Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2210

trabectedin 0.25mg and 1mg powder for concentrate for solution for infusion (Yondelis®)

Immedica

8 November 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission considered under the end of life and orphan process

trabectedin (Yondelis®) is not recommended for use within NHSScotland.

Indication under review: treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

Trabectedin, compared with an alkylating chemotherapy, increased progression-free survival but not overall survival in patients with advanced liposarcoma or leiomyosarcoma who had previously been treated with an anthracycline-based chemotherapy.

The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

Treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.[1]

Dosing Information

The recommended dose is 1.5 mg/m^2 body surface area, administered as an intravenous infusion over 24 hours with a three-week interval between cycles.
Trabectedin must be administered under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to qualified oncologists or other health professionals specialised in the administration of cytotoxic agents.
Administration through a central venous line is strongly recommended and patients must be pretreated with corticosteroids for both anti-emetic and hepatoprotective effects.[1]

Product availability date

October 2007
Trabectedin meets SMC orphan and end of life criteria for this indication.

Summary of evidence on comparative efficacy

Trabectedin is an anti-cancer medicine that binds to DNA triggering a cascade of events that disturb the cell cycle. It has been shown to have anti-proliferative effects in human tumour cells.[1]

An open-label phase III study (ET743-SAR-3007) recruited patients aged at least 15 years with unresectable locally advanced liposarcoma or leiomyosarcoma who were previously treated with at least an anthracycline combined with ifosfamide or an anthracycline plus at least one other cytotoxic chemotherapy regimen. They had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1, adequate bone marrow, renal and liver function and measurable disease on Response Evaluation in Solid Tumours (RECIST) version 1.1. Patients were randomised in a 2:1 ratio to open-label treatment with trabectedin 1.5mg/m^2 by 24-hour intravenous (IV) infusion via central line (after premedication with dexamethasone 20mg IV) or dacarbazine 1g/m^2 by 20 to 120 minute IV infusion. Study drugs were given on day 1 of a 21-day cycle and continued until disease progression or unacceptable toxicity. The primary outcome was overall survival assessed in all randomised patients.[2-4]

At the final analysis of overall survival (on 5 January 2015) there was no significant difference between the groups for overall survival. An interim analysis of overall survival (on 16 September 2013) was the final analysis of progression-free survival (PFS), defined as time from randomisation to progression assessed by investigator using RECIST version 1.1 or death from any cause. PFS was longer with trabectedin compared with dacarbazine.[2,3] Table 1 details these results and other secondary outcomes: objective response rate (ORR), defined as complete or partial response and

clinical benefit rate (CBR), defined as complete or partial response or durable stable disease for at least 18 weeks.[2,3]

Table 1: Primary and secondary outcomes of ET743-SAR-3007 study.[2,3]

		Trabectedin	Dacarbazine
Data cut-off 5.12.15			
Overall survival (primary outcome)	Events (n/N)	258/384	123/193
	Median (months)	13.73	13.14
	Hazard ratio (95% CI)	0.93 (0.75 to 1.15), p=0.49	
Data cut-off 16.9.13			
Progression-free survival	Events (n/N)	217/345	112/173
	Median (months)	4.2	1.5
	Hazard ratio (95% CI)	0.55 (0.44 to 0.70)	
	6-month rate*	37%	14%
Objective response rate	Events	9.9% (34/345)	6.9% (12/173)
	Odds ratio (95% CI)	1.47 (0.72 to 3.2)	
Clinical benefit rate	Events	34%	19%
	Odds ratio (95% CI)	2.3 (1.45 to 3.7)	

PFS = progression-free survival; CI = confidence interval; Events (n/N) = number of patients with an event / number at risk of an event; * = Kaplan-Meier estimate.

In the ET743-SAR-3007 study quality of life was assessed by MD Anderson Symptom Inventory (MDASI), which is a 19-item self-reported questionnaire reflecting patients' experience across 13 symptoms and six measures of interference with physical and mental function). The MDASI was completed by patients prior to dosing on day 1 of each cycle. At the 16 September 2013 cut-off within the trabectedin and dacarbazine groups the baseline mean scores were low across all interference and symptoms items and were comparable for both treatment groups. At each cycle through to cycle 8 mean changes from baseline in symptoms severity and interference were not clinically meaningful for either treatment group.[5]

Similar PFS, overall survival and ORR with trabectedin were observed in a phase II study (which supported the product licence) comparing licensed 3-weekly trabectedin regimen versus a weekly regimen (ET743-STS-201);[6] with trabectedin versus best supportive care in phase II (JapicCTI-121850)[7] and phase III (T-SAR)[8] studies; and in uncontrolled studies (T-DIS and TR1US).[9,10] These are detailed in table 2. All studies were open-label and recruited patients with advanced soft tissue sarcoma (ET743-STS-201 included only liposarcoma or leiomyosarcoma and JapicCTI-121850 included translocation-related sarcoma). Patients had failed on anthracycline-containing chemotherapy, except patients in TR1US and 15% of JapicCTI-121850 patients, who were unsuitable for this chemotherapy.[6-10]

PFS, overall survival and ORR were similar in three reports of real-world evidence where trabectedin was given to patients with advanced soft tissue sarcoma who had failed on chemotherapy in a worldwide early access programme, in a phase IV study in European centres and in a retrospective analysis of patients treated in France.[11-13] These are detailed in table 2.

Table 2: Progression-free survival, overall survival and objective response with trabectedin.[11-13]

Study	Treatment Group	N	Median PFS (months)	Median overallsurvival (months)	ORR (%)
Studies versus best supportive care or with no control group					
ET743-STS-201	Trabectedin licensed dose	136	3.3	13.9	5.6
	Trabectedin weekly	134	2.3	11.8	1.6
JapicCTI-121850	Trabectedin licensed dose*	37	5.6	-	8
	Best supportive care	36	0.9	-	0
T-SAR	Trabectedin licensed dose	52	3.0	-	
	Best supportive care	51	1.4	-	
T-DIS	Trabectedin licensed dose	27	7.2	27.9	
	Trabectedin for 6 cycles	26	4.0	16.5	
TR1US	Trabectedin licensed dose	24	4	9	8
Real-world evidence					
Worldwide	Trabectedin licensed dose	807	-	11.9	5.9
Europe	Trabectedin licensed dose	218	5.9	21.3	27
France	Trabectedin licensed dose	885	4.4	12	17

*1.2mg/m^2 used instead of 1.5mg/m^2; PFS = progression-free survival; OS = overall survival; ORR = objective response rate.

A matched adjusted indirect comparison (MAIC) of trabectedin versus pazopanib was presented. This was based on data from the open-label phase III studies: ET743-SAR-3007 (trabectedin versus dacarbazine)[2-4] and PALETTE (pazopanib versus placebo).[14,15] The results suggested an overall survival benefit for trabectedin over pazopanib, however the confidence interval was wide and included one. The results of the MAIC were applied to the economic analysis.

Summary of evidence on comparative safety

The safety profile of trabectedin is well characterised and includes fatigue, gastro-intestinal, liver and haematological toxicity.[1]

In the ET743-SAR-3007 study adverse events within the trabectedin and dacarbazine groups were consistent with the established safety profiles of these medicines. The following adverse events were reported more frequently in the trabectedin group, compared with the dacarbazine group:

nausea (73% and 49%), fatigue (67% and 51%), vomiting (44% versus 21%), constipation (36% versus 28%), decreased appetite (34% versus 20%), diarrhoea (34% versus 23%), dyspnoea (25% versus 19%) and peripheral oedema (24% versus 14%). Trabectedin was associated with more reports of elevated alanine transaminase (45% versus 6%), aspartate transaminase (35% versus 5%) and alkaline phosphatase (20% versus 7%). Neutropenia (49% and 29%) and anaemia (39% and 29%) were more commonly reported with trabectedin, whereas thrombocytopenia was less frequently reported with trabectedin (30% and 36%).[2]

Summary of clinical effectiveness issues

Soft tissue sarcomas make up a rare and heterogeneous group of cancers.[16] After gastrointestinal stromal tumours (GIST), leiomyosarcoma and liposarcoma are the most common subtypes.[2] Treatment of GIST is not relevant to this submission. Other advanced (locally advanced or metastatic) soft tissue sarcomas are generally treated first-line with anthracycline-based chemotherapy and combination with ifosfamide may be the treatment of choice. Imatinib is standard medical therapy for dermatofibrosarcoma protuberans. After failure of anthracycline-based chemotherapy or where this treatment is unsuitable, patients may be candidates for clinical studies. The following may be options, although high-level evidence is lacking: trabectedin, pazopanib (in non-adipogenic), eribulin (in liposarcomas and leiomyosarcomas), dacarbazine plus gemcitabine or gemcitabine plus docetaxel (in doxorubicin-pre-treated), regorafenib (in doxorubicin-pretreated advanced, non-adipogenic). [16]

In the ET743-SAR-3007 phase III study the primary outcome, overall survival, was not significantly different in the trabectedin and dacarbazine groups. However, trabectedin increased PFS compared with dacarbazine by approximately 2.7 months.[2,3] This study was not assessed at the time of marketing authorisation in the EU, but the improvement in PFS was considered clinically meaningful in the US FDA review.[3]

There were higher rates of several adverse events in the trabectedin group, compared with dacarbazine, including fatigue and gastrointestinal effects such as nausea, vomiting, decreased appetite, diarrhoea and constipation.[2] However, these do not appear to correspond with any between group differences in the assessment of quality-of-life on MDASI, despite this questionnaire including items for fatigue, nausea, lack of appetite, drowsiness and vomiting.[5] The ET743-SAR-3007 study was open-label and this may have an impact on the assessment of subjective outcomes such as adverse events and the patient-reported MDASI quality-of-life questionnaire.[2,3] Although the MDSAI asks patients to grade symptoms “at their worst”, it was completed prior to dosing on day 1 of each cycle.[5] It is possible that the time interval between the post-dose period when patients are likely to have experienced adverse effects and completion of the MDASI questionnaire on the first day of the next cycle may have an impact on the assessment.

Dacarbazine 1g/m^2 IV infusion every three weeks was the comparator in ET743-SAR-3007. This is different from the licensed dacarbazine regimen. Dacarbazine is licensed as part of a combination chemotherapy for advanced adult soft tissue sarcomas (except mesothelioma, Kaposi sarcoma).

The recommended regimen is dacarbazine daily doses of 250mg/m^2 IV infusion daily on days 1 to 5 in combination with doxorubicin every 3 weeks (ADIC regimen).[17]

The ET743-SAR-3007 study population included patients with liposarcoma or leiomyosarcoma, which represents a subgroup of the licensed population of soft tissues sarcomas.[2] However, liposarcoma or leiomyosarcoma are common subtypes of soft tissue sarcoma and there were data on the use of trabectedin in other subtypes of soft tissue sarcoma from supportive studies (JapicCTI-121850, T-SAR, T-DIS and TR1US).[7-10] The ET743-SAR-3007 study excluded patients with ECOG performance status of 2 or greater and those with unresolved toxicity from previous therapy.[2] This may limit the application of results to patients who are less fit.

In addition to the ET743-SAR-3007 phase III study, which compared trabectedin with dacarbazine, the submission included a MAIC versus pazopanib. Pazopanib is licensed for use in a range of soft tissue sarcoma, including leiomyosarcoma, but not liposarcoma.[18] SMC has issued advice (number 820/12) that pazopanib is not accepted for use within NHSScotland for treatment of adult patients with selective subtypes of advanced soft tissue sarcoma who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. There were no direct or indirect comparative data versus other treatment options. Also, there is no recognised standard treatment after failure of anthracycline-based chemotherapy in this group of rare and heterogeneous cancers.

A key weakness of the MAIC was that it was not adequately described, leading to uncertainty in interpretation of the results. There was a lack of clarity around the systematic literature review, study selection process, matching process, input data and presentation of results. The company subsequently provided further details regarding the MAIC but uncertainty remained. There was also heterogeneity across the studies in the subtypes of sarcoma, for example the PALETTE study excluded patients with liposarcoma, but included leiomyosarcoma among a wider range of soft tissue sarcomas. The ET743-SAR-3007 study included only patients with leiomyosarcoma and liposarcoma. Also, there was variation across the studies in baseline demographic and disease characteristics and anti-cancer therapies subsequent to progression.[2,3,14,15]

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of trabectedin, as an end of life and orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Soft tissue sarcomas are a rare and diverse group of cancers affecting patients across a wide age range. Median life expectancy is poor and approximately 18 months at time of diagnosis of advanced disease. Patients generally maintain a good quality of life until a rapid decline in the

final weeks of life. Symptoms depend on the location of the primary tumour and the presence of metastasis.

- Treatment options for advanced soft tissue sarcomas are limited. For patients whose disease does not respond to, or relapses following anthracyclines and ifosfamide, or who are unsuited to receive these agents, there are currently no routinely available treatments in NHSScotland. Without treatment disease progression is inevitable over a period of two to three months.
- Trabectedin has the potential to stabilise disease and maintain patients' quality of life for longer. Experience in clinical practice indicates that a proportion of patients may achieve disease response or have stable disease for many months, allowing them to return to a level of normality and independence in their daily lives and enjoy quality time in their communities.
- Trabectedin is administered as a 24-hour inpatient infusion on one day every three weeks. Adverse effects are generally manageable, becoming less prominent 7 to10 days after treatment. It has a different side-effect profile from other second-line treatments which may be an advantage for some patients.

Additional Patient and Carer Involvement

We received a patient group submission from Sarcoma UK, which is a registered charity. Sarcoma UK has not received any pharmaceutical company funding in the past two years. A representative from Sarcoma UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing trabectedin with pazopanib in adult patients with recurrent/metastatic leiomyosarcoma, which represents a subgroup of the licensed population of soft tissues sarcoma. The company also presented a cost-minimisation analysis comparing the two treatments in the full licensed population and indicated that a positioning is not being sought.

A partitioned survival model was used to estimate results for the cost-utility analysis, which tracked patients across a 200 month time horizon as they progressed across three health states: 'stable disease', 'progressive disease' and 'death'. The model cycle was set to 21 days to match the duration of one treatment cycle with trabectedin. The state distribution of patients at any given time was modelled by fitting parametric curves to the progression free survival (PFS) and overall survival (OS) data from the phase III trials of trabectedin (ET743-SAR-3007) and pazopanib (PALETTE). The original trial data seem to have been adjusted following a MAIC analysis conducted to estimate the relative effectiveness of trabectedin compared to pazopanib in the absence of direct comparison data. The treatment-related adverse events profile was also informed from the phase III trials of the two treatments. For the cost-minimisation analysis, equal efficacy was assumed between trabectedin and pazopanib and the relevant time horizon was the duration of the two treatments.

Utility values were derived from the published literature and a value of 0.770 was applied in the 'stable disease' state and a disutility of -0.210 was applied following progression to the 'progressive disease' state. Disutilities were also applied to the treatment-related adverse events based on the duration observed in the clinical trials.

The costs utilised in the model related to medicines acquisition, administration, delivery, monitoring, managing adverse events, and post-progression treatments, whereas only acquisition and administration costs were included in the cost-minimisation analysis. For the base case results presented below, a treatment duration of 4 x 21-day cycles was applied in the trabectedin arm and 5.47 x 21-day cycles in the pazopanib arm, assuming treatment is discontinued following progression. These estimates were based on the median treatment durations in the respective key studies for trabectadin and pazopanib (ET743-SAR-3007 and PALETTE).

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. A PAS discount is also in place for pazopanib which is available in the public domain and has been incorporated into the results presented below.

Table 3: Base case cost-utility analysis results, with PAS for trabectedin

	Pazopanib arm	Trabectedin arm	Incremental trabectedin vs pazopanib
Life-years	2.35	2.48	0.133
Quality-adjusted life years	1.94	1.98	0.047
Total costs	£11,255	£13,875	£2,620
ICER (£/QALY)			**£56,009**
ICER (£/ life year gained			**£19,656**

In the cost-minimisation analysis, trabectadin was not shown to be cost-minimising.

A limited range of deterministic sensitivity analyses were initially submitted by the company which focused solely on the treatment duration of trabectedin and pazopanib. The submitting company was requested to provide a more complete range of sensitivity analysis to examine uncertainty across a range of parameters in the model. Some limited analyses were subsequently provided to test the uncertainty in the presented base case above (for example to test alternative parametric distributions for OS and PFS modelling and resource utilisation costs), however there were concerns about the validity of the results presented. The use of alternative distributions for OS and PFS resulted in no change to the predicted benefits (only costs changed) and application of a +20% margin on resource costs produced the same result as applying a -20% change in resource costs, which seemed implausible. There were also concerns that the model results did not respond in the expected manner to changes in the assumed treatment durations in each arm of the model.

The economic evaluation submitted by the company suffered from number of weaknesses and limitations including:

- Relative effectiveness: The relative effectiveness estimate utilised in the cost-utility analysis of trabectedin vs pazopanib was derived following a poorly-reported unanchored MAIC which is subject to uncertainty, as noted in the clinical effectiveness section above. Also, with regards to the cost minimisation analysis, there is no robust clinical evidence to support the assumption of equivalent effectiveness between trabectedin and pazopanib in the full licensed population and in addition, trabectadin was not shown to be cost-minimising.
- Extrapolation: Lognormal and Weibull distributions were fitted to extrapolate the PFS and OS curves respectively. However, no justification was provided for the choice of distribution and as noted above, alternative distributions were eventually tested in sensitivity analysis but there was low confidence in the reported results. The methods were not adequately described and it is unclear how the MAIC was used to adjust the curves..This leads to concerns about the long-term health effects estimated from the extrapolation used in the cost-utility analysis.
- Health utilities: Reporting of the utility scores utilised was inadequate and it was not clear what the exact sources were. Also, the face values for the disutility scores associated to the adverse events in the model seem unrealistically high, e.g. 0.357 for nausea/vomiting or 0.327 for diarrhoea, which seems to favour the trabectedin arm given the adverse events profile.
- Post-progression (treatment-independent) therapies: The distributions of post-progression treatments utilised in the model were substantially different between the two arms. This is likely to be a structural bias in the model which favours trabectedin.
- Sensitivity analysis: as noted above, limited sensitivity analysis was presented to test out the uncertainty in the results presented.

A few other errors were identified in the model results presented in table 3 (for example, the administration costs of dexamethasone were not applied in the cost-minimisation analysis and the costs of pazopanib were slightly overestimated). Adjusting the company's model for these issues led to small changes in the ICER (for example the ICER for the CUA was predicted to rise to £58,388).

The Committee considered the benefits of trabectadin in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as trabectadin is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept trabectadin for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

In 2018 the European Society for Medical Oncology (ESMO) published Soft Tissue and Visceral Sarcomas: ESMO–EURACAN Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. These note that advanced soft tissue sarcoma is treated first-line with standard chemotherapy based on anthracyclines. Multi-agent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly in subtypes sensitive to ifosfamide, when a tumour response is felt to be potentially advantageous and patient performance status is good. Imatinib is standard medical therapy for those rare patients with dermatofibrosarcoma protuberans. In general, advanced previously treated patients are candidates for clinical trials. After failure of anthracycline-based chemotherapy or the impossibility to use it, the following may be options, although high-level evidence is lacking: ifosfamide, trabectedin, pazopanib (in non-adipogenic), eribulin (in liposarcomas and leiomyosarcomas), dacarbazine plus gemcitabine or gemcitabine plus docetaxel (in doxorubicin-pre-treated), regorafenib (in doxorubicin-pretreated advanced, non-adipogenic).[16]

Additional information: comparators

pazopanib (in non-adipogenic), eribulin, ifosfamide and other chemotherapies, for example dacarbazine plus gemcitabine or gemcitabine plus docetaxel.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per 21-day cycle (£)
Trabectedin	**1.5mg/m^2 24-hour infusion on day one of 21-day cycle**	**3,821**
Pazopanib	800mg orally once daily	1,570
Eribulin	1.23mg/m^2 intravenously on days 1 and 8 of 21-day cycle	1,083
Ifosfamide	3g/m^2 intravenously daily on days 1 to 3 of 21-day cycle	684

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 2 August 2018. Costs calculated using the full cost of vials/ampoules assuming wastage and assuming a body surface area of 1.8m^2. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated that the population eligible for treatment is 118 patients each year for the first five years. After applying a discontinuation rate of 71% and an uptake rate of 17%, it was estimated that 6 patients will be treated with the new medicine per year.

At list prices the gross additional budget impact i £134k per year while the net impact accounting for the medicines displaced is £50k per year.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 September 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:
No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the

individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.