

Trabectedin in the treatment of metastatic soft tissue sarcoma: cost-effectiveness, cost-utility and value of information

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Background: To assess the cost-effectiveness of trabectedin compared with end-stage treatment (EST) after failure with anthracycline and/or ifosfamide in metastatic soft tissue sarcoma (mSTS).

Design: Analysis was carried out using a probabilistic Markov model with trabectedin → EST and EST arms, three health states (stable disease, progressive disease and death) and a lifetime perspective (3% annual discount rate). Finnish resources (drugs, mSTS, adverse events and travelling) and costs (year 2008) were used. Efficacy was based on an indirect comparison of the STS-201 and European Organisation for Research and Treatment of Cancer trials. QLQ-C30 scale scores were mapped to 15D, Short Form 6D and EuroQol 5D utilities. The outcome measures were the cost-effectiveness acceptability frontier, incremental cost per life year gained (LYG) and quality-adjusted life year (QALY) gained and the expected value of perfect information (EVPI).

Results: Trabectedin → EST was associated with 14.0 (95% confidence interval 9.1–19.2) months longer survival, €36 778 higher costs (€32 816 using hospital price for trabectedin) and €31 590 (€28 192) incremental cost per LYG with an EVPI of €3008 (€3188) compared with EST. With a threshold of €50 000 per LYG, trabectedin → EST had 98.5% (98.2%) probability of being cost-effective. The incremental cost per QALY gained with trabectedin → EST was €42 633–47 735 (€37 992–42 819) compared with EST. The results were relatively insensitive to changes.

Conclusion: Trabectedin is a potentially cost-effective treatment of mSTS patients.

Key words: cancer, economic evaluation, leiomyosarcoma, liposarcoma, quality of life, trabectedin

key findings

Trabectedin improved survival significantly. Trabectedin followed by end-stage treatment (EST) was estimated to result to 14 months of additional survival and 9–10 months of additional quality-adjusted survival [quality-adjusted life years (QALY) gained] compared with EST alone in metastatic soft tissue sarcoma (mSTS) patients who have previously received anthracycline and/or ifosfamide. Trabectedin had an impact on mortality that continued beyond the active trabectedin treatment.

Trabectedin was a potentially cost-effective second-line treatment of mSTS. Trabectedin resulted to €31 590 (€28 192 using hospital price for trabectedin) incremental cost per additional year of life gained and to €42 633–47 735 (€37 992–42 819) cost per additional QALY gained compared with EST. With a threshold of €50 000 per life year gained (LYG), trabectedin had 98.5% (98.2%) probability of being cost-effective.

Results were relatively insensitive to changes in the key parameters. Based on the maximum expected value of perfect information estimate of €3008 (€3188 using the hospital price for trabectedin), the value of additional parameter information is likely to be low.

background

Soft tissue sarcomas (STS) are rare tumours that account for ~1% of all adult cancers. The annual incidence of STS is 1–3/100 000 [1]. Approximately 50%–80% of STS metastasise [2, 3]. Complete surgical resection is rarely accomplished. Therefore, the main treatment of mSTS is systemic chemotherapy (CT) [1, 2, 4], but the role of (neo)adjuvant CT has remained controversial [2]. The standard first-line treatments for mSTS are anthracycline and ifosfamide alone or in combination (A/I [1, 5]). After progression of STS, there are currently no standard therapies.

Trabectedin (TRA) induces tumour regression and inhibits tumour growth [6]. TRA has produced clinical benefits in ovarian cancer, breast cancer and sarcoma [7]. Recent studies have shown that TRA arrests STS growth in ~40%–60% of tumours [8–11] and produces significant clinical benefit in

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patients with STS progression after A/I [9]. At doses used clinically, TRA is well tolerated [12]. The safety and efficacy of TRA shown in clinical trials have been confirmed in compassionate use [8].

The objective of this study was to present the cost-effectiveness of TRA followed by EST (TRA → EST) against EST alone as second-line treatments in patients with STS. The results were presented as incremental cost-effectiveness ratios (ICER), probability of cost-effectiveness and the value of information (VOI). ICER is defined as

$$ICER = \frac{\Delta \bar{C}}{\Delta \bar{E}} = \frac{\bar{C}_1 - \bar{C}_0}{\bar{E}_1 - \bar{E}_0},$$

where \bar{C} stands for average costs and \bar{E} for average health benefits (subscripts indicate treatment; 1 is new and 0 is current). ICER characterises the marginal value of treatments in the form of additional cost per additional unit of health benefit gained or saved during given perspective. In this study, ICERs are produced separately for LYG and QALY gained in a lifelong perspective. The probability of cost-effectiveness was assessed with the cost-effectiveness acceptability frontier (CEAF) and VOI with the expected value of perfect information (EVPI).

materials and methods

patients, treatments and timeframe

The modelled study population consisted of adult patients with mSTS who were previously treated with A/I. The population definition followed the indication of TRA.

Because current evidence does not support any other CTs for mSTS, TRA treatment (24-h infusion every 21 days) was compared with EST initiated immediately after failure with A/I. EST comprises multiple treatment alternatives. This approach was supported by oncological experts and the literature [1, 13].

Analysis was carried out from a health care payer perspective (productivity losses, income transfers and value added taxes were excluded) including costs of drugs, mSTS, serious adverse event (SAE) treatment and travelling. The analyses were based on a lifetime duration where the model was run for a total of 60 monthly cycles, i.e. 5 years.

model structure and simulation

A simplified schematic picture of the model structure is presented in Figure 1. The model started at the point where the treatment with A/I failed. In the model, one cohort was treated with TRA and the other with EST. Patients on TRA could have a treatment response [have a stable disease (SD)], disease progression (PD) or they could die. Patients on EST stayed in PD until death.

The Excel model is based on a probabilistic approach (Monte Carlo simulation [14]) that allows the characterisation of multiple parameter uncertainty (i.e. distributions rather than simple means were modelled). The model applies monthly cycles due to the nature of clinical data. In reality, the treatment cycles of CTs are usually 3 weeks. Half-cycle correction was used (i.e. half of the costs and effects related to the last cycle were accrued, if patient changed health state), but CT-related costs were not corrected as the model assigned all drug costs in the first cycle.

efficacy data

The primary outcome of treatment efficacy was life expectancy. In the model, the efficacy differences were conveyed through transition probabilities. The clinical efficacy, i.e. transition probabilities for staying in a health state or transitioning to another health state, in the TRA arm were taken from STS-201 [9], while the transition probabilities used in the EST arm were obtained from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) trial [15, 16] patient level data. The estimation of transition probabilities is presented in Appendix 1.

The use of the historical EORTC STBSG dataset for the EST arm had inherent limitations. However, those studies using ifosfamide [15, 16] were conducted with similar eligibility criteria and efficacy end points as STS-201. Other studies that investigated the efficacy and safety of drugs not

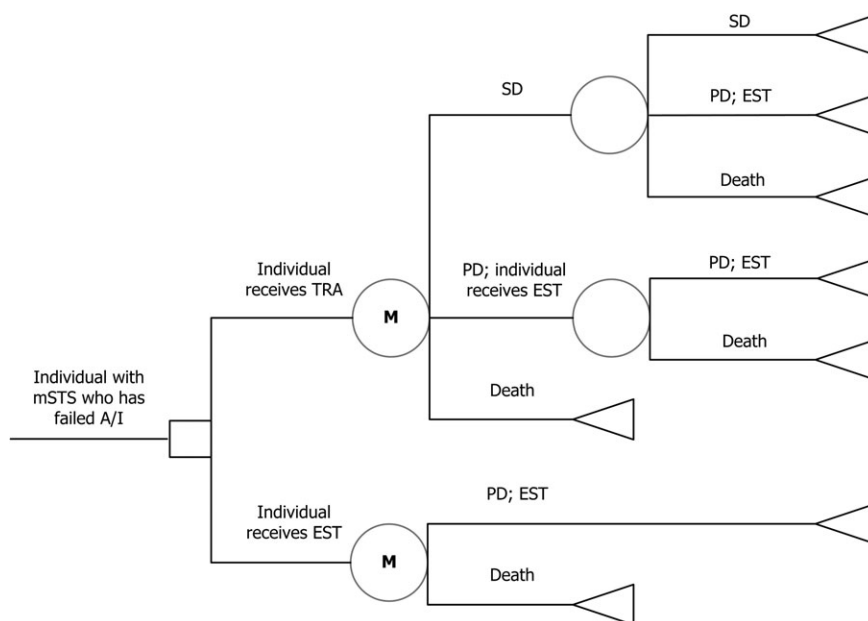


Figure 1. Model structure and health states. A/I, anthracycline and/or ifosfamide; EST, end-stage treatment; M, Markov chain; mSTS, metastatic soft tissue sarcoma; PD, progressive disease; SD, stable disease; TRA, trabectedin.

approved for mSTS were not considered. Typically, mSTS studies were also hindered by poor follow-up (compare Le Cesne et al. [12]). Since the period of interest was the duration PD → death, poor follow-up could have biased the results. However, among sensitivity analyses, patients receiving active EST (33%) were assumed to experience disease stabilisation for 6 months based on dacarbazine (DAC) results [17]. This seems to be a fair estimate for active EST [2].

probabilistic parameters

The probabilistic approach examines parameter uncertainty using distributions around key parameters [14] in the model and relaxes the assumption of linearity typical for the deterministic (point estimate) approach. Specifically, the probabilistic approach included TRA cycles, TRA dose intensity and transition probabilities. The transition probabilities were averaged >1000 simulations to determine the mean transition probabilities [β , 95% confidence intervals (CIs)] for the TRA → EST arm: remaining SD 0.8476 (0.7741–0.9121), SD → PD 0.1457 (0.0840–0.2159), SD → death 0.0067 (0.0039–0.0100) and PD → death 0.1118 (0.0735–0.1570) and for the EST arm: remaining PD 0.8870 (0.8430–0.9265) and PD → death 0.1118 (0.0735–0.1570).

resource use and costs

Resources and costs are presented in detail in Appendix 2. TRA's dose intensity was 1.17 mg/m² in STS-201 and the average body surface area (BSA) was 1.80 m², which results in 2.10 mg per administration (TRA 1.50 mg/m² and BSA of 1.70 m² were assumed in a sensitivity analysis scenario). Given the TRA vial sizes, patients were conservatively assumed to receive two 1-mg vials and one 0.25-mg vial per administration. This included drug wastage (0.15 mg), which can be avoided if infusions are given at the same time for many patients. Average drug cost based on the average of 5.0 TRA cycles in STS-201 was applied equally to all patients in the TRA arm in the first modelling cycle. Conservatively, patients who progress before five cycles with TRA will accrue five cycles worth of costs.

Despite the lack of approved CTs (except TRA) after A/I exhaustion, further CTs are commonly initiated [1, 13]. Conservatively, only 33% of patients were assumed to receive active CT during EST. The type of off-label CT administered at this stage varies based on, e.g., patient toleration and the histology of disease. In the base case, further CT was assumed to be based on etoposide (ETO) and DAC (67% and 33%, respectively). The impacts of these EST assumptions were tested in sensitivity analyses. In the EST arm, the expected EST CT costs were applied to patients at the beginning of the model and, in the TRA → EST arm, the expected EST CT costs were applied once patients transitioned to PD.

After A/I failure, patients consume a variety of resources [13]. There were no Finnish data available on the ongoing costs after A/I failure. Thus, costs of metastatic renal cell carcinoma (mRCC) treatment from two Finnish hospital settings [18] were used because these patients were also without efficient treatments, both mSTS and mRCC have similar progression patterns and imaging examinations and clinician visits of mSTS and mRCC patients seem to be relatively comparable [13, 18]. The sensitivity of this assumption was tested by using UK mSTS costs [13].

Finnish unit costs [19] indexed to the year 2008 using official health care index were used to estimate the administration costs of TRA and treatment of SAEs. Conservatively, all TRA patients were assumed to be treated on an inpatient basis in cancer clinic (outpatient administration is presented as a sensitivity analysis scenario) and the administration costs were applied in the first cycle of the model. Though TRA was well tolerated in STS-201, the model accounts for the cost impact of seven SAEs related to drugs that led to hospitalisation. Since vomiting and nausea were common, it was assumed that the cost of inpatient treatment of gastroenteritis was an appropriate proxy for the SAE treatment cost. No costs for treating any SAEs were applied in the EST arm and no death costs were assumed. The

impacts of death and TRA SAE costs were explored among sensitivity analyses.

utilities

Incremental cost per LYG does not include the quality of survival, and thus, it falls short of a measure that can be more readily assessed against other health care interventions, such as the cost per QALY gained. A systematic search of the literature yielded no data on the generic quality of life (QoL) associated with the STS health states used in the model. Thus, the disease-specific scale score results of EORTC QoL questionnaire (QLQ-C30) by Poveda et al. [20] in mSTS population were mapped to 15D [21], Short Form 6D (SF-6D [22]) and EuroQoL 5D (EQ-5D [23]) generic QoL index values using the ordinary least-squares regression equations on Kontodimopoulos et al. [24]. The numbers used in the estimation are presented in Appendix 3.

The average expected QoL indexes based on 15D, SF-6D and EQ-5D were 0.736, 0.668 and 0.654, respectively. QoL was set to 0 for death. SAEs produced by TRA were taken into account by assuming a disutility (QoL decrease) of 0.200 per SAE. No disutilities due to EST SAEs were included.

sensitivity analysis

As the base case analysis was probabilistic and explored the effect of multivariate parameter uncertainty, figures presenting simulated ICERs as cost-effectiveness plane (CEP) and CEAF based on the probabilistic sensitivity analysis were appealing. Percentile method was used to derive CIs from the 1000 probabilistic simulation results. CEAF illustrates the sensitivity of the conclusion of cost-effectiveness to various thresholds of acceptability that a payer may hold, recognises the uncertainty of the generated cost-effectiveness estimate and presents the optimal treatment options [25] that have the highest expected net monetary benefit (NMB = $E \times \text{willingness to pay} - C$).

CEAF does not consider the consequences of a wrong decision or VOI. Thus, per patient EVPI was estimated [14, 25], which combines both the probability of wrong decision and the consequences of that wrong decision as NMB forgone. The EVPI estimate also represents the value of parameter uncertainty that could be resolved by acquiring additional research evidence for model parameters (i.e. how much would be reasonable to invest for a new study at patient level given the willingness to pay, if parameter uncertainty needs to be decreased and willingness to pay means the acceptable cost for benefit).

In addition, the following scenarios were simulated

- Discounting not employed
- Ongoing costs based on UK mSTS cost data from Judson et al. [13]: €2320.26 (€2511.76 in 2008 value) for 119 days (€633.22 per cycle in 2008 value, £1 = €1.153245)
- Death costs included based on Judson et al. [13] mSTS cost data: €566.70 (€618.27 in 2008 value) per patient
- 0%, 20% or 50% receive active EST
- TRA wholesale/hospital price (in hospital €1994.00 per 1 mg and €530.00 per 0.25 mg)
- TRA as outpatient (ambulatory pumps)
- TRA dose intensity of 1.50 mg/m² and BSA of 1.70 m²
- TRA SAE costs doubled
- ETO monotherapy 120 mg/m² days 1, 3 and 5; every 21 days as EST
- DAC monotherapy 250 mg/m² days 1–5; every 21 days as EST
- IADIC; doxorubicin 50 mg/m² day 1, ifosfamide 1 g/m² with mesna 40 mg/kg days 1–5 and DAC 250 mg/m² days 1–5; every 21 days as EST
- IE; ifosfamide 1 g/m² with mesna 40 mg/kg days 1–5, ETO 100 mg/m² days 1, 3, 5, phenobarbital 100 mg p.o. days 0–6 and growth hormone; every 21 days as EST

- IMVP-a6; ifosfamide 1 g/m² with mesna 40 mg/kg days 1–5, ETO 100 mg/m² days 1–3, methotrexate 30 mg/m² days 3 and 10; every 21 days as EST
- Patients on active EST (33%) experience disease stabilisation for 6 months [17] in both EST groups or in EST-only group
- All patients treated with EST receive active treatment and EST alone patients experience disease stabilisation for 6 months [17]. Actually, this is TRA versus ETO/DAC setting, which conservatively assumes no additional benefit with active EST after TRA.

results

According to the STS-201 and EORTC STBSG data analysis, the transition probability of PD → death in TRA naive patients was higher than that of death for those patients who were treated with TRA. Once a TRA-treated patient progressed after SD, the probability of death increased markedly, but it remained lower than for those patients who were TRA naive.

effectiveness and costs

TRA → EST had both a statistically and clinically significant advantage over EST in terms of mean overall survival (OS): 21.1 (95% CI 16.2–26.4) versus 7.2 (95% CI 6.4–8.1) months, respectively, in mSTS patients who received priority A/I (Table 1). The extra months TRA → EST patients survived compared with EST patients were 14.0 (95% CI 9.1–19.2), i.e. 1.16 (95% CI 0.76–1.60) LYGs.

Based on the QoL tool, TRA → EST resulted to the quality-adjusted survival of 1.16–1.30 QALYs and the respective QALY amount due to EST was 0.39–0.44 QALYs (Table 1). Consequently, the lowest QALYs gained due to TRA → EST compared with EST was 0.77 (95% CI 0.55–1.04) based on EQ-5D and the highest 0.86 (95% CI 0.61–1.16) based on 15D. The 15D results were also most credible based on Kontodimopoulos et al. [24].

Expected lifetime costs for TRA → EST were €44 346 (95% CI €34 073–56 269) assuming the pharmacy retail price for TRA and €40 384 (95% CI €31 282–50 247) assuming the hospital price for TRA. EST resulted in €7568 (95% CI €7129–8158) lifetime costs (hospital prices assumed). Consequently, the incremental cost of TRA → EST compared with EST was €36 778 (95% CI €26 397–48 801) assuming the pharmacy retail price for TRA and €32 816 (95% CI €23 315–42 317) assuming the hospital price for TRA.

cost-effectiveness

The use of TRA → EST in mSTS patients was associated with an incremental cost of €31 590 (95% CI €21 279–47 630) per LYG compared with EST when the pharmacy retail price for TRA was assumed. The correspondent result was €28 192 (95% CI €16 833–39 551) with the wholesale/hospital price for TRA. The cost for a QALY gained with TRA → EST compared with EST was €42 633–47 735 based on the pharmacy retail price of TRA and €37 992–42 819 based on the hospital price for TRA, depending on the utility tool. The cost-utility based on SF-6D and EQ-5D was almost equivalent, whereas the 15D-based results were €5000 lower (Table 1).

sensitivity analysis

CEP is presented in Figure 2 and CEAF in Figure 3. According to CEP, TRA provides significant gain in life years with significantly higher costs. However, the uncertainty related to ICER is not significant with the generally approved ICER thresholds: according to CEAF, the 50%, 75%, 90% and 95% probabilities of cost-effectiveness for TRA → EST were obtained with the willingness to pay (WTP) levels of €31 797, €36 445, €41 534 and €44 967 per LYG when TRA had the pharmacy retail price (€28 464, €33 461, €38 755 and €43 058 per LYG with the hospital price for TRA), respectively.

The highest EVPI estimate was obtained with the ICER value, which was equivalent to the change of optimal treatment in the CEAF from EST to TRA → EST (Figure 3). With the WTP of €31 590 (€28 192 assuming the hospital price for TRA) per LYG, the EVPI estimate was €3008 (€3188). With WTP levels of €30 000, €40 000 and €50 000 per LYG, the respective EVPI estimates were €2101, €566 and €75 (€2328, €374 and €59 with the hospital price for TRA).

Generally, the results were robust to changes in the key parameters. For example, when all patients treated with EST were assumed to receive off-label active CT treatment and EST alone patients were assumed to experience disease stabilisation for 6 months (TRA versus ETO/DAC setting), the result was €33 830 (95% CI €22 237–55 822) per LYG. Yet, the results were somewhat sensitive to the administered dose and price of TRA (Table 1). The increase of TRA to the recommended dose in place of that actually observed in STS-201 resulted to €35 849 (95% CI €26 479–52 164) per LYG (TRA's pharmacy retail price assumed). This was unrealistic, as the base case scenario accounted for dose reductions and withdrawals, which were expected with CTs. When the pharmacy premium was excluded from the price of TRA and the hospital/wholesale price was used, the incremental cost per LYG decreased to €28 192. This can be more readily applicable in countries where the pharmacy premium is low or when TRA is used in the public hospital settings in Finland.

discussion

TRA → EST results in a significantly higher OS than EST, but with higher costs. Thus, we asked whether TRA → EST is a cost-effective second-line treatment of mSTS patients.

TRA slowed progression and had an impact on mortality that continued beyond the TRA treatment. The incremental cost per LYG and QALY gained were €31 590 and €42 633–47 735 for TRA → EST versus EST when the pharmacy retail price for TRA was assumed, respectively, which indicate that TRA → EST was potentially cost-effective. The results were in line with the previous cost-effectiveness results obtained in the Finnish setting [17, 26, 27]. When the wholesale/hospital price was assumed for TRA, the incremental cost per LYG and QALY gained was €28 192 and €37 992–42 819, which are more applicable in countries with lower pharmacy premium (e.g. Sweden) or in the Finnish public hospital setting. Also the highest EVPI estimate per patient was relatively low €3008 (€3188 assuming the hospital price for TRA) compared with the total per patient costs, meaning that gathering additional

Table 1. Results of base case cost-effectiveness, sensitivity and CUA

Cost-effectiveness scenarios	Costs (€)			Life years			ICER
	TRA	EST	Incr.	TRA	EST	Incr.	
Base case, TRA's retail price (SE)	44 346 (11 324)	7568 (525)	36 778 (11 431)	1.760 (0.438)	0.596 (0.072)	1.164 ^a (0.429)	31 590 (13 444)
Base case, TRA's hospital price (SE)	40 384 (9676)	7568 (525)	32,816 (9695)	1.760 (0.438)	0.596 (0.072)	1.164 ^a (0.429)	28 192 (11 591)
Undiscounted	44 349	7618	36 732	1.795	0.603	1.192	30 807
UK mSTS ongoing cost data	44 657	7706	36 950	1.755	0.598	1.156	31 951
Death cost data from UK included	44 764	8138	36 626	1.764	0.595	1.169	31 330
EST: 0% seek EST CT	40 454	4106	36 347	1.764	0.598	1.166	31 162
EST: 20% seek EST CT	42 449	6185	36 264	1.753	0.597	1.156	31 363
EST: 50% seek EST CT	46 180	9295	36 885	1.760	0.595	1.165	31 653
TRA: wholesale/hospital price	40 384	7563	32 821	1.756	0.595	1.161	28 273
TRA: given as outpatient	39 033	5475	33 558	1.754	0.597	1.157	29 005
TRA: 1.5 mg/m ² , BSA 1.7 m ²	49 589	7568	42 021	1.768	0.596	1.172	35 849
TRA: SAE costs doubled	44 526	7571	36 955	1.766	0.597	1.169	31 602
EST: ETO monotherapy	45 097	8420	36 677	1.765	0.599	1.166	31 442
EST: DAC monotherapy	42 201	5912	36 289	1.768	0.598	1.170	31 003
EST: IADIC	45 903	9157	36 746	1.758	0.593	1.165	31 550
EST: IE	47 822	10 991	36 831	1.765	0.597	1.168	31 539
EST: IMVP-6a	45 384	8703	36 681	1.767	0.596	1.171	31 322
EST: on average 2 month disease stabilisation in both EST groups	44 581	7775	36 806	1.840	0.629	1.211	30 402
EST alone: on average 2 month disease stabilisation	44 393	7787	36 606	1.766	0.631	1.135	32 241
EST: 100% active EST; on average 6 month stabilisation in EST alone	51 619	15 263	36 357	1.772	0.697	1.075	33 830
CUA: 15D, TRA's retail price (SE)	44 395 (11 087)	7559 (509)	36 835 (10 868)	1.302 ^b (0.332) ^b	0.438 ^b (0.051) ^b	0.864 ^{ab} (0.281) ^b	42 633 ^c (18 521)
CUA: 15D, TRA's hospital price (SE)	40 384 (9676)	7559 (509)	32 825 (9695)	1.302 ^b (0.332) ^b	0.438 ^b (0.051) ^b	0.864 ^b (0.281) ^b	37 992 ^c (15 786)
CUA: SF-6D, TRA's retail price	44 473	7568	36 905	1.175 ^b	0.398 ^b	0.777 ^b	47 523 ^c
CUA: SF-6D, TRA's hospital price	40 384	7568	32 816	1.175 ^b	0.398 ^b	0.777 ^b	42 234 ^c
CUA: EQ-5D, TRA's retail price	44 130	7585	36 545	1.157 ^b	0.392 ^b	0.766 ^b	47 735 ^c
CUA: EQ-5D, TRA's hospital price	40 384	7585	32 799	1.157 ^b	0.392 ^b	0.766 ^b	42 819 ^c

Pharmacy retail prices without value added tax assumed for trabectedin, if not otherwise stated.

^aSignificant amount of LYGs or QALYs.

^bQALY.

^cIncremental cost-utility ratio.

BSA, body surface area; CT, chemotherapy; CUA, cost-utility analysis; DAC, dacarbazine; EQ-5D, EuroQol 5D; EST, end-stage treatment; ETO, etoposide; Incr., increment; IADIC, doxorubicin, ifosfamide, mesna and DAC; ICER, incremental cost-effectiveness ratio; IE, ifosfamide, mesna, ETO, phenobarbital and growth hormone; IMVP-6a, ifosfamide, mesna, ETO and methotrexate; LYGs, life year gained; mSTS, metastatic soft tissue sarcoma; SAE, serious adverse event; SE, standard error; SF-6D, Short Form 6D; QALY, quality-adjusted life year; TRA, trabectedin.

information for model parameters based on the setting presented in this study may have little impact on the results.

The results were most sensitive to the administered dose and price of TRA. None of the other sensitivity analyses showed a marked effect on the cost-effectiveness and probabilistic

approach took into account the relatively small sample sizes of STS-201 and EORTC STBSG. mSTS also lacked generic QoL data. Given STS is an orphan disease, however, this is unsurprising. Though utilities were estimated using mapping and the impact of QoL was tested using different tools, these

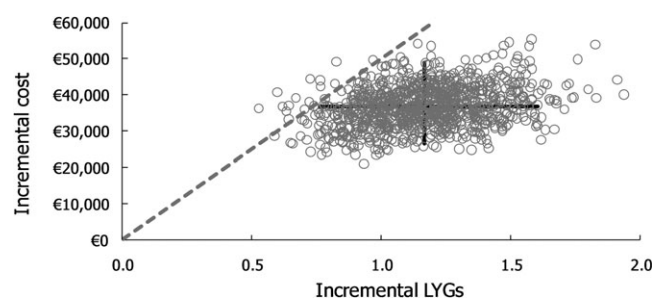


Figure 2. The cost-effectiveness plane (CEP) represents the results of 1000 simulations for incremental lifetime costs (the pharmacy retail price for trabectedin was assumed) and life years gained (LYG) for TRA → end-stage treatment (EST) versus EST (EST is fixed in the origin of the CEP). 95% confidence intervals for incremental costs and effects, and a dashed line showing where the threshold for €50 000 per LYG stands are shown in the CEP; all points under this line were associated with an incremental cost-effectiveness ratio of <€50 000 per LYG. This characterised 98.5% of the simulations.

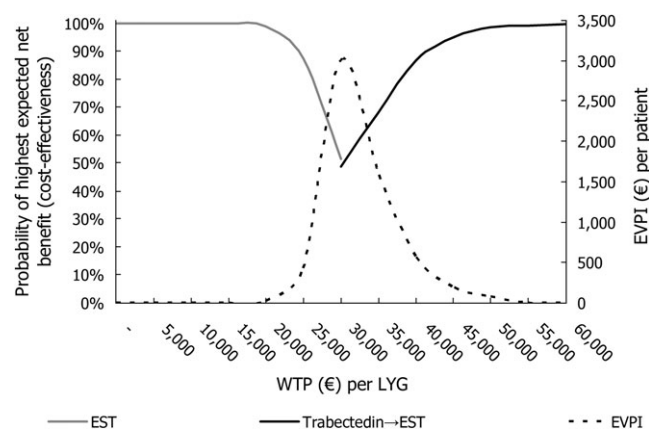


Figure 3. Cost-effectiveness acceptability frontier (solid curves), which presents the optimal treatment options, together with expected value of perfect information (EVPI, dashed curve) frontier. The pharmacy retail prices were assumed for trabectedin. EST, end-stage treatment; LYG, life years gained.

analyses were subject to uncertainty and were conservative for TRA (i.e. usually SD utility > PD utility, but here, SD utility = PD utility [17, 26, 27]). Nonetheless, TRA demonstrated potential cost-utility, which could also be acceptable, e.g. in the UK.

A modelled economic evaluation was essential to capture the potential costs and benefits associated with TRA → EST and EST in a therapeutic setting outside the STS-201 [9] and EORTC STBSG [15, 16]. The STS-201 was aimed at assessing the efficacy of two different TRA doses. For both STS-201 regimes, the 6-month PFS rates were considerably greater than, e.g., the 6-month PFS of 14% reported by van Glabbeke and Verweij [28] for active regimes in pre-treated patients with STS, and the TRA results generally [8, 10–12, 29] were consistent. Also the ifosfamide-based EORTC STBSG [15, 16] data used for the EST arm were in line with DAC and ETO results [17, 30].

The primary limitation was the use of historical data for EST arm rather than head-to-head data. Acknowledging the limitations of historical comparisons, STS-201 survivals compare favourably with survivals reported for patients after failure of second-line ifosfamide [15, 16] using the correspondent eligibility criteria as in STS-201 and for patients who received DAC [17] or ETO [30] after the failure on standard CT. Also, the trial-based efficacy and safety of TRA has been recently confirmed by a compassionate use study [8], and TRA trials have been found to be well designed [12], which improved the feasibility of this approach. A randomised data of TRA against current clinical practice was not available for such a late cancer stage due to ethical concerns and a lack of appropriate comparators.

The economic evaluation illustrated the incremental cost-effectiveness associated with treating mSTS patients who have failed A/I. The results were within the bounds of what would usually be considered as good value for money for a cancer treatment. Before TRA, for mSTS patients no significant therapeutic improvements had occurred over three decades.

conclusions

TRA was a potentially cost-effective treatment of mSTS patients who have received priory A/I. In fact, the cost-effectiveness of TRA was comparable with or superior to many other cancer drugs for nonorphan conditions. The value of additional parameter information using equivalent setting and parameter definitions is likely to be low.

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disclosure

E.J.O.S. is employee and shareholder of ESiOR Oy, commissioned by Oy Swedish Orphan Ab to perform this study; ESiOR carries out commissioned studies and health economic analysis for several pharmaceutical companies, food industry companies, and hospitals. B.G.S.A. is employee of PharmaMar and T.J. is employee and joint owner of Docrates. All authorship decisions were made on the basis of scientific consideration.

references

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appendix 1. The estimation of transition probabilities

Transition probabilities SD → PD treated with TRA, PD → death after TRA and PD → death with EST were estimated using the same principle: the number of months that it took for ≥20% of the population to remain in health state (SD or PD) was used to calculate the per cycle probabilities of progression to PD or death. This conservative cut-off ensured that only the most robust data were used. The outliers who took an unusually long time to SD → PD relative to the rest of the TRA population were excluded because the inclusion of these outliers would distort the transition probabilities and boost the cost-effectiveness associated with TRA.

TRA → EST arm transition probabilities per cycle (STS-201 24-h q3wk regime)

- Total SD → PD; for 9 months ≥20% remained SD: 0.1578 (i.e. $1 - [(1 - 0.787) (1/9)] = 0.1578$; compare Fleurence and Hollenbeak [1] for the equation). This comprised SD → PD and SD → death
- SD → death; proportion of patients for whom TTP = OS multiplied by SD → PD: 0.0070
- SD → PD; SD → death was subtracted from the total SD → PD: 0.1508
- Remaining PF; complement of the total SD → PD: 0.8422
- PD → death; for 26 months ≥20% remained PD: 0.0573.

EST arm transition probabilities per cycle (EORTC STBSG)

- PD → death; for 11 months ≥20% remained PD: 0.1147
- Remaining PD; complement of PD → death: 0.8853.

Source for Appendix 1

[1] Fleurence RL, Hollenbeak CS. Rates and probabilities in economic modelling: transformation, translation and appropriate application. *Pharmacoeconomics* 2007; 25: 3–6.

appendix 2. Resources, unit costs and resource use

Resource	Unit cost (2008 €)	Source	Units/ cycle	Cycles
TRA treatment				
Yondelis 2 × 1 mg + 1 × 0.25 mg; dexamethasone, pharmacy Or hospital price for above (optional base case scenario)	5236.47 4528.68	[1]	1	5
Administration; laboratory tests; travelling ^a	751.14	[2] ^b	1	5
ETO EST (120 mg/m²)				
Etoposid 20 mg/ml, 3 × 5 ml	60.00	[1]	3	6
Administration	679.42	[2] ^b	3	6
Laboratory tests and travelling ^a	66.90	[2] ^b	1	6
DAC EST (250 mg/m²)				
Dadatic 2 × 200 mg + 1 × 100 mg	53.93	[1]	5	6
Administration	679.42	[2] ^b	5	6
Laboratory tests and travelling ^a	108.62	[2] ^b	1	6
IADIC EST				
Adriamycin 2 mg/ml, 2 × 25 ml; Haloxan 1 g/m ² , 2 g; Uromitexan 100 mg/ml, 40 mg/kg, 2 × 10 ml + 1 × 4 ml; Dadatic 2 × 200 mg + 1 × 100 mg	231.75	[1]	1	6
Administration	679.42	[2] ^b	5	6
Laboratory tests and travelling ^a	108.62	[2] ^b	1	6
IE EST				
Haloxan 1 g/m ² , 2 g; Uromitexan 100 mg/ml, 40 mg/kg, 2 × 10 ml + 1 × 4 ml	42.58	[1]	5	6
Etoposid 100 mg/m ² , 20 mg/ml, 2 × 5 ml	40.00	[1]	3	6
Luminaletten 100 mg, 7 × 15 mg	0.85	[1]	6	6
Neulasta 6 mg	1298.08	[1]	1	6
Administration	679.42	[2] ^b	5	6
Laboratory tests and travelling ^a	66.90	[2] ^b	1	6
IMVP-a6 EST				
Haloxan 1 g/m ² , 2g; Uromitexan 100 mg/ml, 40 mg/kg, 2 × 10 ml + 1 × 4 ml	42.58	[1]	5	6
Etoposid 100 mg/m ² , 20 mg/ml, 2 × 5 ml	40.00	[1]	3	6
Methotrexate 30 m ² , 25 mg/ml, 3 × 1 ml	8.73	[1]	2	6
Administration	679.42	[2] ^b	7	6
Laboratory tests and travelling	33.87	[2] ^b	1	6
Travelling to administration	33.03	[2] ^b	2	6
SAE related to TRA				
Treatment and travelling after A/I failure	1472.90	[2] ^b	0.054	1
Ongoing treatment	607.32	[3] ^c	1	

appendix 2. (Continued)

^aTravelling to administration (€33.03) and to laboratory (€6.49).

^bIndexed from 2006 to 2008 price level with the factor of 1.0951 obtained from the Official Statistics Finland.

^cIndexed from 2005 to 2008 price level (€3042.44 during 4.98 months; €607.32 per cycle).

A/I = anthracycline and/or ifosfamide; DAC, dacarbazine; EST, end-stage treatment; ETO = etoposid; IADIC, doxorubicin, ifosfamide, mesna and DAC; IE, ifosfamide, mesna, ETO, phenobarbital and growth hormone; IMVP-6a, ifosfamide, mesna, ETO and methotrexate; SAE = serious adverse event; TRA, trabectedin.

Sources for Appendix 2

[1] Finnish Medicine Tariff. Helsinki, 1/2010.

[2] Hujanen T, Kapiainen S, Tuominen U et al.

Terveystieteiden tutkimuskeskuksen tutkimusraportti Suomessa vuonna 2006, Helsinki: Stakes, 2008.

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appendix 3. Quality of life estimation

Disease-specific EORTC QLQ-C30 scale values [1] were mapped to 15D, SF-6D and EQ-5D generic quality of life values (utilities) by multiplying them with coefficients obtained from the regression models [2]

Tool	QLQ-C30 predictor	Scale value ^a	Multiplier ^b	Outcome ^c
15D	Physical functioning	63.477	0.00299	0.18980
	Global health status	53.526	0.00262	0.14024
	Insomnia	27.084	-0.00096	-0.02600
	Cognitive functioning	86.409	0.00198	0.17109
	Constant	1.000	0.26114	0.26114
	Utility ^d			0.73626
SF-6D	Social functioning	67.451	0.00082	0.05531
	Global health status	53.526	0.00085	0.04550
	Emotional functioning	70.577	0.00167	0.11786
	Pain	28.972	-0.00122	-0.03535
	Constipation	17.019	-0.00110	-0.01872
	Dyspnoea	8.481	-0.00064	-0.00543
Constant	1.000	0.50842	0.50842	
Utility ^d			0.66760	
EQ-5D	Physical functioning	63.477	0.00508	0.32246
	Emotional functioning	70.577	0.00313	0.22091
	Global health status	53.526	0.00546	0.29225
	Constant	1.000	-0.18143	-0.18143
	Utility ^d			0.65419

^aWeighted means from Table III in [1].

^bBs from Table 3 in [2].

^cOutcome = scale value × multiplier.

^dSum.

EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQol 5D; SF-6D, Short Form 6D.

Sources for Appendix 3

[1] Poveda A, López-Pousa A, Martín J et al. Phase II Clinical Trial With Pegylated Liposomal Doxorubicin (CAELYX(R)/Doxil(R)) and Quality of Life Evaluation (EORTC QLQ-C30) in Adult Patients With Advanced Soft Tissue Sarcomas: A study

of the Spanish Group for Research in Sarcomas (GEIS). *Sarcoma* 2005; 9: 127–132.

[2] Kontodimopoulos N, Aletras VH, Paliouras D et al. Mapping the Cancer-Specific EORTC QLQ-C30 to the Preference-Based EQ-5D, SF-6D, and 15D Instruments. *Value Health* 2009; 12: 1151–1157.