. **Conclusion:** Mogamulizumab is a cost-effective alternative to ECM in UK patients with previously treated advanced MF/SS.

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Cutaneous T-cell lymphomas (CTCLs) are a very rare, serious and life-threatening form of non-Hodgkin's lymphoma with profound and debilitating extensive skin and systemic manifestations that severely impact the quality of life of patients when this primary cutaneous malignancy is poorly controlled. To date, once patients require systemic therapies, there remain very few effective and tolerable options and this often means, without newer innovative therapies, recycling previously used treatment options becomes common practice. There are many different sub-types of CTCL: mycosis fungoides (MF) represents 55% of all CTCL cases and the closely related condition of Sézary syndrome (SS) represents approximately 2.5% of cases [1].

Patients with MF, in the early stages of their diseases, will usually have relative minor symptoms, including slightly scaly, itchy patches and/or plaques on the skin (Figure 1) [2,3]. However, for around 30% of MF patients who are diagnosed with advanced disease, the disease can be extremely fatal and debilitating. On the other hand, SS is more aggressive, being the leukemic variant, which also affects a patient's whole body and blood [3]. All SS patients are considered to be at an advanced stage of the disease [4]. SS patients may have lymphadenopathy (enlarged lymph nodes) and may also have thickened, scaly and fissured skin, especially on the palms and soles, causing clear disfigurement, or experience hair loss, changes in their nails or drooping of their eyelids [5]. MF and SS can affect the skin, blood, lymph nodes and viscera [6] and these four compartments of the body are used to assess disease stage and prognosis [7,8]. An updated international global composite response scoring system was published in 2011, that accounted for all four of these potential disease compartments [9].

Between 2009 to 2013, there were 1659 cases of diagnosed CTCL recorded in England, of which 920 were MF and 42 were SS [1]. In advanced disease (stage ≥IIB MF and all SS patients) in the UK, survival is poor, especially from second-line systemic treatments, where overall survival (OS) is 1.5 years (95% CI: 0.9–2.0) with MF and 1.0 year (95% CI: 0.9–not available) with SS [10]. Due to the visible nature of the disease, the intense schedule of

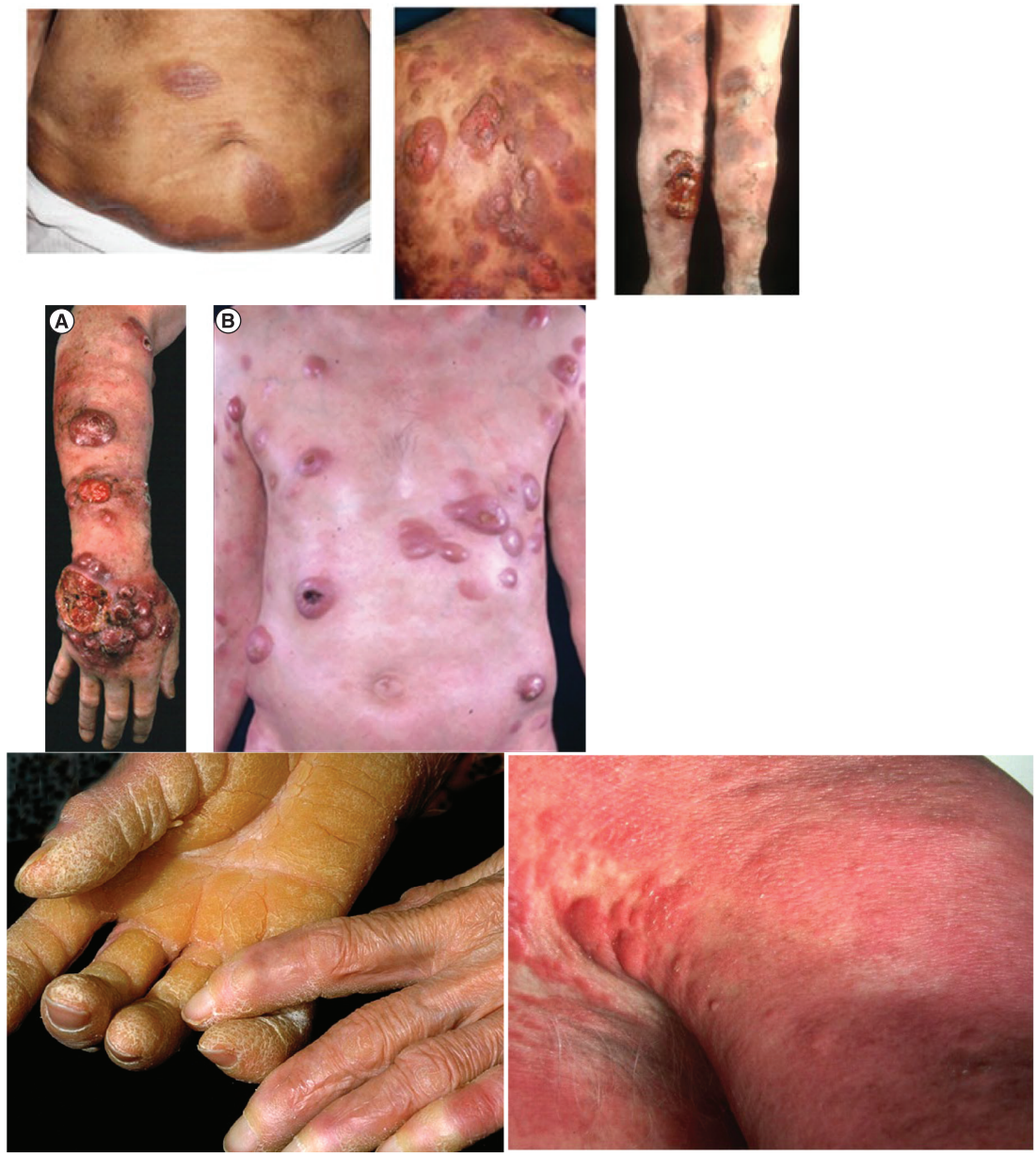

Figure 1. Representative clinical photos of advanced mycosis fungoides and Sézary syndrome.
Reprinted from [1,2,3].

dressings and extensive skin symptoms (noting that skin is largest organ of the body), the impact of MF and SS on both the patients' and the carers' quality of life is very substantial [11–15]. It has been described as 'a traumatic illness, traumatic to witness' [12].

The aim of treatments in MF and SS is to achieve disease control with improved quality of life and thus extend periods of remission and to potentially bridge certain eligible patients onto a curative intent such as allogeneic stem cell transplant (aSCT). Patients with advanced disease have very few effective and tolerable systemic treatment options left, and many treatments are used off-label as a last attempt. In the UK, first-line systemic treatment consists of systemic treatments such as bexarotene, interferon, methotrexate, extracorporeal photopheresis (ECP) and electron beam radiotherapy (EBRT) [16,17]. For patients who progress on or following first line systemic treatment, there are little data on the effects of the limited treatment options. Brentuximab vedotin is an option for CD30 positive advanced MF, primary cutaneous anaplastic large cell lymphoma or SS after at least one systemic therapy [18]; however, the pivotal trial for brentuximab vedotin excluded patients with SS. Additionally, very few SS

patients could be classed as CD30 positive [19]. For advanced MF and SS patients, off-label chemotherapy regimens are used for those whom are clinically ineligible for, or refractory to, treatment with brentuximab vedotin and require another systemic therapy after having cycled through first line treatment options [16,17]. Third-line options are limited to entry into a clinical trial, or a repeat of treatments previously received. For a small proportion of well-performing patients reduced intensity aSCT, which may be associated with a long-term remission in patients with MF/SS, is also an option after complete or good partial response (CR or PR) with minimal tumour burden to previous line of therapy [16].

At the end of 2021, the National Institute for Health and Care Excellence (NICE) recommended mogamulizumab, a first-in-class defucosylated humanized IgG1κ monoclonal antibody, for the treatment of SS in adults who have had at least one systemic treatment and in the treatment of advanced MF in adults if they have had at least two systemic treatments [20]. Similarly, the Scottish Medicines Consortium (SMC), after a full submission assessed under the orphan medicine process, recommended mogamulizumab "for the treatment of patients with advanced MF or SS (stage ≥IIB MF and all SS) following at least one prior systemic therapy, who are clinically ineligible for or refractory to treatment with brentuximab vedotin" [21].

Mogamulizumab (Poteligeo®) is a novel immuno-oncology medicinal product which has orphan designation in the EU [22]. It is a humanized IgG1 kappa immunoglobulin that selectively binds to CCR4, a G-protein-coupled receptor involved in trafficking of lymphocytes to various organs including the skin. Mogamulizumab was granted Promising Innovative Medicine (PIM) designation by the UK Medicines and Healthcare products Regulatory Agency (MHRA) in March 2018 for the treatment of advanced refractory MF and SS [23].

The efficacy and safety of mogamulizumab was assessed in the MAVORIC trial, the largest phase III clinical trial ever conducted in any subgroup of patients with this very rare cutaneous lymphoma. The MAVORIC trial compared mogamulizumab to vorinostat in patients with stage IB to IVB MF or SS who have failed at least one prior therapy [24]. The study design with the comparison to vorinostat was approved by the European Medicines Agency despite vorinostat not having had full regulatory approval in Europe for CTCL. This was so because, a new agent was needed in the efficacy and safety comparison to mogamulizumab to enable ethical recruitment of patients in this rare cutaneous lymphoma who had relapsed and/or refractory to medicines typically used in this population. Significant improvements in progression free survival (PFS) were seen in patients treated with mogamulizumab compared with those treated with vorinostat (HR: 0.53; 95% CI: 0.41–0.69; $p < 0.0001$) [24]. In the advanced population, the advantage of mogamulizumab is even more pronounced (HR: 0.43; 95% CI: 0.31–0.58; $p < 0.0001$) [25]. Additionally, significant improvements have been seen with overall response rate (ORR) using the global composite response scoring system, median time to next treatment (TTNT) and health-related quality of life (HRQoL) with no new safety concerns identified [24–27]. Measurement of an OS benefit was confounded by a high proportion (72.6%) of subjects switching from vorinostat to mogamulizumab and there was no significant difference between the comparators [24].

Economic evaluations are crucial to inform health technology appraisals and support payer and clinical decision making on the 'value' of new treatment options. Therefore, this study evaluates the cost–utility for mogamulizumab versus established clinical management (ECM) in the England and Wales for SS patients who had at least one systemic treatments and stage ≥IIB MF patients with at least of two systemic treatments.

Materials & methods

To assess the cost–effectiveness of mogamulizumab compared with ECM, a cost–utility analyses was conducted from the perspective of the UK National Health Service (NHS) and Personal and Social Services (PSS).

The EMA marketing authorization for mogamulizumab, in line with the inclusion/exclusion criteria of the MAVORIC trial, is 'for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy' [28]. However, in clinical practice in the UK mogamulizumab is likely to be used for advanced patients (stage ≥IIB MF and all SS patients), where there is a greater clinical unmet need with limited treatment options. As SS patients have fewer treatment options few patients being classed as CD30 positive [19], SS patients who had at least one systemic treatments and stage ≥IIB MF patients having received two prior systemic treatments were chosen as the target population.

The economic evaluation compares mogamulizumab to current clinical practice in the NHS (ECM) which comprises several treatments currently in use in England and Wales for patients with relapsed or refractory advanced MF and SS. The composition of the ECM arm was determined based on clinical expert opinion through a short survey and in-depth interviews of leading NHS consultants experienced with the treatment and care of MF and

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Table 1. Composition of the established clinical management arm.

Treatment	Proportion (%)	Treatment schedule and dosing
Methotrexate	15.4	25 mg, one day per week
Bexarotene	23.5	300 mg/m^2 daily
IFN-α-2a† (peginterferon)	19.5	180 mcg once a week
Gemcitabine	7.6	1,000 mg/m^2 on day 1 and 8 of 21-day cycle
CHOP	4.5	Cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 on day 1, prednisolone 40 mg/m^2 on days 1–5 of 21-day cycle
Liposomal doxorubicin	1.5	20 mg/m^2 twice monthly
Etoposide	1.7	120–240 mg/m^2 for five days every month
Prednisolone	10.4	40 mg/m^2 on days 1–5 of 21-day cycle
PUVA	2.4	2 per week for 14 weeks
ECP	12.4	On 2 consecutive days every 28 days
TSEBT	1.1	4 per week for 4 weeks (may be repeated once)

†As IFN-α-2a has been withdrawn from the market and the stores are being used up, it is substituted with pegylated derivatives of IFN-α (peginterferon).
CHOP: Combination of cyclophosphamide, doxorubicin, vincristine and prednisolone; ECP: Extracorporeal phototherapy; PUVA: Psoralen plus ultraviolet A photochemotherapy; TSEBT: Total skin electron beam therapy.

SS patients in an NHS England setting (two consultant in clinical oncology and one dermatology consultant and professor of cutaneous oncology), while treatment schedules and dosing were determined based on the respective marketing authorizations supplemented by expert opinion (Table 1).

Due to the chronic and progressive nature of advanced MF and SS and to reflect all differences in costs and outcomes between mogamulizumab and ECM, the time horizon for the cost–utility analysis was patients' lifetime according to NICE guidelines [29]. Based on prior NICE assessment in MF/SS, lifetime translated to 45 years [18].

Since MF and SS affects the life expectancy (mortality) and quality of life (QoL; morbidity) of patients, a cost–utility analysis (CUA) was undertaken as the primary analysis. In addition, cost–effectiveness analyses were undertaken and took only mortality into account. Thus, health effects were expressed in terms of life years (LYs) and quality-adjusted life years (QALYs) gained.

According to the NICE guideline, an annual discount rate of 3.5% was applied to both costs and health benefits [29]. Due to the short (1 week) cycle length, half-cycle correction was not required.

Model structure

The model structure is based on the standard partitioned survival analysis approach (PartSA). This technique is commonly used in modelling oncology and is appropriate for capturing progressive, chronic conditions which are described with clinical outcomes requiring an ongoing, time-dependent risk, such as progression and death [30,31] and it is in line with prior NICE TA in MF/SS [18].

However, given the novel mechanism of action, two changes were made to the traditional PartSA approach:

- As in MF and SS disease control is crucial, the use of disease control or time to next treatment (TTNT) in place of progression determining the health states;
- Inclusion of the potential for patients to receive the potentially curative treatment of aSCT as seen in the NICE TA577 and the SMC assessment of brentuximab vedotin [18,32] and to reflect UK clinical practice.

Patients can experience benefit from mogamulizumab after stopping treatment and after progression. Compared with PFS, TTNT, another measure of clinical benefit, is more closely aligned with symptoms and disease control and as a result is a better proxy not only for treatment changes, but also for quality of life and resource utilization, thereby, for determining health states.

Bridging to aSCT can happen after good PR with minimal tumour burden or CR in any line of treatment, if the patients are eligible. Accordingly, in the model patients have the potential to receive aSCT after ECM or mogamulizumab after the required washout period [28], and also after subsequent treatments as seen in the MAVORIC trial [24]. aSCT is an important part of the patients' pathway and due to its potential to result in long-term remission, it can have a substantial effect on both costs and health outcomes. Therefore, it is important to include in the cost–utility model.

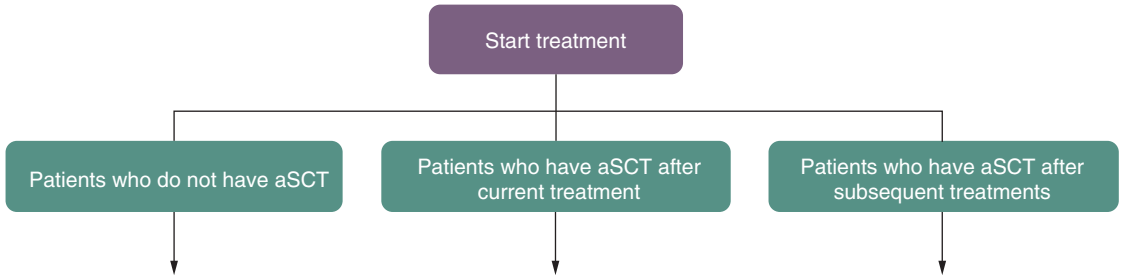

Figure 2. Three parallel model structures for three patient pathways.
aSCT: Allogenic stem cell transplant.

To include aSCT, the economic evaluation comprises of three separate patient pathways represented by three PartSA models running in parallel (Figure 2):

- patients who do not undergo aSCT;
- patients who undergo aSCT after the current treatment; and
- patients who undergo aSCT after subsequent treatments.

In the model, all patients start in the 'Disease control' health state receiving their current treatment (mogamulizumab or ECM) (Figure 3). In any cycle, patients may stop treatment. For those not undergoing aSCT, if the symptoms do not necessitate starting a new treatment immediately, patients may remain in the 'Disease control' health state and enter a treatment-free period, i.e., 'Surveillance' health state or can. Eventually patients require subsequent therapies including symptomatic care and increased monitoring due to the progression of their disease. The last 6 months of life, were also tracked separately to account for the increase in resource utilization [33] and reduction in quality of life. Patients may die at any time point.

Patients who undergo aSCT after their current treatment, receive their current treatment until a prespecified time point when they are scheduled to receive aSCT. Patients in the mogamulizumab arm require a 50-day wash-out period [34], therefore the aSCT was assumed to take place 7 weeks after treatment discontinuation. No such wash-out period was required for patients in the ECM arm. After aSCT, patients may experience a disease-free period, or they may relapse. Patients may also die at any time point following their aSCT.

Patients who undergo aSCT after a subsequent treatment follow a similar pathway to reach the 'Subsequent treatment' health state as those who do not undergo aSCT. At a prespecified time-point all patients in the model move to the aSCT health state. After aSCT, patients may experience a disease-free period, or they may relapse.

Model inputs

Efficacy & safety inputs

Efficacy inputs were based on the MAVORIC pivotal trial. As vorinostat is not part of the UK clinical practice, indirect comparison of mogamulizumab to current UK clinical practice is required. As due to the rare nature of MF and SS and the off-label treatment use, limited data is available in this patient population, hence, no network was available for indirect comparison.

To reduce the uncertainty stemming from the limited data, two different approaches were employed:

- Naive and conservative indirect comparison was conducted using published trial data; and
- Real-world evidence (RWE) external control arm of current UK clinical practice, details of which are presented elsewhere [35].

For the indirect comparison only one RCT, the ALCANZA trial comparing brentuximab vedotin to physicians' choice (oral methotrexate or oral bexarotene) [36] was identified for this target patient population. However, there were important differences in the inclusion and exclusion criteria between the two trials (e.g., CD30 positivity and in terms of inclusion of patients with SS, high blood tumour burden and primary cutaneous anaplastic large cell lymphoma) and the MAVORIC trial included a more severe population (e.g., more heavily pretreated, more advanced patients with higher disease burden according to ECOG) [24,36].

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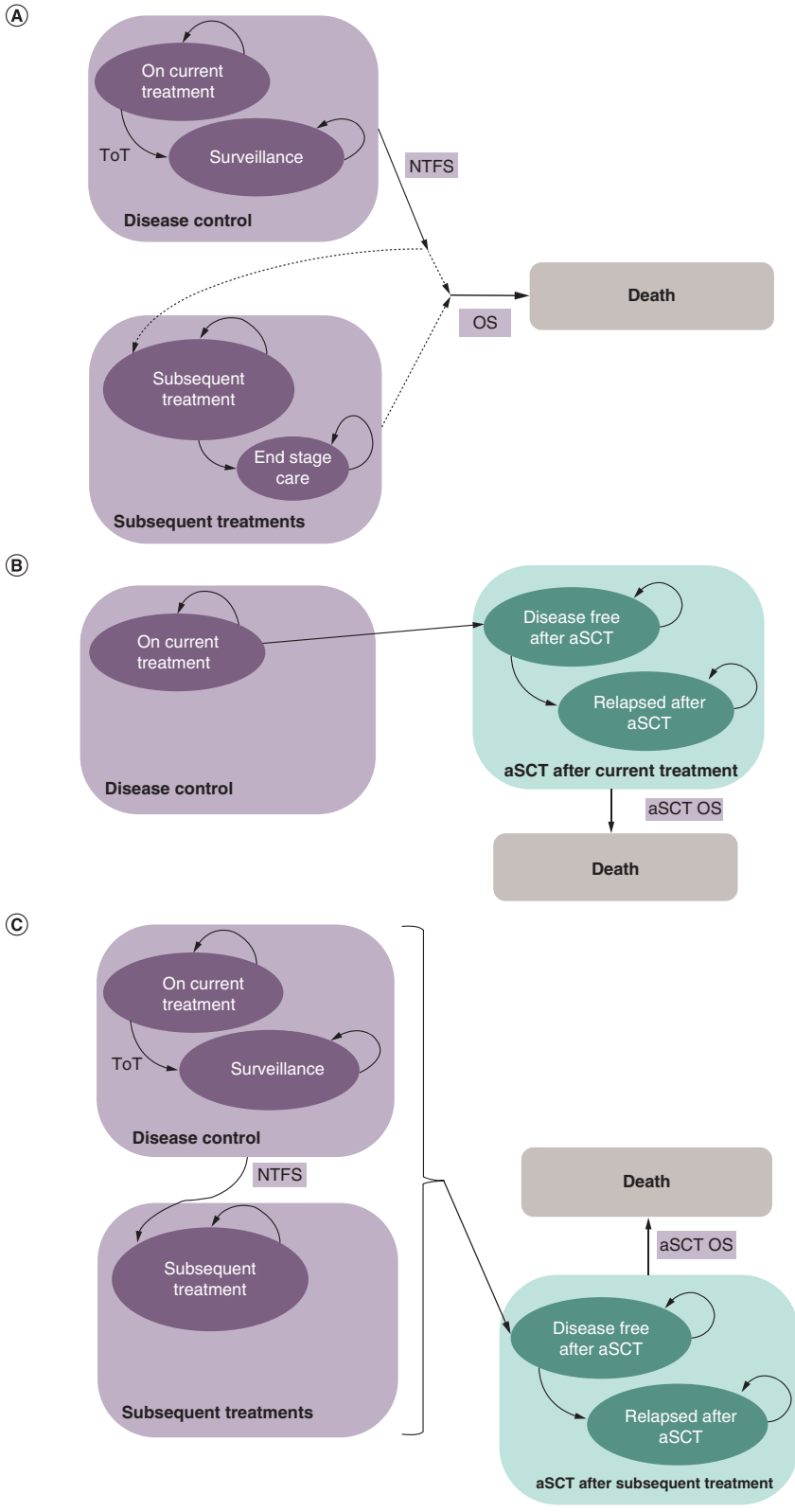

Figure 3. Model structure. (A) Model schematic for patients who do not have aSCT. **(B)** Model schematic for patients undergoing aSCT after their current treatment. **(C)** Model schematic for patients undergoing aSCT after a subsequent treatment.
aSCT: Allogenic stem cell transplant; NTFS: Next treatment-free survival; OS: Overall survival; ToT: Time on treatment.

As a result, for PFS and skin response a naive comparison between vorinostat and physician's choice arm was considered as informative, accounting for the differences in the patient populations. Comparison of OS was not appropriate given the differences in the crossover rates (46% in the ALCANZA trial and 73% in the MAVORIC trial) [18,24]. The PFS curves from the two trials overlapped with a HR of 1.05 (95% CI: 0.76–1.46) (Figure in web appendix). Due to the differences in assessment schedules in MAVORIC and ALCANZA trials in blood assessments, an analysis of ORR was conducted only using response derived using skin assessments. This comparison showed no statistically significant difference (RR: 0.72; 95% CI: 0.35–1.49). Since the vorinostat arm resulted in the same PFS in a population with a worse prognosis – as the physician's choice arm in a population with better prognosis – the results for PFS and ORR are likely to underestimate the relative efficacy of vorinostat due to the differences in patient populations. This analysis was supplemented by non-RCT evidence [37], where bexarotene demonstrated a similar response rate to vorinostat in the skin compartment.

In conclusion, while vorinostat is not approved in Europe, it is a reasonable and ethical comparator option in this heavily pre-treated population, who have a rare hematological malignancy and are already refractory to the limited standard agents and appears comparable to the options used from second line systemic treatments.

To adjust for the treatment switching in the MAVORIC trial, three methods were considered [38]. Predicted survival for the MAVORIC control arm, post-crossover adjustment, was validated using the HES data, published observational data and survey to inform the selection of the appropriate methods for adjustment. Based on an assessment of assumptions and validation, the inverse probability of censoring weighting method was considered the most appropriate resulting in an OS HR of 0.42 (95% CI: 0.18–0.98) for mogamulizumab versus vorinostat [38].

In the use of RWE comparator arm, mogamulizumab was directly compared with UK clinical practice, represented by data from 2009–2019 in the Hospital Episode Statistics (HES) database, an administrative dataset that includes all MF/SS patients treated in secondary care in NHS England [10]. To ensure populations from the HES database and the MAVORIC trial are similar an unanchored indirect comparison has been conducted.

The patient populations were matched using seven potential prognostic factors and/or treatment modifiers according to NICE guideline [39]. These included diagnosis, number and type of prior systemic therapies and disease stage used to select the HES population to align with the MAVORIC trial inclusion criteria and age, sex, disease sub-type used to reweight the mogamulizumab arm was to reflect the selected patient population in the HES database. The resulting HRs were 0.36 (0.24–0.53) and 0.38 (0.25–0.59) depending on the inclusion of age and sex in the matching, showing a clear advantage for mogamulizumab compared with current clinical practice. Further details are available in Hawkins *et al.* [35].

This approach provides a direct comparison of mogamulizumab against current UK clinical practice represented by RWE, reflects the current UK MF/SS population and does not require any adjustment for treatment switching with its attendant uncertainties as no patients in current clinical practice received mogamulizumab.

Time-to-event data used in the model included:

- OS, next-treatment-free survival (NTFS) and time on treatment (ToT) for patients not receiving aSCT were based on patient level data from the MAVORIC trial data for patients with advanced disease. However, patients receiving aSCT have longer survival and only one patient who underwent aSCT died during the trial follow-up period, resulting in informative censoring. Therefore, patients who have received aSCT were excluded from the OS analysis. NTFS is defined as time from randomisation to the start of next treatment or death.
- In the RWE comparator arm matched MAVORIC trial data was used for mogamulizumab excluding patients who have received aSCT and HES data for ECM. It was not possible to exclude patients who have received aSCT in the HES data, therefore the synthetic comparator arm overestimates OS for patients not receiving aSCT, as it includes the mortality benefit of aSCT.
- Disease-free survival (DFS) and OS for patients undergoing SCT were based on real-world data from the London supra-regional centre using the minimal intensity Stanford Protocol in the NICE TA577 [18]. The DFS and OS KM curves were digitalized (using GetData software) [40] and standard parametric survival models were fitted to the derived pseudo-patient-level data [18].

In line with guidance from NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 [41], six alternative parametric model structures were used to capture and extrapolate data for OS and NTFS: exponential, generalized gamma, Gompertz, Weibull, log-logistic, log-normal [41]. TTE analyses were conducted in R: KM plots were produced using 'survminer' package [42]. The package "flexsurv" was used for parametric survival analysis [43].

For each outcome, it was assessed whether treatment effect was best captured using a treatment arm covariate in a single parametric model (a "joint" model), or by separate ("independent") models fitted to each treatment arm. Visual inspection of KM data and diagnostic plots were used, with consideration of the different implicit assumptions of modelling treatment effect as a covariate across different parametric models.

Selection of the base case parametric model for each TTE outcome was based on standard criteria, following Technical Support Document (TSD) 14:

- Objective statistical measures of goodness of fit to observed KM data: Akaike information criterion (AIC) [44] and Bayesian information criterion (BIC) statistics [45];
- Visual inspection of goodness of fit to observed KM data;
- Visual inspection of diagnostic plots, including log cumulative hazard plots, Schoenfeld residuals plot and quantile-quantile plot;
- Additionally, similarly to the crossover adjustment, the clinical plausibility of OS extrapolations beyond observed KM data was explored, comparing predictions with the different models to three alternative sources of data:
- Published observational data;
- HES data;
- Clinical expert survey.

As ToT Kaplan–Meier curves were complete no extrapolation was required and the Kaplan-Meier estimates were used directly in the cost–effectiveness model. NTFS data is almost complete; therefore, all fits were close to one another. For the vorinostat arm log-logistic models provide the best statistical fit according to AIC/BIC statistics, while for the mogamulizumab arm, the log-normal model provides the best fit. Therefore, these were selected as the base case. (Tables of AIC/BIC, graphs of fitted curves available in the Supplementary data.)

For mogamulizumab OS the statistically best fitting exponential curve provided a good fit visually and was clinically plausible. Therefore, it was chosen to be the base case for mogamulizumab. For ECM OS an exponential model provided the best fit in both the crossover adjusted data from the MAVORIC trial and the HES-based comparator arm, based on goodness-of-fit statistics, visual inspection of the goodness-of-fit to observed KM data, diagnostic plots and clinical plausibility [38]. The two approaches for estimating OS for the ECM arm led to very similar results, reducing the inherent uncertainty of each of these methods. For DFS and OS after aSCT, the lognormal model provided the best fit.

The MAVORIC trial was designed to treat to progression. As a result, its protocol did not allow did not allow patients to receive aSCT prior to progression, only after subsequent treatment. 8.1% of patients received aSCT in the after progression in the mogamulizumab arm and 2.0% in the vorinostat arm, at 81 weeks and 67 weeks, respectively. In UK clinical practice represented by the HES data, patients receive aSCT after second line treatment also. Based on the clinical expert survey 8.0% of mogamulizumab and 4.6% of ECM patient would receive aSCT after current treatment. This was included in scenario analysis. Timing of aSCT after ECM is assumed to be 18 weeks after treatment initiation and, after mogamulizumab treatment, 18 weeks and an additional 7 weeks of washout period, same assumption used in the brentuximab vedotin NICE appraisal [18].

Adverse events (AEs) were taken from the safety population of the MAVORIC trial assuming the same rate of events for ECM as for the vorinostat arm. Only grade 3 and 4 AEs were assumed to have important impact on the costs and quality of life.

Utilities

Patient utilities were collected in the MAVORIC trial with the help of the Euroqol 5 dimension, 3 level (EQ-5D-3L) questionnaire. Mean utility values were estimated for both Disease control (mogamulizumab arm: 0.773, ECM arm: 0.762) and Subsequent treatment health states (for both comparators: 0.682). For the subsequent treatment health state mean values measured at the last observation post-progression in the mogamulizumab arm of the MAVORIC trial were applied, as values in the comparator arm also include the impact of cross-over to mogamulizumab. End stage utilities for the last 6 months of life and post aSCT were from the brentuximab vedotin NICE appraisal [18].

Given the caregiver burden associated with CTCL, there is a strong argument for considering caregiver burden in the assessment of any new treatment. This is particularly important as mogamulizumab can delay or prevent patients reaching the most advanced stages of the disease, when the caregiver burden is greatest [15]. Carer utilities are

available for second- and third-line treatment (0.559 [95% CI: 0.511–0.607] and 0.366 [95% CI: 0.322–0.411], respectively) [15].

There are no gold standard ways to apply carer utilities. If carer utilities are only accounted for while the patient is alive, it would confer a survival benefit on to carers too, which would be methodologically incorrect. If carer utilities were to be accounted for even after the patient's death, due to the rebound in utility values, then treatments where patients die earlier would be deemed more beneficial, which raises ethical questions. Therefore, a conservative approach was used including only the incremental difference between caring for a patient in second line of treatment versus caring for a patient in third line of treatment (utility value of 0.559–0.366 = 0.193) only for carers for mogamulizumab patients and only for the incremental time-period spent by patients in the mogamulizumab arm versus the ECM arm in the disease control health state. Carer utilities were included in scenario analysis according to NICE guidelines [29].

Cost & healthcare resource

To reflect the perspective of NHS and PSS, only direct medical costs were included. All costs were estimated to be £20,119 GBP. Health state costs included inpatient and outpatient costs from the HES database [10,33] and community-based costs based on the previous NICE appraisal (TA577) in MF/SS [18]. Drug acquisition costs were taken from publicly available databases (British National Formulary [BNF] and the Drugs and pharmaceutical electronic market information tool [eMIT]) and included a patient access scheme (PAS) for mogamulizumab [46,47]. Dosing was based on the EMA European public assessment reports (EPARs) and BNF where label was available and clinical guideline and clinical expert survey for drug used off-label [18,46,48–52].

For mogamulizumab wastage with dose banding was included. This is used by NHS England for monoclonal antibodies and allows a 10% discrepancy in the administered dose. Therefore, patients whose required dose is less than 10% higher than the dose available in a given number of vials, can still receive only those vials without the need to open a new vial. For patients above the 10% limit, a new vial would be opened, leaving some of the contents unused and discarded.

Due to lack of data for the treatments in the ECM arm, the mean dose intensity reported during the randomized treatment period of MAVORIC (97.5%) for mogamulizumab was used for both treatment arms [53].

Administration costs were taken from the NHS reference costs [54] and AE costs were from previous NICE TAs [55–58]. The costs of aSCT was estimated as the weighted average of three NHS Reference Costs Total HRGs (SA38A, SA39A and SA40Z) [54], while the follow-up costs, £43,706.81, for 2 years was from NICE TA567 [56] and inflated to 2018/2019 [59]. The costs of treatments after aSCT were estimated based on NICE TA577 [18]. Subsequent treatments were based on clinical expert survey. Table 2 summarizes all the model inputs and sources.

Sensitivity analyses

One way sensitivity analysis was performed where each input with parameters uncertainty was varied according to its 95% CI or standard error, while holding all other parameters constant. Where the published study or source for parameter values did not report standard errors or *CIs*, 20% variation of the mean was assumed. Unit costs and resource use for non-drug resources were not independently varied, but as health state costs. Parameters were ordered to show to which the results were most sensitive to.

Probabilistic sensitivity analysis (PSA) was performed to account for variability in outcomes due to parameter uncertainty. The probabilistic analyses were run for 1,000 replications where parameter estimates were repeatedly sampled from probability distributions to determine an empirical distribution for costs, LYs and QALYs. NTFS, OS, ToT, disease-free survival (DFS) for aSCT, probabilities, costs and utilities were varied simultaneously and independently of each other.

Scenario analyses were conducted to test the robustness of the model considering the structural and methodological uncertainties. Scenarios assessed included:

- The use of the other best fitting parametric model, log-normal for the extrapolation of OS.
- Inclusion of aSCT after current treatment to reflect current clinical practice seen in both the HES data and in clinical expert interviews. Based on clinical expert survey, aSCT was assumed to be given to 8.0% of patients after mogamulizumab taking into account the required washout period [28] and to 4.6% of patients after ECM. Based on the previous NICE appraisal in MF/SS, patients on average receive aSCT at 18 weeks after treatment initiation.

Table 2. Summary of variables applied in the economic model.

Variable	Value (reference to appropriate table or figure in submission)	Ref.
Patient characteristics		
Mean age	63.04 years	MAVORIC trial
Mean body surface area	1.91 m^2	MAVORIC trial
Mean body weight	76.77 kg	MAVORIC trial
Female proportion of patients	41.9%	MAVORIC trial
Use of aSCT		
% receiving aSCT after subsequent treatment to mogamulizumab	8.1%	MAVORIC trial
% receiving aSCT after subsequent treatment to ECM	2.0%	MAVORIC trial
Timing of aSCT after subsequent treatment to mogamulizumab	81 weeks	MAVORIC trial
Timing of aSCT after subsequent treatment to ECM	67 weeks	MAVORIC trial
Survival curves		
DFS after aSCT	Log-normal distribution	Best clinical and statistical fit, NICE TA577
OS after aSCT	Log-normal distribution	Best clinical and statistical fit, NICE TA577
ToT for mogamulizumab	Kaplan-Meier curve from MAVORIC trial	MAVORIC trial
ToT for ECM	Kaplan-Meier curve from MAVORIC trial	MAVORIC trial
OS for mogamulizumab excluding aSCT patients	exponential distribution	Best clinical and statistical fit from MAVORIC trial
OS for ECM excluding aSCT patients	exponential distribution	Best clinical and statistical fit from HES database / MAVORIC trial
NTFS for mogamulizumab	Log-normal distribution	Best clinical and statistical fit from MAVORIC trial
NTF for ECM	Log-logistic distribution	Best clinical and statistical fit from MAVORIC trial
Utilities		
Utilities for Disease control –Mogamulizumab arm	0.773	EQ-5D data from the MAVORIC trial
Utilities for Disease control – ECM arm	0.762	EQ-5D data from the MAVORIC trial
Utilities for subsequent treatment	0.682	EQ-5D data from the MAVORIC trial
Utilities for End stage care	0.38	Swinburn *et al.* (2015)
Post-aSCT utilities	0–2 weeks: 0.42 3 weeks-month 4: 0.60 3 months onwards: 0.77	Van Agthoven *et al.* (2001)
Carers' utilities	Disease control: 0.559 Subsequent treatment: 0.366	Williams *et al.* (2020)
Costs		
Comparator drug costs (per cycle)	£0.39 for methotrexate to £537.55 for TSEBT	BNF, eMIT
Administration costs (per administration)	£141, £229 and £286	NHS Reference costs
Health state costs (per cycle)	Disease control: £195.07 Subsequent treatment: £197.61 End stage care: £889.99 Monitoring post aSCT relapse: £197.61	HES data and literature
Grade 3 and 4 adverse event costs (per cycle)	Mogamulizumab: £4.81 ECM: £15.88	Costs from literature and probabilities from the MAVORIC trial
Subsequent treatment costs (total)	£13,184.79	Clinical expert opinion, BNF, eMIT
Subsequent treatment costs after aSCT (total)	£5,405.07	Literature

aSCT: Allogenic stem cell transplant; BNF: British National Formulary; DFS: Disease-free survival; ECM: Established medical management; HES: Hospital Episode Statistics; NTFS: Next-treatment-free survival; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; OS: Overall survival; ToT: Time-on-treatment.

Table 3. Cost–utility analysis base case results including confidential patient access schemes for mogamulizumab.

Technologies	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
ECM (based on HES data)	2.46	1.60	£86,998	4.38	3.08	£28,233
Mogamulizumab	6.85	4.68				
ECM (based on MAVORIC data)	2.46	1.59	£79,487	2.83	2.04	£38,888
Mogamulizumab	5.28	3.63				

ECM: Established medical management; HES: Hospital Episode Statistics; ICER: Incremental cost–effectiveness ratio; LYG: Life year gained; QALY: Quality-adjusted life year.

Table 4. Scenario analyses.

Parameter	Scenario analysis	Base case	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base case			**£86,998**	**3.08**	**£28,233**
OS extrapolation	Lognormal for both treatment arms	Exponential for both treatment arms	£94,773	3.53	£26,859
aSCT after current treatment	Included to reflect clinical practice	Excluded	£87,475	3.19	£27,383
Caregiver utilities	Included	Excluded	£86,998	3.20	£27,150
PFS-based analyses	Use of PFS and OS to determine health states	Use of NTFS and OS to determine health states	£87,001	2.91	£29,871
Population	2nd line MF/SS	3rd line MF and 2nd line SS	£84,664	2.73	£30,981

aSCT: Allogenic stem cell transplant; ECM: Established medical management; ICER: Incremental cost–effectiveness ratio; MF: Mycosis fungoides; NTFS: Next-treatment-free survival; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life year; SS: Sézary syndrome.

- The inclusion of caregiver utilities to account for the burden on carers based on Williams *et al.* [60]. There are no gold standard ways to apply carer utilities. If carer utilities are only accounted for while the patient is alive, it would confer a survival benefit on to carers too, which would be methodologically incorrect. If carer utilities were to be accounted for even after the patient's death, due to the rebound in utility values seen in Williams *et al.* [60], treatments where patients die earlier would be deemed more beneficial, which opens up ethical questions. Therefore, in the evaluation a carer utility gain was included in the value of the incremental difference between caring for a patient in second line of treatment versus caring for a patient in third line of treatment (utility value of 0.559–0.366 = 0.193) only for carers for mogamulizumab patients and only for the incremental time-period spent by patients in the mogamulizumab arm versus the ECM arm in the disease control health state.
- Use of the gold standard of progression-free survival instead of NTFS; and
- Including patients with only one prior systemic therapy for both advanced MF and SS.

Results

In the base case, mogamulizumab results in a discounted incremental QALY gain of 3.08 years compared with the HES-based synthetic ECM arm and 2.83 compared with the MAVORIC trial-based ECM arm (Table 3). Including the confidential PAS, due to the increased disease management costs due to the longer life expectancy and the mostly cheaper generic comparator treatments, mogamulizumab was associated with an incremental cost of £86,998 and £79,487 compared with the HES-based and MAVORIC-based ECM arms respectively, resulting in ICERs of £28,233 and £38,888 per QALY gained.

The one-way sensitivity analyses showed that the results are most sensitive to OS extrapolations, the utility and cost for the 'Subsequent treatment' health state and mogamulizumab costs. The probability of mogamulizumab being cost-effective at the £30,000/QALY threshold is 68.3%, while at the £50,000/QALY threshold 99.8% compared with the HES-based ECM arm (Figure 4). The scenarios assessed resulted in only minor changes (Table 4).

Discussion

MF and SS are two subtypes of CTCL [1]. CTCL is a rare cutaneous lymphoma that is serious, debilitating and life-threatening, with a very high disease burden and high unmet need [2,4,16].

Mogamulizumab (Poteligeo®) is a novel immuno-oncology medicinal product which has orphan designation in the EU [22] approved by the European Commission for the treatment of adult patients with MF/SS who

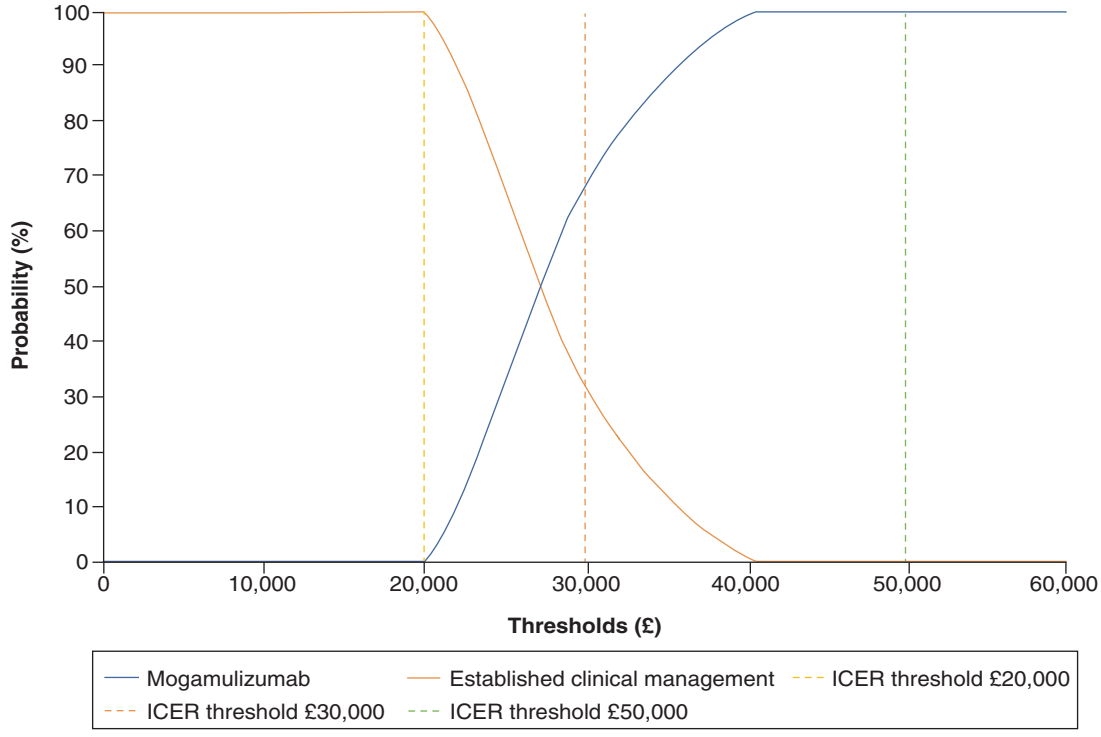

Figure 4. Cost–effectiveness acceptability curves.
ICER: Incremental cost–effectiveness ratio.

have received at least 1 prior systemic therapy [28]. Mogamulizumab was granted Promising Innovative Medicine (PIM) designation by the MHRA in March 2018 [23]. In the MAVORIC trial, mogamulizumab compared with vorinostat has demonstrated improved efficacy in all key areas of disease management, including PFS, OS, TTNT and HRQoL, compared with vorinostat in adults with advanced MF/SS who have received at least 1 prior systemic therapy [24].

A flexible, transparent cost–utility model was developed based on the pivotal, MAVORIC trial using the standard partitioned survival analysis approach, incorporating the possibility of patients receiving aSCT, the only potentially curative treatment, as seen in the MAVORIC trial and in previous NICE appraisal in MF/SS [18]. Due to its unique mechanism of action, disease control or TTNT was used in place of progression determining the health states, i.e., NTFS was incorporated instead of PFS. The model compared mogamulizumab to the ECM in a subpopulation, that is in line with clinical practice and has the highest unmet need, SS patients who had at least one systemic treatment and stage ≥IIB MF patients with at least two systemic treatments were chosen as the target population, who are ineligible or refractory to brentuximab vedotin.

While vorinostat is not approved in Europe, it is a reasonable and conservative representative of the currently used treatment options based on naive indirect comparisons. Given the very limited data in this orphan population from the literature, as also mentioned by the NICE Evidence Review Group (ERG), this indirect comparison has important uncertainties [61]. To reduce this uncertainty, an alternative approach has been used, which compared mogamulizumab to UK clinical practice using RWE from the HES database. The HES database represents all MF/SS patients treated in NHS England secondary care from 2009 to 2019 can be used as a RWE ECM arm after adjusting for differences in the MAVORIC and HES populations.

In the base case, mogamulizumab results in a discounted incremental QALY gain of 3.08 years compared with the HES-based synthetic ECM arm and 2.83 compared with the MAVORIC trial-based ECM arm. Incremental costs were £86,998 and £79,487, respectively. The higher costs were due to the increased disease management costs of the longer life expectancy with mogamulizumab and the mostly cheaper generic comparator treatments. This led to ICERs of £28,233 and £38,888 per QALY gained. Results were robust in scenario analyses and were most

sensitive to OS extrapolations, the utility and cost for the 'Subsequent treatment' health state and mogamulizumab costs.

As with all models, especially those for orphan populations, there are important uncertainties. As a rare disease, there is only a small patient population. This fact goes hand in hand with significant challenges to gather data in a scientifically robust way and hence address all possible questions and uncertainty. Despite such challenges in patient numbers, the pivotal clinical trial investigating mogamulizumab, the MAVORIC study, is the largest clinical trial ever conducted in any subgroup of patients with CTCL and it is the first phase III trial to include patients with SS.

Additionally, multiple additional steps were taken to reduce these uncertainties where possible. To reduce the uncertainty regarding the OS for the ECM arm, two different approaches based on clinical trial data (MAVORIC trial) and real-word evidence (HES data) were implemented. These led to very similar results, reducing the inherent uncertainty of each of these data sources. The HES data also provided understanding of the significant reduction in overall survival from diagnosis to the start of second-line treatment [10]. According to clinical experts, during the NICE appraisal process, the "HES data is very important: it provides the first 'real world' data that provide information on survival from second line treatment" [62]. As a result, NICE stated "that the HES data provide the best available source of evidence" and was consequently used as the basis of the NICE guidance [20,62].

Using an unanchored comparison with RWE carries uncertainty. While all available prognostic factors and treatment effect modifiers were accounted for either in the patient selection (diagnosis, number and type of prior systemic therapies and disease stage) or in the matching (age, sex and disease subtype), there might be potential other factors that were not reported in both HES and MAVORIC datasets. This is an inherent uncertainty with any database, especially RWE which are not expected to record patient characteristics as extensively as clinical trials. The NICE Appeal Panel "judged that the company had taken a thoughtful and reasonable approach to attempting to match the HES data to data from the MAVORIC trial" [62]. This was echoed by the NICE Final Appraisal Determination (FAD), which emphasized, that while there were uncertainties, "it was unlikely that these could have been addressed" [20].

Multiple addition studies were conducted to reduce the data gaps highlighted in the previous NICE technology appraisal in MF/SS [18]. A retrospective cost study was conducted in the HES database to provide a more reliable health state costs [10,33], a vignette study was done to estimate the carers' burden, a short clinician survey filled any additional data gaps, such as the probability of aSCT after current treatment and provided validation for long-term survival estimates.

The clinical plausibility of the survival extrapolations was explored using published observation data [4,7,63,64], the HES database and clinical expert input using multiple in-depth interviews with leading NHS consultants experienced with the treatment and care of MF and SS patients in an NHS England setting. This later also included extensive validation of model structure, assumptions, inputs and generalizability to the UK patient population. Conducting extensive sensitivity analyses, including parameter and structural sensitivity analyses assessed the impact of uncertainty.

Additionally, conservative base case was adopted with not including carer utilities, the exclusion of aSCT after current treatment despite it being clinical practice as seen in HES data and expert survey. Using this base case, the HES-based ECM included effect of aSCT after current treatment, while the mogamulizumab arm excluded this.

These efforts resulted in a model, where, despite the uncertainties, the results were stable with the ICERs of almost all scenarios and one-way sensitivity analyses falling between £26,859 and £38,888 per QALY. Only clinically implausible scenarios have ICERs outside this range. Commentary on the interim results has been published by the NICE ERG in a non-peer reviewed publication and subsequent Erratum [65,66]. However, the criticism was based on the interim base case using the MAVORIC-based comparison and not the final HES-based comparison recommended by both the clinical experts and the NICE Appeal Committee. Additionally, it has used data, assumptions and descriptions that were subject to appeal at the time. This commentary described a prior recommendation not recommending mogamulizumab [66], however a subsequent NICE Appeal Decision upheld multiple appeal points (including the use of incorrect survival data from diagnosis rather than from the target population of 2nd line systemic treatment) and recommended the revision of the guidance and the use of the HES data [62]. Based on this model and the HES data, mogamulizumab is now recommended by NICE and SMC in the UK [21,67].

Additional methodological research and consensus into implementation of carer utilities and further RWE for community-based disease management costs would further strengthen the analysis.

Conclusion

In a rare disease with a high unmet need and high disease burden, using conservative approaches, mogamulizumab is cost-effective compared with current clinical practice based on the HES database and the ICER is around the NICE threshold in all plausible scenarios using trial-based indirect comparisons. In rare diseases, such as MF/SS, where there is a paucity of data and no single standard of care, the use of RWE can be essential when assessing the value of new treatments. In estimating the cost–effectiveness of mogamulizumab, instead of extrapolating evidence from diagnosis, the use of the HES data provided crucial information on the survival of patients receiving standard of care from second line onwards and increased our understanding of advanced MF and SS. Additional methodological research and consensus into implementation of carer utilities and further RWE for community-based disease management costs would further strengthen the analysis.

Summary points

- Mycosis fungoides and Sézary syndrome are rare, serious, debilitating and life-threatening cutaneous lymphomas with a very high disease burden and high unmet need.
- Mogamulizumab (Poteligeo®), a novel immuno-oncology medicinal product with orphan designation in the EU, is approved for the treatment of adult patients with mycosis fungoides and Sézary syndrome who have received at least 1 prior systemic therapy.
- In the MAVORIC trial, both in the intention-to-treat and the advanced populations, mogamulizumab has demonstrated improved efficacy compared with vorinostat in adults with mycosis fungoides and Sézary syndrome who have received at least 1 prior systemic therapy.
- A flexible, transparent cost–utility model with partitioned survival analysis approach was developed to assess the cost–utility of mogamulizumab versus current clinical practice in UK patients in previously treated advanced mycosis fungoides and Sézary syndrome.
- The model incorporated the possibility of patients receiving aSCT, the only potentially curative treatment, as seen in the MAVORIC trial, real-world evidence and in previous NICE appraisal in mycosis fungoides and Sézary syndrome.
- Due to its unique mechanism of action, disease control or next-treatment-free survival was used in place of progression determining the health states.
- As the trial comparator, vorinostat, is not available in the UK and there is no standard of care treatment, real-world evidence from the Hospital Episode Statistics data representing all mycosis fungoides and Sézary syndrome patients treated in NHS England secondary care in 2009–2019 was used as the comparator arm after adjusting for differences in the trial and real-world populations.
- Discounted incremental quality-adjusted life years (QALYs) and costs were 3.08 and £86,998 respectively, resulting in an incremental cost–effectiveness ratio of £28,233/QALY.
- Mogamulizumab is a cost-effective alternative to current clinical practice in UK patients with previously treated advanced MF/SS and was recommended both by the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC).
- In orphan diseases, where there is a paucity of data and no standard of care, the use of real-word evidence can be essential when assessing the value of new treatments.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0028

Author contributions

N Muszbek has led the conception, design of the model, interpretation of results and drafting of the paper and was involved in the analysis of data. She is responsible for the final approval of the version to be published and agrees to be accountable for all aspects of the work. E Remak has led the programming of the model and was involved in conception, design of the model, interpretation of results, analysis of data, drafting of the paper. E Remak agrees to be accountable for all aspects of the work. Q Xin worked on the collection of data, programming and was involved in the analyses, interpretation of results and the drafting of the paper. She agrees to be accountable for all aspects of the work. L McNamara and T Jones were involved in the conception, design of the model, interpretation of results and the drafting of the paper. L McNamara and T Jones agree to be accountable for all aspects of the work.

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This study was funded by Kyowa Kirin. N Muszbek, E Remak and Q Xin are partners/employees of Visible Analytics Ltd, which developed this model, conducted this survey and received consultancy fees from Kyowa Kirin. L McNamara and T Jones are employees of Kyowa Kirin. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

No ethical disclosure was needed, as no data relating to humans or animals were collected.

Data sharing statement

The authors certify that this manuscript reports the secondary analysis of the MAVORIC trial data that have been shared with them and the Hospital Episode Statistics data that was shared in aggregate format, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt.

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