Olaratumab in Combination with Doxorubicin for Treatment of Advanced Soft Tissue Sarcoma: an Evidence Review Group Perspective of a National Institute for Health and Care Excellence Single Technology Appraisal

Running heading: Olaratumab with Doxorubicin for Advanced Soft Tissue Sarcoma

Irina A. Tikhonova[1,3], Tracey Jones-Hughes[1], James Dunham[1], Fiona C. Warren[1], Sophie Robinson[1], Peter Stephens[2], Martin Hoyle[1]

[1] Peninsula Technology Assessment Group (PenTAG), Exeter, UK

[2] Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

[3] Phone: (+44)07508540174

Abstract

The manufacturer of olaratumab (Lartruvo®), Eli Lilly & Company Limited, submitted evidence for the clinical and cost-effectiveness of this drug, in combination with doxorubicin, for untreated advanced soft tissue sarcoma (STS) not amenable to surgery or radiotherapy, as part of the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal process. The Peninsula Technology Assessment Group, commissioned to act as the Evidence Review Group (ERG), critically reviewed the company's submission. Clinical effectiveness evidence for the company's analysis was derived from an open-label randomized control trial, JGDG. The analysis was based on a partitioned survival model with a time horizon of 25 years. The perspective was of the UK National Health Service (NHS) and Personal Social Services. Costs and benefits were discounted at 3.5% per year. Given the available evidence, olaratumab is likely to meet NICE's End-of-Life criteria. To improve the cost-effectiveness of olaratumab, the company offered a discount through a Commercial Access Agreement (CAA) with NHS England. When the discount was applied, the mean base-case and probabilistic incremental cost-effectiveness ratios (ICERs) for olaratumab plus doxorubicin vs. the standard-of-care doxorubicin were £46,076 and £47,127 per quality-adjusted life-year (QALY) gained, respectively; the probability of this treatment being cost-effective at the willingness-to-pay threshold of £50,000 per QALY gained, applicable to End-of-Life treatments, was 0.54. The respective ICERs from ERG's analysis were ~£60,000/QALY gained, and the probability of the treatment being cost-effective was 0.21. In August, 2017, the NICE Appraisal Committee recommended olaratumab in combination with doxorubicin for this indication for use via the UK Cancer Drugs Fund under the agreed CAA until further evidence being collected in the ongoing phase 3 trial, ANNOUNCE, becomes available in December, 2020.

Key Points for Decision Makers

The cost-effectiveness analysis was based on clinical evidence derived from a randomized control trial, JGDG. In the trial, the efficacy and safety of olaratumab plus doxorubicin were compared with doxorubicin alone for advanced soft tissue sarcoma not amenable to surgery or radiotherapy.
Based on the evidence available, this therapy is likely to meet NICE's End-of-Life criteria. However, under a discount offered by the company through a Commercial Access Agreement (CAA) with NHS England, NICE considered that this treatment is not cost-effective.
Therefore, the NICE Appraisal Committee did not recommend olaratumab plus doxorubicin for this indication for routine use in the NHS. However, the treatment is recommended via the UK Cancer Drugs Fund if the conditions in the CAA are followed, until further evidence on the effectiveness of this therapy becomes available in December, 2020.

1 Introduction

Soft tissue sarcoma (STS) tumors are uncommon accounting for approximately 1% of all cancers [1]. STS are most often diagnosed in middle aged and older adults, with about 43% of all sarcoma cases in people over 65 years old [2]. Whilst STS can occur anywhere in the body - in muscles, blood vessels, fat tissue or in other

mesenchymal (or connective) tissues that support, surround and protect the organs – three quarters of STS tumors occur in extremities [3]. There are over 50 histological types of soft-tissue sarcomas, which differ in terms of their tissue of origin, clinical behavior, age of occurrence, aggressiveness, the way they spread, genetic alterations, and their sensitivity to certain therapies. The most common subtypes of STS in the UK are leiomyosarcoma, fibroblastic sarcoma and liposarcoma [2].

A number of STS classification systems have been proposed [4-6] (see [3] for a comparative analysis). The World Health Organization classification of soft tissue and bone tumors (2013) [3] classifies STS as benign, intermediate, or malignant; intermediate tumors are described as either locally aggressive or rarely metastasizing.

Surgery is the primary treatment for resectable local STS. The aim is to cure the disease by completely excising the tumor with a margin of normal tissue. Tumor resectability depends on the stage and the anatomical location of the tumor, and the patient's comorbidities [1]. Radiotherapy is commonly used either prior to or after surgery in patients with grade II and III tumors [6]. For patients with STS not amenable to surgery, observation is an option for asymptomatic disease. Symptomatic patients may be treated with chemotherapy, radiotherapy, palliative surgery, or best supportive care. The choice of treatment will take into account the disease histology, distribution, volume, and likely sensitivity to systemic treatment.

Standard first-line chemotherapy treatment for advanced STS, specified in the current UK guidelines for the management of soft tissue sarcomas [1], is single-agent doxorubicin; treatment with ifosfamide can also be offered if anthracyclines are contraindicated. Second-line therapies are ifosfamide, trabectedin, and the combination of gemcitabine and docetaxel. A number of other agents, such as dacarbazine and pazopanib, can be considered beyond second-line, depending on patient fitness, comorbidity and funding provision. Systemic anticancer treatment for advanced STS is not curative, with reported median survival time of 15 to 18 months [7].

In a recent US study, an open-label randomized phase 2 trial, JGDG, the addition of olaratumab (Lartruvo®, Eli Lilly & Company Limited, hereinafter referred to as Lilly) to doxorubicin chemotherapy for STS patients resulted in prolongation of overall survival of 11.8 months [8]. Olaratumab is a monoclonal antibody that can bind to platelet-derived growth factor receptor alpha (PDGFRα, a protein that plays an important role in cancer cell proliferation) and thus inhibit tumor growth. In September 2016, the European Medicines Agency recommended granting a conditional marketing authorisation to olaratumab, in combination with doxorubicin, for the treatment of adults with advanced soft tissue sarcoma, for whom surgery or radiotherapy is not suitable and who have not been previously treated with doxorubicin [9].

2   The Decision Problem

The National Institute for Health and Care Excellence (NICE) invited the manufacturer of olaratumab, Lilly, to submit evidence for the clinical effectiveness and cost effectiveness of this drug, in combination with doxorubicin, for advanced STS not amenable to surgery or radiotherapy, as part of the Institute's Single Technology Appraisal (STA) process (for a description of the NICE STA process refer to [10]). The Peninsula Technology Assessment Group, commissioned to act as the Evidence Review Group (ERG), critically reviewed

the submitted evidence and conducted an additional analysis. The report was submitted to NICE on 9 March, 2017, followed by an addendum with an additional analysis requested by NICE, which incorporated a discount offered by Lilly through a Commercial Access Agreement (CAA) with NHS England. The STA was completed in June, 2017. Herein we present a summary of the company's submission, the analysis prepared by the ERG, and the NICE guidance. For further details on this appraisal refer to the NICE website [11].

3   The ERG's Review

The company examined the clinical effectiveness and cost effectiveness of combination treatment with olaratumab (Ola) plus doxorubicin (Dox), hereinafter referred to as OlaDox, compared with treatments with doxorubicin (Dox) only and ifosfamide plus doxorubicin (IfoDox), listed in NICE's Final Scope for this appraisal. Based on clinical advice, the IfoDox chemotherapy is rarely used for treating STS in the UK. Therefore, the NICE Appraisal Committee concluded that the most relevant comparator for OlaDox was Dox chemotherapy, and did not consider IfoDox as a comparator in the Final Appraisal Determination. Nonetheless, we present clinical effectiveness and cost-effectiveness results for IfoDox as this comparator may be of relevance to healthcare systems in other countries.

The company's evidence was submitted in anticipation that olaratumab would be considered as an alternative to doxorubicin which has been used as a first-line treatment for advanced STS for over three decades. The company argued that, since the maximum cumulative lifetime dose of doxorubicin allowed in UK clinical practice is 450 mg/m^2 (equal to 6 treatment cycles at a dose of 75 mg/m^2) [11], patients who have already received Dox in the first-line setting would not be eligible for OlaDox in the subsequent lines of treatment.

3.1   Clinical Evidence Provided by the Company

A systematic literature review was conducted to identify randomized clinical trials of olaratumab and other interventions for the treatment of adult patients with advanced STS. The only clinical trial of olaratumab that had been identified and reported by Lilly in the clinical-effectiveness systematic review was an open-label phase 1b (15 patients) and randomized phase 2 (133 patients) trial, JGDG (Lilly), conducted in the United States [8]. Data on the clinical effectiveness and safety of olaratumab in combination with doxorubicin, utilised in the company's economic analysis, was derived from the JGDG phase 2 trial, in which patients were randomized to OlaDox (N=66) and Dox monotherapy (N=67); the dosage, route and duration of administration are detailed in Online Resource 1. Approximately 65% of patients in the pivotal trial received first-line therapy, while other patients were on second- and third-line treatments (see our report for further details [11]). In the trial, patients in the Dox arm were allowed to receive Ola after discontinuing the Dox treatment (due to disease progression during or after completion of the initial treatment with the Dox chemotherapy) until progressive disease, unacceptable toxicity or discontinuation for any other reason.

In patients who had no prior lines of therapy for advanced disease, an investigator-assessed improvement in median progression-free survival (PFS) was 2.5 months: 6.6 months ([95% confidence interval (CI) 3.1-9.3] in the OlaDox arm vs. 4.1 months [95% CI 2.8–6.2] in Dox arm; hazard ratio (HR) = 0.771; p = 0.2842) [7]. All patients were followed for a minimum of 30 days after the last dose of olaratumab and thereafter every 4 to 6 weeks until all olaratumab-related toxicities resolved, stabilised, returned to baseline, or were deemed irreversible. Patients were followed for survival at regularly scheduled intervals (approximately every 3 months)

for at least 2 years. Treatment with OlaDox improved median overall survival (OS) in the ITT population by 11.8 months compared with Dox alone (26.5 months [95% CI 20.9-31.7] vs. 14.7 months [95% CI 9.2-17.1]; HR = 0.463 [95% CI: 0.301-0.710]; p = 0.0003), signifying 53.7% reduction in risk of death in patients treated with OlaDox. Further analysis, performed on the first-line subpopulation, also displayed improved OS in the OlaDox arm: the median OS was 29.1 months [95% CI 16.3-not estimates (NE)] in patients treated with OlaDox, and 14.7 months [95% CI 8.0-18.7] in patients on Dox (stratified HR = 0.47 [95% CI 0.27-0.81]; p = 0.0051).

More patients on Dox than on OlaDox discontinued the study treatment due to treatment emergent adverse events (16.4% vs. 7.6%). The most frequent adverse events at Grade 3 or above, reported in the OlaDox and the Dox arms respectively, were neutropenia (54.7% and 33.9%), anaemia (12.5% and 9.2%), and febrile neutropenia (12.5% and 13.8%).

A network meta-analysis was conducted to compare the effectiveness of OlaDox vs. IfoDox since no trials had been identified in the systematic literature review that provide head-to-head evidence of the efficacy and safety of these treatments. It was implemented in WinBUGS. A network diagram is shown in Fig. 1.

Fig. 1 Evidence for the network meta-analysis. [1] Tap et al. (2016) [8], [2] Seddon (2015) [12], [3] Judson et al. (2014) [13], [4] Santoro et al. (1995) [14], [5] Le Cesne et al. (2000) [15], [6] Maurel et al. (2009) [16] *Doc* docetaxel, *Dox*, doxorubicin, *Gem* gemcitabine, *GemDoc* gemcitabine+docetaxel, *Ifo* ifosfamide, *IfoDox* ifosfamide+doxorubicin, *Ola* olaratumab, *OlaDox* olaratumab+doxorubicin

The analysis included data from six studies with seven treatments, six of which were relevant to the decision problem. With regard to the modelling of patients' survival, the company opted for the second-order fractional polynomials method. This method, however, requires individual patient data, which was only available for the JGDG trial. Hence, for the remaining studies, individual patient data was reconstructed from digitised Kaplan-Meier (KM) plots and numbers at risk/numbers of events using the method described by Guyot et al. [17]. The fixed-effects modelling approach was adopted by the company because of its simplicity and transparency (the results of the analysis are confidential [11]).

3.1.1 Critique of the Clinical Evidence

The company conducted a systematic literature review of clinical effectiveness in accordance with the NICE reference case [18]. The primary focus of the company's submission, the JGDG study, was generally an appropriately-designed randomized control trial, although the study population was small, with only 133 patients, due to the rarity of STS. With regard to histological subtypes of STS, the patients in the JGDG trial were representative of the UK population. Baseline characteristics were generally balanced in the OlaDox and Dox treatment groups.

However, the protocol for the doxorubicin monotherapy in the trial differed from UK practice: patients received up to eight cycles of doxorubicin as part of the combination treatment with OlaDox, while a maximum of six cycles of the Dox monotherapy is typically administered in the NHS.

Approximately 45% of participants in the Dox arm subsequently received Ola monotherapy, which is a limitation to the study design due to confounding of outcome measures.

The open-label design of the trial, although unavoidable as the treatments generally require different levels of medical intervention, is likely to increase the risk of bias.

In the network meta-analysis, the company adopted the fixed-effects modelling approach which ERG considered appropriate.

3.2 Cost-effectiveness Evidence Provided by the Company

3.2.1 Methods

Lilly conducted a systematic review of cost-effectiveness evidence. The searches did not identify any studies directly related to the decision problem. The company, therefore, developed a *de novo* economic model, which was informed by: the JGDG study [8]; a systematic review of country-specific resource use, costs and utilities; the company's own observational study of resource cost and use specific to UK patients with advanced STS [11, 19]; and multiple oncologists' and external consultants' advice on STS and model implementation.

Fig. 2 Model structure. *BSC* best supportive care

A partitioned survival model [20] was developed in Excel, with a standard model structure that was used in numerous health technology assessments: "Progression-free", "Progression" and "Death" (Fig. 2). In the base-case analysis, patients entered the model upon commencement of first-line treatment. In progressive disease, patients received up to three further lines of therapy and best supportive care (BSC) [21]. "Death" was an absorbing state in this model.

The primary health outcomes were life-years (LYs) and quality-adjusted life-years (QALYs), attained in each treatment arm; the economic outcome was the incremental cost-effectiveness ratio (ICER). The model cycle length was one week. The baseline model time horizon was 25 years, which was justified as a lifetime horizon of patients with advanced STS, based on the OS data from the JGDG study, extrapolated beyond the study observation period of approximately four years. Due to the short model cycle, no half-cycle correction was implemented. In the base-case analysis, the perspective was of the NHS and Personal Social Services; and costs and benefits were discounted at 3.5% per year in accordance with the NICE reference case [18].

3.2.1.1 Survival estimates

Progression-free survival (PFS) for OlaDox vs. Dox was modelled using KM data for the first-line patients, reported in the JGDG trial (Fig. 3a). No extrapolation of PFS was performed since the data were mature. The effect of various parametric models for PFS on model predictions was explored in scenario analyses.

Fig. 3 First-line PFS and OS from the company's base-case analysis. [a] Kaplan-Meier estimates (with 95% CI) of investigator-assessed PFS for patients treated with OlaDox and Dox from Tap et al. (2016) [8]; [b] Kaplan-Meier estimates (with 95% CI) of OS, and gamma and log-normal models of OS for patients treated with OlaDox and Dox; [c] PFS and [d] OS estimates for patients on OlaDox and IfoDox, obtained in the network meta-analysis using second-order fractional

polynomials. *CI* confidence interval, *Dox* doxorubicin, *IfoDox* ifosfamide+doxorubicin, *OlaDox* olaratumab+doxorubicin, *OS* overall survival, *PFS* progression-free survival

Log-cumulative hazard plots for overall survival were approximately parallel, and the company argued that this justified assuming proportional hazards for OS. Due to a small number of patients and events (i.e., deaths and censored observations) in the first-line subgroup of JGDG study (40 patients and 21 events in the OlaDox arm, with 47 and 36 in the Dox arm), in the base case, the company employed the "arms together" approach when modelling overall survival, i.e., parametric survival models were fitted to the ITT dataset with the line of therapy as a covariate to allow the inclusion of data on more patients compared with the "individual arms" approach. Other covariates were sex; tumor type (leiomyosarcoma vs. other); Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. 1 or 2); interactions between treatment and tumor type, and treatment and the line of therapy. Patient's age and PDGFRα expression (positive vs. negative) were also explored for inclusion. However, they were found to be non-significant and were later removed from the parametric models to avoid model over-fitting.

Several parametric models were fitted to the KM estimates of overall survival reported in the pivotal trial: exponential, Weibull, gamma, Gompertz, log-logistic and log-normal. Since the OS data were immature (the length of the observation period in the JGDG trial was 47 months), survival was extrapolated beyond the observation period to estimate the costs and effects of the treatments over the life span of patients with advanced STS. The company then used external evidence from Van Glabbeke et al. (1999) [22] to validate extrapolated OS for Dox at 10 years after diagnosis of advanced disease. The company stated that selection of the parametric survival functions for inclusion in the company's economic model was based on Akaike information criterion (AIC), Bayesian information criterion (BIC), the visual fit to the KM curves and clinical plausibility. On the basis of these criteria, only the gamma function provided a plausible extrapolation for OS in Dox patients. Of note, the predictions of the gamma model were 5% and 11% for patients on Dox and OlaDox, respectively, surviving 10 years after the diagnosis of advanced STS; at about 25 years after diagnosis, virtually all patients have died.

Since it was not possible to predict survival beyond 10 years either from the JGDG data set or the results from Van Glabbeke et al. [22], the company compared the hazard of death for patients from the Van Glabbeke study and patients from the general population of England and Wales of the same age and sex [23]. At the end of follow-up in the Van Glabbeke study, the hazard for death for patients with STS was 5.19 times higher than that for the general population. Therefore, for the base-case analysis, for times after the end of follow-up, the HR of 5.19 was applied to the general mortality rates to account for the extra risk of death for cancer patients. The resulting OS curves based on the gamma model are shown in Fig. 3b.

In the pivotal trial, among the 67 patients in the Dox arm, 30 received Ola monotherapy upon disease progression. The company examined a number of naïve and more complex methods for the adjustment of treatment switching. Two methods, the Rank Preserving Structural Failure Time Model (RPSFTM) and the Iterative Parameter Estimation (IPE) algorithm, were deemed inappropriate since both methods critically rely on a limiting assumption of the "common treatment effect"—that is, the treatment effect received by "switchers" must be the same (relative to the time the treatment is taken for) as the treatment effect received by patients

initially randomized to the experimental arm. This assumption is not valid for the JGDG trial as the treatments were different: in the experimental arm, the treatment was OlaDox followed by Ola monotherapy after discontinuation of Dox (without progression) vs. Ola monotherapy in the "switchers" (following progression) from the control arm. The company also considered the Inverse Probability of Censoring Weights (IPCW) and the two-stage methods. These methods estimated HRs similar to the one from the ITT analysis. The company concluded that the control-arm patients who received Ola monotherapy had similar OS compared with patients who did not receive Ola after discontinuation of Dox. Therefore, OS in Dox patients was not adjusted for the post-progression Ola monotherapy, and no sensitivity analysis addressing potential uncertainty related to treatment switching was reported in the company's submission.

For the OlaDox vs. IfoDox comparison, PFS and OS estimates were derived from the network meta-analysis (Section 3.1) and were estimated from second-order fractional polynomials (Fig. 3c, d) [11]. Due to the relatively small sample size in the JGDG trial, the entire ITT population data set was utilised to estimate the fractional polynomial models rather than the data set for the first-line patient subgroup. The resulting hazard functions for both PFS and OS were based on median estimates of the coefficients of the fractional polynomials (for further details refer to Section 4.3 of our report [11]).

3.2.1.2 Costs

Total costs in the company's model, reported in GBP (2015), included the costs of drug acquisition and administration, disease management, the cost of treating adverse events and cardiac monitoring costs (a detailed description is provided in Online Resource 2).

Olaratumab and G-CSF (filgrastim) were dosed based on patient's weight; the doses of other drugs were given proportional to body surface area (BSA). In the main analysis, the company assumed the mean weight of 77.3 kg referencing GeDDiS trial which was conducted mainly in the UK [12]; the mean BSA of 1.91 m^2 was derived from Health Survey of England (2013).

In the US-based JGDG trial, olaratumab was given intravenously (IV) on days 1 and 8 of 21-day treatment cycles until disease progression; Dox was administered IV once per 21-day treatment cycle for up to eight cycles or disease progression (a cumulative dose of 600mg/m^2). Both treatments could be discontinued due to occurrence of severe adverse events or other causes. To mitigate the risk of cardiotoxicity due to Dox, patients could also receive the cardioprotectant dexrazoxane in cycle five to eight (Online Resource 1). UK patients usually receive up to six cycles of Dox (a total dose of 450mg/m^2) due to the risk of cumulative cardiotoxicity; dexrazoxane is not routinely used with Dox in the treatment of STS. While in the company's base-case analysis the use of Dox and dexrazoxane was modelled as per JGDG (Online Resource 2), a UK practice scenario analysis, conducted by the company, explored the use of Dox as per UK practice (i.e., maximum of six cycles instead of eight) and the exclusion of dexrazoxane.

Since Lilly could not identify a study reporting the IfoDox regimen most commonly used in the UK, Dox 60 mg/m^2+Ifo 9 g/m^2, it was assumed that the regimes, Dox 60 mg/m^2+Ifo 9 g/m^2 and Dox 75 mg/m^2+Ifo 10 g/m^2 (for which evidence was available), have similar efficacy. Besides, there were no data available to estimate the extent of dose reduction for patients on IfoDox. Therefore, the company modelled the planned dose of IfoDox as

in JGDG, while costing of OlaDox was based on the dose reported in the pivotal trial (Online Resource 2). The 20% decrease in IfoDox dose was explored in a sensitivity analysis.

The company assumed availability of 500mg and 190mg vial sizes of Ola (in anticipation of marketing authorisation for the 190mg vial of Ola). In the company's model, no vial sharing was assumed for all intravenously administered drugs.

The costing of drug administration was based on the assumption that the OlaDox administration (with premedication for both drugs) can take up to two hours, and administration of Dox (including premedication) can take up to 60 mins (relevant Healthcare Resource Group codes and costs per administration are provided in Tables 4 and 5, Online Resource 2).

In the JGDG study, patients with advanced STS received up to four lines of systemic anticancer therapy after the study treatments. In the base case, the company assumed that the total treatment cost in progressive disease is independent of survival post-progression, i.e., the cost of post-progression treatment was identical in both treatment arms (Table 11, Online Resource 2).

In the base case analysis, the cost of treating adverse events of Grade 3 or higher was calculated by combining the proportion of events likely to require hospitalisation based on data from the JGDG trial, with the estimates of costs per event derived from NHS reference costs (Table 9, Online Resource 2). The costs of managing adverse events were accounted for in the first year of the model.

3.2.1.3   Utilities

Since the JGDG trial did not collect any health-related quality of life (HRQoL) data, the company conducted a systematic literature review to identify published health-state utility estimates. The utility values of 0.72 and 0.56 reported by Reichardt et al. (2012) [24] were assumed in the base-case analysis for progression-free and progressed health states, respectively (Table 12, Online Resource 2); they were measured from patients with metastatic STS and metastatic bone sarcoma with favourable response to chemotherapy, using EQ-5D. In the company's base case, disutilities arising from grade 3/4 adverse events were also accounted for; they are listed in Table 8 (Online Resource 2).

3.2.1.4   Results

The mean OS of patients with advanced STS, predicted by the company's model, was 4.18 and 2.32 years in the OlaDox and Dox arms, respectively. The OlaDox arm accrued the most QALYs, 2.11, with 0.46 in the progression-free state and 1.66 in progressed disease; the Dox arm had 1.22 QALYs, with 0.36 QALYs in progression-free and 0.86 QALYs in progressed disease.

In the OlaDox vs. IfoDox comparison, the respective mean overall survival estimates were 4.35 and 2.67 years. The model predicted 2.18 QALYs accrued in the OlaDox arm, with 0.63 in the progression-free state and 1.55 in progressed disease; IfoDox treatment resulted in 1.43 QALYs, with 0.56 QALYs and 0.86 QALYs in progression-free and progressed disease states, respectively.

Of note, in these analyses, the estimated OS for OlaDox patients differ (Fig. 3b, d). The company argued that the network meta-analysis provided an adjusted indirect comparison based on average outcomes for Dox rather than a naïve comparison of individual trial arms [11].

The base-case ICERs for both comparisons, estimated under the list price of olaratumab, are confidential. When the CAA discount proposed by the company was applied, the ICERs for OlaDox vs. Dox and IfoDox were £46,076 and £28,201 per QALY gained, respectively; the ICERs obtained in probabilistic sensitivity analyses were £47,127 and £30,604 per QALY; the respective probabilities of the OlaDox being cost-effective at the threshold of £50,000/QALY gained were 0.54 and 0.88 (parametric uncertainty was represented with probability distributions, see Online Resource 2 and [11]). In the UK practice scenario analysis (with maximum of six cycles of Dox and the exclusion of dexrazoxane), the ICER for the OlaDox vs. Dox comparison decreased only slightly.

With regard to the deterministic sensitivity analysis and scenario analyses conducted by the company, the model inputs that had the greatest impact on the results were the parametric survival functions for the OlaDox vs. Dox comparison, plausible variations in the health-state utility values and the cost of drug administration in post-progression health state. The CAA, the detailed results from the base-case, sensitivity and scenario analyses constitute Commercial-in-Confidence information and are therefore not presented here.

3.2.2 Critique of the Cost-effectiveness Evidence

The perspective of the NICE reference case [18] was adopted by the ERG when critiquing the company's economic evaluation. In this section, we highlight the key issues identified in the company's submission; for further details refer to our report to NICE [11].

We consider the structure of the company's economic model appropriate and consistent with the natural history of advanced STS. However, we disagree with Lilly's selection of the gamma function as the best fit for the Kaplan-Meier estimates of overall survival from the pivotal trial. The patient population in Van Glabbeke et al. (1999) [22], used by the company for external validation of extrapolated OS, was substantially younger than the population in the pivotal trial (with 75.5% of patient ≤ 60 years old), which might overestimate the long-term survival of the patient population relevant to this appraisal. Based on our clinical expert's opinion, the log-normal distribution, presented in the company's submission among other candidate models for OS, would be more relevant to the decision problem since it provides more clinically reasonable prediction of 10-year survival in patients with advanced STS (Fig. 3b). According to the log-normal model, 1.7% of Dox patients and 4.3% of patients on OlaDox are expected to survive 10 years after the diagnosis of advanced disease, while the relevant predictions of the gamma model are higher, 5% and 11%.

Lilly underestimated drug administration costs by underestimating administration time for OlaDox and Ola monotherapy. We were advised by our clinical expert that the OlaDox administration (including premedication for Ola and Dox) may take 2.5 to 3 hours, and administration of Ola monotherapy (with premedication for Ola) up to 90 minutes (further details including a description of the relevant HRG codes and costing of drug administration can be found in Online Resource 2).

When estimating the acquisition cost of olaratumab, the company assumed the mean patients' weight of 77.3 kg, referencing GeDDiS trial, conducted mainly in the UK [12]. Of note, the US-based JGDG study reported higher estimates of patients' mean weight: 85.8 kg (SD = 23.00) and 82.5 kg (SD = 23.40) in the OlaDox and Dox arms, respectively. The weight estimate from the company's model could not be verified by the ERG since the evidence source was available as an abstract only.

The health-state utility values in the company's base-case analysis were adopted from the study by Reichardt et al. (2012) [24]. The company acknowledged that the study selection criterion (i.e., favourable response to chemotherapy) may have resulted in higher utility values than would be expected for all STS patients with advanced disease. We believe that age heterogeneity may bias the results further since patients in the referred study were significantly younger than patients in the pivotal trial: in the evidence source, the mean age of patients at diagnosis was 49.5 (SD = 17.1), while the mean age of patients from the OlaDox and the comparator arms in the JGDG trial was 56.8 (SD = 12.53) and 58.3 (SD = 12.50), respectively.

Lilly examined the effect of the subsequent treatment with Ola monotherapy on survival outcome in the Dox arm. The company's conclusion of no effect of Ola treatment on survival in the Dox arm may not be valid due to a number of reasons such as the small sample size, immaturity of survival data, and other assumptions made by the company (detailed in our report [11]), which are not supported by data from JGDG. This may further contribute to uncertainty in survival and, therefore, cost-effectiveness.

The company's assumption made in the base-case that the cost of subsequent treatment does not depend on post-progression survival is not supported by the results of the Lilly's observational study, reported by Mytelka et al. (2016) [19], on which (as the company stated in the submission) the model parameterisation was based; data reported by the authors suggest that the drug costs increase substantially with the line of treatment.

Finally, the cost-effectiveness evidence of OlaDox compared with IfoDox, provided by the company, is highly uncertain since it was based on an indirect comparison. Importantly, the survival curves in the company's model were estimated from the median values of the coefficients of the fractional polynomials obtained in the network meta-analysis (not mean values), which is not in line with the NICE reference case [18].

3.3   Additional Work Undertaken by the ERG

As a result of our critique of the company's submission to NICE, we developed our base case by adjusting the relevant items in the company's model (Table 1).

Table 1: Derivation of ERG's base-case **ICER (cost per QALY gained)** for OlaDox vs. Dox, with the CAA discount applied

		ERG's base case[a]	Lilly's base case
1	Parametric survival function for OS	Log-normal	Gamma
2	Patients' mean weight	82.5 kg [8]	77.3 kg [12]
3	HRG codes and unit costs	(see Table 4, Online Resource 2)	

Overall effect of 1, 2 and 3	£60,000	£46,076

The ERG's mean base-case ICER for the OlaDox vs. Dox comparison (Table 1) was higher, approximately £60,000 per QALY gained, compared to the company's ICER of £46,076 per QALY due to differences in (a) extrapolation of overall survival, (b) drug administration costs, and (c) the assumption on the mean patients' weight used to estimate the cost of drug acquisition. Assuming the log-normal model for OS (Fig. 3b), longer administration time for OlaDox and Dox, and the mean patient weight of 82.5 kg (as per JGDG) increased the ICER for OlaDox vs. Dox from £46,076 to ~£60,000 per QALY gained. The ERG's base-case ICER for OlaDox vs. IfoDox was also higher than the company's estimate (Online Resource 3). The increase in the ICER was primarily driven by the difference in drug administration costs.

We conducted deterministic and probabilistic sensitivity analyses for our preferred base-case ICERs. The model predictions were most sensitive to changes in the health-state utility values, the OS models, and the assumption on the cost of treatment post-progression [11]. Probabilistic sensitivity analyses yielded ICERs similar to the base-case values (the results are confidential).

3.3.1 End-of-life Criteria

Lilly argued that the presented evidence supported inclusion of olaratumab into NICE's End-of-Life treatments since, first, the life expectancy for patients treated with the comparators is under 24 months and, second, there is sufficient evidence, based on Tap et al. (2016) [8], for the intervention to increase patients' survival by at least 3 months. Of note, the JGDG study reported the median overall survival of 14.7 months in patients on the standard-of-care doxorubicin, and improvement in median OS of 11.8 months in patients treated with OlaDox compared with Dox.

The ERG, however, noted that estimates of life expectancy, i.e., mean survival, should have been considered in the End-of-Life analysis in accordance with the NICE guidance [18]. In the company's base case, predicted life expectancy of patients on Dox and IfoDox were 2.32 and 2.67 years, respectively, and therefore the criterion of short life-expectancy would not have been met; olaratumab would not qualify for the End-of-Life category; and the cost-effectiveness threshold of £30,000 per QALY gained would be applicable.

Unlike the company's base case, the ERG's main analysis predicted life expectancy of 1.83 years for patients on the Dox. Hence, the short-life expectancy criterion was likely to be met. Besides, as shown in the JGDG trial, treatment with olaratumab is highly likely to prolong patients' survival, on average, by more than 3 months, signifying that OlaDox also meets the extension-to-life criterion. Therefore, the combination therapy with olaratumab and doxorubicin seems to qualify as an End-of-Life treatment. However, this conclusion is based on the model predictions which are highly uncertain due to immaturity of survival data reported in the pivotal trial, JGDG.

3.4 Conclusions of the ERG Report

The only randomized control trial of olaratumab, JGDG, used by Lilly in the analysis, had a small patient population of 133 patients. Survival data was immature since about 40% and 20% of patients in the OlaDox and Dox treatment arms, respectively, were alive at the end of the study. The overall survival estimates available for approximately 4 years, were extrapolated by the company up to 25 years and externally validated on survival data for a substantially younger population. Therefore, due to the limitations in the clinical effectiveness evidence base, the estimates of the cost effectiveness of olaratumab plus doxorubicin are highly uncertain.

Based on the available evidence, olaratumab is likely to fulfil NICE's End-of-Life criteria. However, the combination treatment with olaratumab is not cost-effective, under the Commercial Access Agreement proposed by the company, at the threshold of £50,000 per QALY gained usually considered by NICE when appraising End-of-Life treatments.

4 National Institute for Health and Care Excellence Guidance

In March 2016, the NICE Appraisal Committee reviewed the evidence available on the clinical effectiveness and cost effectiveness of olaratumab in combination with doxorubicin for advanced soft tissue sarcoma. The Committee acknowledged that the main driver of the cost effectiveness of the combination therapy was the extrapolation of immature overall survival data. Based on clinical advice, the company's estimates of overall survival for both OlaDox and Dox, were considered by the Committee over-optimistic, and those from ERG's analysis were regarded as more plausible. The Committee agreed with the ERG in the use of higher drug administration costs compared with those presented by the company, and considered the mean patient weight assumed in the company's analysis reasonable. The Committee concluded that the most plausible ICER for the OlaDox vs. Dox comparison is likely to be closer to ERG's estimate of £60,000 per QALY gained than the estimate of £46,076, reported by the company. It considered that the combination treatment is likely to meet the End-of-Life criteria. Based on the available evidence, the Committee could not recommend olaratumab for routine use in the NHS [7]. However, the Committee acknowledged that olaratumab has the potential to be cost-effective. It was aware that further data from the ANNOUNCE trial is anticipated to be available in December, 2020 [25]. The Committee understood that NICE, NHS England and the company would undertake further discussions to formalise the Access Agreement before the publication of guidance. The Committee, therefore, recommended that olaratumab be used in the UK Cancer Drugs Fund if the conditions in the Access Agreement are followed. NICE's Final Appraisal Determination was published on 9 June, 2017 [7].

5 Conclusions

Olaratumab in combination with doxorubicin is recommended for untreated, advanced soft tissue sarcoma through the UK Cancer Drugs Fund until further evidence on survival and health-related quality of life being collected in the ANNOUNCE trial becomes available in December, 2020.

Author Contributions

IAT drafted the final version of the manuscript; TJH, JD, FSW, SR, PS and MH revised the manuscript prior to submission. MH is the overall guarantor of the content. This summary has not been externally reviewed by PharmacoEconomics.

Compliance with Ethical Standards

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Conflict of Interest

IAT, TJH, JD, FCW, SR, PS and MH declared no conflict of interest.

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