NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trifluridine–tipiracil for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after 2 or more treatments (Review of TA669) [ID6167]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Trifluridine–tipiracil for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after 2 or more treatments (Review of TA669) [ID6167]

Contents:

The following documents are made available to consultees and commentators:

Link to TA669 on the NICE website

1. **Company Review submission** from Servier
   a. Review submission
   b. Response to Clarification question

2. **External Assessment Report** prepared by the School of Health and Related Research (ScHARR)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Single technology appraisal

Document B

Company evidence submission

Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies [ID6167]

August 2022

File name	Version	Contains confidential information	Date
Servier Submission Trifluridine–tipiracil [ID 6167]	**1**	**Yes**	**Aug 2022**

Tables

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Severity

Trifluridine Tipiracil meets the criteria for the highest severity weight, yielding a weighting of 1.7 times the usual weight. The FAD published in Dec 2020 concluded that the company's economic model was suitable for decision making and calculations have been derived from this model. The model shows 0.37 discounted QALYs for BSC in the 3L population. Using the ScHARR app (https://r4scharr.shinyapps.io/shortfall/)[1], this then gives an estimated *proportional* QALY shortfall of 96.84% which resides in the most severe tier (i.e., greater than 95%). The absolute shortfall is calculated at 11.33. Based on Section 6.2.18 of the new manual: *"The QALY weightings for severity are applied based on absolute and proportional shortfall, whichever implies the greater severity level. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply."* This is important as we meet the highest for proportional shortfall, but not absolute shortfall.

Table 1 shows the company's further analysis that was previously presented to the committee taking the third line only population from Shitara et al, 2018[2]. From this a sex distribution of 33.6 female, and starting age of 62 is calculated for this population, as shown in Table 2

Table 1: Baseline patient characteristics – third line only population

	Trifluridine/tipiracil (n=126)	Placebo (n=64)
Age (years) Median (IQR) <65 ≥65	[redacted]	
Sex Male Female		
Ethnicity White Asian Other Not available		
Region USA Europe* Japan		
ECOG performance status 0 1		
Primary site Gastric		

GEJ Both	[redacted]
Measurable disease	
Histology Diffused Intestinal Mixed Unknown Not available	
HER2 status Positive Negative Not assessed or unknown	
No. of metastatic sites 1–2 ≥3	
Peritoneal metastases	
Previous gastrectomy	
No. of prior regimens 2 3 ≥4	
Prior systemic cancer therapeutic agents Platinum Fluoropyrimidine Taxane Irinotecan Ramucirumab Anti-HER2 therapy† Immunotherapy (anti–PD-1/PD-L1)† Other†	

Key: ECOG PS: Eastern Cooperative Oncology Group performance status; HER2: human epidermal growth factor receptor 2; PD-1: programmed death-1; PD-L1: programmed death-ligand 1.
Note: Data are n (%) unless noted otherwise. *Please note that Europe refers to Belarus, Belgium, Czech Republic, France, Germany, Ireland, Israel, Italy, Poland, Portugal, Romania, Russia, Spain, Turkey, and the UK. †Servier could not identify these values at this time.

Table 2 Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)
Sex distribution	33.6% female (table 1)
Starting age	62 (table 1)

There are no relevant previous evaluations to include on QALY shortfall. This is essentially borne out by the fact that the comparator is BSC. Therefore, there are no

previous evaluations that would provide relevant information regarding QALY shortfall

Table 3 Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
Progression free	[redacted]	[redacted]
Post Progression	[redacted]	[redacted]

Table 4 Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
11.7	0.37	96.84%/11.33

Company Base Case

The company's base case is the population of patients that were treated in the third line setting only (i.e., patients with only 2 prior therapies), as this population is expected to most closely resemble the population of patients eligible for treatment with Trifluridine/Tipiracil (T/T) in National Healthcare System (NHS) practice[3]. This is because in NHS practice, there is no other active treatment option that is routinely considered for use at this line, nor formally recommended in accordance with National Institute for health Care and Excellence (NICE) guideline[3]. The improved outcomes associated with T/T exclusively in a third-line population (versus a third line *and beyond* population) is aligned with clinical expectation – that is, treatment at later lines of therapy is associated with a poorer prognosis, and hence reduced capacity to derive benefit from active treatment (Table 5).

Table 5: Efficacy outcomes of TAGS study in the 3L only population and ITT[4]

	3L only (months)		ITT population (months)	
	T/T (n=126)	BSC (n=64)	T/T (n=337)	BSC (n=170)
OS	6.8	3.2	5.7	3.6
	HR: 0.68 (95% CI, 0.47-0.97), p=0.0318		HR: 0.69 (95% CI, 0.56-0.85), p=0.0006	
PFS	3.1	1.9	2.0	1.9
	HR: 0.54 (95% CI, 0.38-0.77), p=0.0004		HR: 0.57 (95% CI, 0.47-0.70), p<0.0001	

BSC: best supportive care; HR: hazard ratio; ITT: intention to treat; OS: overall survival; PFS: progression free survival; T/T: trifluridine/tipiracil

The TAGS trial recruited patients in the third line and beyond treatment setting, of which 190 patients were treated in the 3rd line setting and 90% of those were European.

On 3 March 2020, a teleconference was held between the NICE and the company (Servier) concerning the use of T/T for patients with metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after 2 or more therapies. During this

call, NICE invited the company to provide additional analysis concerning the third line only population enrolled within the TAGS trial (i.e., patients with only 2 prior therapies), accounting for any potential imbalances in patient baseline characteristics. As part of this teleconference, NICE highlighted five potentially important characteristics that would need to be acknowledged as part of the weighting analysis. These were:

- **Peritoneal metastases:** Patients with an absence or presence of peritoneal metastases (also known as peritoneal involvement)
- **Eastern Cooperative Oncology Group Performance Status (ECOG PS):** Patients with an ECOG PS of 0 versus 1
- **Histology:** Patients with intestinal versus non-intestinal histology
- **Ethnicity or Region:** Patients residing in Japan or the rest of the world ("region") or patients who are Asian versus non-Asian ("ethnicity")
- **Prior irinotecan:** Patients with previous exposure to irinotecan versus no previous exposure to irinotecan

This analysis was previously submitted to the committee, and patients in both arms were reweighted to minimise the difference in potentially important variables at baseline, though it should be noted that any re-weighting approach is subject to limitations owing to the number of patients available to inform the analysis. The FAD issued by NICE in Dec 2020 states that the committee concluded that this adjusted analysis provided by the company was acceptable

Results

The -population of patients considered within this analysis are the third-line patients ("3L only")

It should be noted that this report contains results based on a revised patient access scheme (PAS) discount of [redacted] on the list price of T/T. This revised discount applies to both the metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma (relevant to this appraisal) and the previously recommended metastatic colorectal cancer indication (NICE TA405).

Table 6: Cost-effectiveness results produced by the company

Arm	Costs	QALYs	Costs	QALYs	ICER
BSC	[redacted]	0.367	-	-	-
T/T	[redacted]	[redacted]	[redacted]	[redacted]	£45,662

The QALY weighting of 1.7 is then applied to the incremental QALY gain as seen in table 7.

Table 7: Cost-effectiveness results with severity modifier applied

Arm	Costs	QALYs	Costs	QALYs	ICER
BSC	[redacted]	0.367	-	-	-
T/T	[redacted]	[redacted]	[redacted]	[redacted]	£26,860

Therefore, application of the severity modifier to the company base case of the third line population gives an ICER of £26,860, falling within the recommended threshold of £20,000-£30,000.

Following communication from NICE, the third line European subgroup has also been explored.

Table 8: Baseline patient characteristics – third-line, European only population

	Trifluridine/tipiracil (n=126)	Placebo (n=64)
Age (years) Median (IQR) <65 ≥65	[redacted]	
Sex Male Female		
Ethnicity White Asian Other Not available		
Region USA Europe* Japan		
ECOG performance status 0 1		
Primary site Gastric GEJ Both		
Measurable disease		
Histology Diffused Intestinal Mixed Unknown Not available		
HER2 status Positive Negative Not assessed or unknown		
No. of metastatic sites 1–2 ≥3		
Peritoneal metastases		
Previous gastrectomy		
No. of prior regimens 2 3 ≥4		
Prior systemic cancer therapeutic agents Platinum Fluoropyrimidine Taxane Irinotecan Ramucirumab Anti-HER2 therapy† Immunotherapy (anti–PD-1/PD-L1)†		

Other†	[redacted]

Table 9 Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)
Sex distribution	28.9% female (table 8)
Starting age	62 (table 8)

Table 10 Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
11.67	0.37	96.83%/11.3

Table 11: Cost-effectiveness results produced by the company

Arm	Costs	QALYs	Costs	QALYs	ICER
BSC	[redacted]	0.371	-	-	-
T/T	[redacted]	[redacted]	[redacted]	[redacted]	£49,771

The QALY weighting of 1.7 is then applied to the incremental QALY gain as seen in table 12.

Table 12: Cost-effectiveness results with severity modifier applied

Arm	Costs	QALYs	Costs	QALYs	ICER
BSC	[redacted]	0.371	-	-	-
T/T	[redacted]	[redacted]	[redacted]	[redacted]	£29,347

References

1.Paul Schneider, Simon McNamara, James Love-Koh, Tim Doran, Nils Gutacker. QALY Shortfall Calculator. 2021. https://r4scharr.shinyapps.io/shortfall/

2. Shitara K, Doi T, Dvorkin M, Mansoor W, Arkenau H-T, Prokharau A, et al. Trifluridine/tipiracil versus placebo in patients with heavily pre-treated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 2018;19(11):1437-48.

3.National Institute for Health and Care Excellence (2018). Oesophago-gastric cancer: assessment and management in adults. [NICE guideline NG83] https://www.nice.org.uk/guidance/ng83/resources/oesophagogastric-cancer-assessment-and-management-in-adults-pdf-1837693014469

4.Tabernero J, Shitara K, Zaanan A, et al. Trifluridine/tipiracil versus placebo for third or later lines of treatment in metastatic gastric cancer: an exploratory subgroup analysis from the TAGS study. ESMO Open. 2021 Aug;6(4)

Response to NICE clarification 9th Sept 2022

Servier apologises for the error on the calculation of the sex distribution and agrees it should be 33.3% as calculated by NICE. Table 1 and 2 now show adjusted calculations for the QALY shortfall analysis in the 3rd line European population, remaining in the 1.7 x severity modifier.

Table 1 Summary features of QALY shortfall analysis

Factor	**Value (reference to appropriate table or figure in submission)**
Sex distribution	33.3% female
Starting age	62

Table 2 Summary of QALY shortfall analysis

Expected total QALYs for the general population	**Total QALYs that people living with a condition would be expected to have with current treatment**	**QALY shortfall**
11.69	0.37	96.84%/11.3

Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
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1 Background

In January 2021, National Institute for Health and Care Excellence (NICE) published guidance on Technology Appraisal 669 (TA669) which appraised trifluridine–tipiracil (TFT) for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after 2 or more therapies.[1] TFT was not recommended, with the appraisal committee deciding that TFT did not meet NICE's criterion to be considered a life-extending treatment at the end of life. As such, the committee's preferred incremental cost-effectiveness ratio (ICER) of £49,771 per quality-adjusted life-year (QALY) gained compared with best supportive care (BSC) was much higher than £30,000 per QALY gained which is the upper published threshold for interventions that are not considered to meet the end-of-life criteria.

As stated, in the appraisal for TA669 the end-of-life criteria was considered not to have been met. Unusually, this was due to not meeting the extension to survival criterion of robustly more than three months, rather than not meeting the short life expectancy criterion, which is, on average, less than 2 years of survival without the intervention. For information, in the committee's preferred analysis the overall survival gain was 2.7 months in addition to 6.6 months estimated for patients on standard of care.

The methods guide published by NICE in January 2022 removed the end-of-life criteria, replacing these with severity modifiers.[2] Following this change, NICE invited the company to resubmit evidence to review TA669 incorporating severity modifiers, as the short life expectancy criterion had been met. The company submitted a document in August 2022, with a later document focussing on the committee's preferred analysis.

[1] Overview | Trifluridine–tipiracil for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after 2 or more therapies | Guidance | NICE (Accessed 31st August 2022)
[2] Introduction to health technology evaluation | NICE health technology evaluations: the manual | Guidance | NICE

2 The company's analysis

2.1 Calculation of the absolute and proportionate QALY shortfall

In Table 1 of the company's first document, baseline characteristics are reported for people receiving third-line treatment. The summary data was a mean age of 62 years and with 33.6% of patients being female. The company clarified that for a European population receiving third-line treatment these values were 62 years and 33.3% female.

The company used a third-party app (https://r4scharr.shinyapps.io/shortfall/) to calculate the absolute and proportionate shortfall. It was estimated that for a population aged 62 years and with 33% female, 11.69 QALYs would be gained for a population without the disease, while the QALYs gained for patients receiving third-line treatment without TFT was estimated to be 0.37 based on the committee's preferred assumption. From these values it is predicted that the absolute shortfall was 11.32 years, and the proportional shortfall is 96.84%. These numbers would warrant the highest weighting associated with severity which is a QALY weight of 1.7.

2.2 The committee's preferred analysis when using the severity modifier

The deterministic results provided by the company using the committee's preferred analysis are shown in Table 1 when using a severity modifier of 1, and in Table 2 when using a severity modifier of 1.7; probabilistic results were similar to deterministic results.

Table 1: The committee's preferred assumption using a severity modifier of 1

	Cost (£)	QALY	Inc Costs (£)	Inc QALYs	ICER (£)
BSC	[redacted]	0.371			
TFT	[redacted]	[redacted]	[redacted]	[redacted]	49,771

Table 2: The committee's preferred assumption using a severity modifier of 1.7

	Cost (£)	QALY	Inc Costs (£)	Inc QALYs	ICER (£)
BSC	[redacted]	0.371			
TFT	[redacted]	[redacted]	[redacted]	[redacted]	29,347

2.3 The External Assessment Group's critique of the company's documents

The External Assessment Group (EAG) could replicate the analyses documented by the company and supports the company's view that the severity modifier of 1.7 appears appropriate in this appraisal.

Conclusion

The EAG agrees that the highest severity modifier appears to be appropriate within this appraisal. If the incremental QALYs are multiplied by 1.7 the committee's previously preferred ICER of £49,771 is reduced to a value of £29,347.