SMC2839

zolbetuximab powder for concentrate for solution for infusion (Vyloy®)

Astellas Pharma Ltd

05 December 2025

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 full submission assessed under the end of life and orphan medicine process

zolbetuximab (Vyloy®) is accepted for use within NHSScotland.

Indication under review: In combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.

In two phase III studies in adult patients with HER2-negative, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma whose tumours were positive for CLDN18.2, the addition of zolbetuximab to chemotherapy was associated with statistically significant increases in progression-free survival.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

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

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Zolbetuximab is a monoclonal antibody that targets the tight junction molecule CLDN18.2 and depletes CLDN18.2-positive cells via both antibody-dependent cellular toxicity and complement-dependent cytotoxicity. Cytotoxic medicines can increase CLDN18.2 expression in human cancer cells which improves zolbetuximab cytotoxic activities.[1] Zolbetuximab is administered in combination with fluoropyrimidine- and platinum-containing chemotherapy and should be continued until disease progression or unacceptable toxicity. The recommended loading dose of zolbetuximab is 800 mg/m^2 via intravenous (IV) infusion on cycle 1, day 1 (the cycle duration of zolbetuximab is determined based on the respective chemotherapy backbone). The recommended maintenance dose of zolbetuximab is either 600 mg/m^2 via IV infusion every 3 weeks or 400 mg/m^2 via IV infusion every 2 weeks.[1]

1.2. Disease background

Gastric cancer is the fifth most common cancer worldwide, and the fourth leading cause of death with over 700,000 deaths in 2020.[2] In the UK, gastric cancer accounts for 2% of all new cancer cases. Evidence suggests that approximately 50% of gastric cancers in the UK occur in people aged 75 years and older; it is twice as frequent in men than women.[3, 4] Gastric cancer is often diagnosed at an advanced stage due to a lack of specific symptoms, and curative treatments are not appropriate for a large proportion (approximately 60%) of patients.[5] Survival rates at 12 months after diagnosis of metastatic gastric/gastro-oesophageal cancer are estimated to be as low as 20%. As gastric cancer and gastro-oesophageal junction (GEJ) cancers are similar, both histologically and in terms of treatment response, they are commonly a combined target population in clinical studies.[4, 6]

1.3. Treatment pathway and relevant comparators

The most relevant comparator in this setting is fluoropyrimidine and platinum-containing chemotherapy. Immunotherapies nivolumab (SMC2458) and pembrolizumab (SMC2660) have been accepted for use in combination with chemotherapy for PDL1-positive patients however clinical experts consulted by SMC confirmed that zolbetuximab would rarely displace use of these treatments and would largely be used in patients who are not eligible or not suitable for immunotherapy.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Zolbetuximab received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway from the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting

Zolbetuximab meets SMC end of life and orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of zolbetuximab comes from the SPOTLIGHT and GLOW studies. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies.[7-10]

Criteria	SPOTLIGHT	GLOW
Study design	International, randomised, double-blind, phase III study	
Eligible patients	• Adult patients with histologically confirmed gastric or GEJ adenocarcinoma. • Radiologically confirmed, locally advanced unresectable or metastatic disease. • Patients had not received prior systemic chemotherapy for locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma however neo-adjuvant/adjuvant chemotherapy immunotherapy or other systemic anticancer treatments were permitted if completed at least 6 months prior to randomisation. • Patient's tumour was CLDN18.2 positive (defined as ≥75% of tumour cells showing moderate-to-strong membranous CLDN18 staining as determined by central IHC testing. • Known HER2-negative tumour. • ECOG performance status 0 to 1. • Predicted life expectancy ≥12 weeks in the opinion of the investigator. • Adequate organ function.	
Treatments	Zolbetuximab intravenously 800 mg/m^2 loading dose followed by subsequent doses of 600 mg/m^2 every three weeks plus mFOLFOX6 or placebo plus mFOLFOX6. mFOLFOX6 was administered intravenously as oxaliplatin 85 mg/m^2 concurrent with folinic acid 400 mg/m^2 (or levofolinate 200 mg/m^2), followed by a 5-FU 400 mg/m^2 intravenous bolus, followed by a continuous infusion of 5-FU 2,400 mg/m^2 over 46 to 48 hours. All components of mFOLFOX6 were administered every two weeks for four or more cycles (3 treatments per cycle). Patients received up to 12 mFOLFOX6 treatments (or components of mFOLFOX6 if some components were discontinued due to toxicity). After 12 mFOLFOX6 treatments, patients could continue to receive 5-FU and folinic acid at the investigator's discretion.	Zolbetuximab intravenously 800 mg/m^2 loading dose followed by subsequent doses of 600 mg/m^2 every three weeks plus CAPOX or placebo plus CAPOX. CAPOX was administered as intravenous oxaliplatin 130 mg/m^2 on day 1 of each 21-day cycle and capecitabine oral tablets 1,000 mg/m^2 twice daily on days 1 to 14 of each 21-day cycle. Patients received up to 8 CAPOX treatments. Patients without disease progression after eight cycles continued with zolbetuximab or placebo, plus capecitabine at investigator's discretion.
	Treatment continued until disease progression, development of toxic effects, start of another anticancer treatment, or other discontinuation criteria were met,	

	as specified in the protocol.
Randomisation	Patients were randomised equally, with stratification according to region (Asia versus non-Asia), number of organs with metastatic sites (0 to 2 versus ≥ 3), and prior gastrectomy (yes versus no).
Primary outcome	Progression-free survival, defined as the time from the date of randomisation until the date of radiological progression of disease (per RECIST 1.1 by independent review committee) or death from any cause, whichever is earliest.
Selected secondary outcomes	OS, DOR, ORR, HRQoL.
Statistical analysis	Efficacy analyses were performed in the full analysis set, which included all patients who underwent randomisation. Formal hypothesis testing for overall survival at the interim and final OS analyses was only to be performed if PFS was significant. An O'Brien-Fleming type alpha-spending function was utilised to control the overall 1-sided significance level for OS interim and final analyses.

Abbreviations: 5FU = 5-fluorouracil; CAPOX = capecitabine and oxaliplatin; CLDN = Claudin; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; GEJ = gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2; HRQoL = Health-related quality of life; mFOLFOX6 = folinic acid, fluorouracil and oxaliplatin; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria In Solid Tumours Version 1.1.

The addition of zolbetuximab to chemotherapy resulted in statistically significant improvements in PFS and overall survival in the SPOTLIGHT and GLOW studies. See Table 2.2 for details.

Table 2.2. Key efficacy results from SPOTLIGHT (data-cut: 08 September 2023) and GLOW (data-cut: 12 January 2024) (full analysis set).[9]

	SPOTLIGHT		**GLOW**	
	Zolbetuximab plus mFOLFOX6 (n=283)	**mFOLFOX6 (n=282)**	**Zolbetuximab plus CAPOX (n=254)**	**CAPOX (n=253)**
Primary outcome: progression-free survival (IRC-assessed, RECIST 1.1)				
Median follow-up	18.0 months	17.9 months	20.6 months	23.5 months
Events, n	159	187	153	182
Median PFS	11.0 months	8.9 months	8.2 months	6.8 months
Hazard ratio (95% CI)	0.73 (0.59 to 0.91) p=0.002		0.69 (0.55 to 0.86) p<0.001	
KM estimate of PFS at 12 months	49%	39%	34%	19%
Key secondary outcome: overall survival				
Median follow-up	33.3 months	31.4 months	31.7 months	33.0 months
Events, n	197	217	180	207
Median OS	18.2 months	15.6 months	14.3 months	12.2 months
Hazard ratio (95% CI)	0.78 (0.64 to 0.95) p=0.008		0.76 (0.62 to 0.94) p=0.005	
KM estimate of OS at 12 months	67%	61%	57%	50%

Secondary outcome: objective response rate (IRC-assessed, unconfirmed responses)				
Best overall response	90%	94%	83%	89%
Complete response	7.4%	4.6%	4.3%	1.6%
Partial response	41%	43%	38%	38%
Secondary outcome: duration of response				
Median DOR	9.0 months	8.1 months	6.3 months	6.1 months

Abbreviations: CAPOX = capecitabine and oxaliplatin; CI = confidence interval; DOR = duration of response; FAS = full analysis set; IRC = independent review committee; mFOLFOX6 = folinic acid, fluorouracil and oxaliplatin; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria In Solid Tumours Version 1.1.

The submitting company also presented an ad-hoc pooled analysis of SPOTLIGHT and GLOW. The PFS hazard ratio (HR) of zolbetuximab plus chemotherapy versus placebo plus chemotherapy was 0.71 (95% confidence interval [CI]: 0.61 to 0.83) and the overall survival HR was 0.77 (95% CI: 0.67 to 0.89).[9]

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30), the Quality of Life Oesophago-Gastric (QLQ-OG25), and the EQ-5D-5L questionnaires. Overall, baseline scores were similar in the treatment groups in both SPOTLIGHT and GLOW, and mean total and subscale scores throughout the treatment and follow-up periods were also similar, suggesting that zolbetuximab had no adverse impact on quality of life.[7]

2.3. Supportive studies

The FAST study was a randomised, open-label, phase II study evaluating the efficacy and safety of zolbetuximab in combination with EOX (epirubicin, oxaliplatin, and capecitabine) as a first-line treatment in patients with advanced gastric/GEJ/oesophageal adenocarcinoma and moderate-to-strong CLDN18.2 expression in ≥40% of cells.[11] This chemotherapy combination is not used in NHSScotland.[12]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing zolbetuximab plus chemotherapy with nivolumab/pembrolizumab plus chemotherapy, the submitting company presented an indirect treatment comparison. This has been used to inform the economic analysis, although the comparison between zolbetuximab plus chemotherapy and nivolumab/pembrolizumab plus chemotherapy was not thought relevant to decision-making.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Spline NMA with proportional hazards and non-proportional hazards with fixed effects
Population	**zolbetuximab plus chemotherapy:** in patients ≥ 18 years, CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma, compared with: **nivolumab plus chemotherapy:** in patients ≥18 years, previously untreated, unresectable advanced or metastatic, G/GEJ, or oesophageal adenocarcinoma with PD-L1 CPS ≥ 5 **pembrolizumab plus chemotherapy:** in patients ≥18 years, confirmed HER2-negative, G/GEJ that was locally advanced, unresectable or metastatic, no previous treatment, had measurable disease and PD-L1 CPS ≥ 1

Comparators	Nivolumab plus XELOX or FOLFOX Pembrolizumab plus cisplatin and fluorouracil or capecitabine Pembrolizumab plus cisplatin and fluorouracil or capecitabine and oxaliplatin
Studies included	**SPOTLIGHT**[7]: Zolbetuximab plus mFOLFOX6 versus placebo plus mFOLFOX6 **GLOW**[10]: Zolbetuximab plus CAPOX versus placebo plus CAPOX **CheckMate-649**[13]: Nivolumab plus XELOX/FOLFOX versus XELOX/FOLFOX **KEYNOTE-062**[14]: Pembrolizumab plus cisplatin and fluorouracil or capecitabine versus placebo plus cisplatin and fluorouracil or capecitabine **KEYNOTE-859**[15]: Pembrolizumab plus cisplatin and fluorouracil or CAPOX versus placebo plus cisplatin and fluorouracil or CAPOX
Outcomes	Progression-free survival and overall survival
Results	Overall, zolbetuximab plus chemotherapy, pembrolizumab plus chemotherapy, and nivolumab plus chemotherapy had similar hazard ratios compared with chemotherapy alone for both PFS and overall survival, with overlapping credible intervals.

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

3. Summary of Safety Evidence

Safety data are available from an integrated analysis of SPOTLIGHT (data-cut: 9 September 2022) and GLOW (data-cut: 7 October 2022) which provides data versus relevant comparators; median follow-up in SPOTLIGHT was 8.6 months in the zolbetuximab group and 8.9 months in the placebo group and in GLOW was 7.0 months and 7.2 months respectively. Any treatment-emergent adverse event (AE) was reported by 99% (529/533) of patients in the zolbetuximab plus chemotherapy group and 99% (521/527) in the placebo plus chemotherapy group and these were considered treatment-related in 98% and 95% respectively. In the zolbetuximab plus chemotherapy and chemotherapy groups respectively, patients reporting a grade 3 or higher AE were 80% versus 74%, patients with a reported serious AE were 46% versus 46%, the proportion of AEs that led to dose interruptions were 77% versus 54% and TEAEs leading to permanent discontinuation of study medicine was 37% versus 32%.[8]

The most frequently reported treatment-emergent AEs of any grade with an incidence >20% in the zolbetuximab plus chemotherapy group versus the placebo plus chemotherapy group were: nausea (76% versus 56%), vomiting (67% versus 33%), decreased appetite (44% versus 34%), anaemia (36% versus 37%), diarrhoea (36% versus 40%), neutrophil count decreased (31% versus 28%), peripheral sensory neuropathy (30% versus 33%), neutropenia (28% versus 24%), constipation (26% versus 31%), fatigue (21% versus 25%), aspartate aminotransferase increased (21% versus 22%), abdominal pain (20% versus 26%), asthenia (20% versus 18%), weight decreased (20% versus 15%), and platelet count decreased (19% versus 21%).[8]

The most common and severe toxicities observed with zolbetuximab plus chemotherapy were gastrointestinal disorders such as nausea and vomiting.[8]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Zolbetuximab is a first-in-class monoclonal antibody that targets CLDN18.2. With its novel mechanism of action zolbetuximab offers a targeted treatment option for patients who would otherwise receive doublet chemotherapy alone.
- SPOTLIGHT and GLOW were well-conducted phase III studies that support the addition of zolbetuximab to fluoropyrimidine- and platinum-containing chemotherapy regimens.[7, 10] The control groups of these studies (mFOLFOX6 and CAPOX) are relevant comparators in this setting.
- The addition of zolbetuximab to chemotherapy was associated with statistically significant and clinically relevant improvements in both PFS and overall survival in SPOTLIGHT and GLOW. In SPOTLIGHT, median PFS improved by 2.1 months and median overall survival improved by 2.6 months. Prespecified sensitivity analyses of PFS including investigator-based assessment and analyses to address likely informed censoring were consistent with the primary findings which in conjunction with the relative maturity of the data suggests the results are robust.[8]

4.2. Key uncertainties

- There is some uncertainty in the treatment effect of zolbetuximab in White patients. In the subgroup analysis of the combined studies (SPOTLIGHT and GLOW), the PFS HR for White patients (n=458/1,072) was 0.88 (95% CI: 0.70 to 1.10) compared with the Asian subgroup (n=509/1,072) which had a PFS HR of 0.58 (0.46 to 0.72); a similar pattern was observed for overall survival also. Investigators hypothesise that the difference can be explained due to lower exposure to zolbetuximab in White patients caused by higher rates of treatment interruptions and discontinuations from AEs, mainly nausea and vomiting. Regulators considered that the lack of benefit due to treatment-emergent AEs may be acceptable provided that side effects are appropriately managed and do not impact on exposure to the backbone chemotherapy treatments. Additional warnings and precautions to mitigate the risks have been implemented in the SPC as a result.[8, 9]
- GLOW predominantly recruited in Asia which may limit the generalisability of study results to the Scottish population; 63% of the study population were Asian. Moreover, the median weight of patients and the proportion of patients with GEJ adenocarcinoma in GLOW is likely to differ to the Scottish population.[8]
- No benefits were observed for the secondary outcomes ORR, DOR, and quality of life outcomes; results were generally similar between zolbetuximab plus chemotherapy and chemotherapy. In gastric cancer it is acknowledged that ORR does not always correlate with PFS and overall survival.[8]
- There are limited data to support the use of zolbetuximab in patients aged 75 years or older; approximately 6% of patients in SPOTLIGHT and GLOW were aged 75 or older. Almost half (49%) of all new stomach cancer cases in the UK are diagnosed aged 75 and over.[4, 8] Information provided by the Cancer Medicines Outcome Programme-Public Health Scotland

described the median age of patients treated for first line HER2 negative gastric or GEJ cancer as lower at 67 years.[12]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that zolbetuximab in combination with chemotherapy fills an unmet need and is a therapeutic advancement in this setting particularly for patients who are ineligible for immunotherapy (i.e. PDL1-negative) or for patients who are contraindicated to immunotherapy.

4.4. Service implications

The addition of zolbetuximab to chemotherapy may have implications for the service as it will require increased chair time in chemotherapy units and more resource from aseptic pharmacy services. Testing for CLDN 18.2 may impact on pathology services.

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information.

5. 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 zolbetuximab, as an orphan and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Stomach cancer is a severe, life-threatening, and debilitating condition which is difficult to treat. Nearly half of all patients diagnosed with stomach cancer already have advanced and incurable disease and prognosis is poor. For patients, the impact on everyday life is immediate and severe. Eating becomes difficult early on; socialising around food, an important part of family life, can be painful and isolating. Swelling of the abdomen, fatigue, weakness, and vomiting reduce mobility and independence. Everyday tasks quickly become impossible. Patients often need increasing physical support at home, and caregivers may give up work to provide it. The emotional and psychosocial toll is profound. The symptoms that matter most to patients are those that strip away both independence and dignity - pain, inability to eat, overwhelming tiredness, and loss of mobility.

- Few effective treatment options exist for patients with advanced HER2-negative stomach cancer, particularly for those who are unsuitable for immunotherapy. Chemotherapy is associated with only modest benefit and can have side effects that impact on everyday activities such as peripheral neuropathy and hand-foot syndrome. Treatment places a heavy burden on daily life. Many patients will not be fit enough to receive second-line treatment, there is therefore a high unmet need for more effective treatment options.

- Zolbetuximab is the first treatment licensed to treat tumours that are CLDN18.2 positive; it

offers eligible patients a targeted treatment option where at present they may only receive chemotherapy. The addition of zolbetuximab to chemotherapy may increase the time before disease progression and may improve overall survival. This can translate into patients having more time feeling well, and more time with loved ones which is a considerable improvement in quality of life compared with existing treatments. With an increasing number of younger patients being diagnosed with advanced gastric cancer, zolbetuximab may also help younger patients remain in work for longer. Zolbetuximab offers the chance of more durable responses; patients who respond are much more likely to be independent at home and less likely to require in-patient hospital treatment.

- Zolbetuximab (plus chemotherapy) would provide an additional, effective treatment option which is highly valued by families and caregivers. Zolbetuximab may not only give their loved ones more time but also delay loss of independence, reduce the need for intensive caregiving, and ease the emotional burden. It may also alleviate some financial pressures for families or carers as less time may be spent on care-related activities. Younger patients with an advanced gastric cancer diagnosis may have caring responsibilities of their own, zolbetuximab could allow these patients to continue to provide care for longer.

- PACE participants noted that zolbetuximab is associated with some side effects, the main ones being nausea and vomiting. However, it was felt that most of these adverse events can be managed with supportive medicines and through dose modifications. Patients are willing to endure potential significant side effects in exchange for expected additional survival time and delay in decline. Management of nausea and vomiting associated with zolbetuximab has improved since the publication of clinical studies.

Additional Patient and Carer Involvement

We received a patient group submission from Gastric Cancer UK, which is a charitable incorporated organisation. Gastric Cancer UK has not received any pharmaceutical company funding in the past two years. Representatives from Gastric Cancer UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 summaries the economic case.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	40 years, with a starting age of 58.5 years
Population	The population in the economic analysis matched the licensed indication
Comparators	The primary analysis considered chemotherapy alone to be the main comparator. In line with the licence, chemotherapy comparators were fluoropyrimidine plus platinum doublet regimens (CAPOX or FOLFOX). Additional subgroup analyses were performed which considered nivolumab plus chemotherapy and pembrolizumab plus chemotherapy as comparators, for patients with PD-L1 CPS≥5 and PD-L1 CPS≥1 respectively.
Model description	The model was a three-state partitioned survival model which comprised of pre-progression, post-progression, and death states. Patients started in the pre-progression state and could move to post-progression or death.
Clinical data	Clinical data were taken from the phase III SPOTLIGHT and GLOW studies which compared zolbetuximab plus chemotherapy and chemotherapy alone.[7-10] For the chemotherapy reference arm, OS and PFS data from SPOTLIGHT and GLOW were supplemented with data from the chemotherapy arm and the PD-L1 CPS≥5 subgroup of the CheckMate-649 study.[13] Duration of treatment (DoT) was sourced from the clinical data from GLOW study only. Comparative effectiveness for zolbetuximab plus chemotherapy versus chemotherapy were informed by the non-proportional hazards NMA outputs, as was the comparative effectiveness of nivolumab plus chemotherapy and pembrolizumab plus chemotherapy. AE rates were sourced using pooled data from SPOTLIGHT and GLOW.
Extrapolation	In the base case, the OS and PFS outcomes in the chemotherapy arm were modelled by extrapolating the pooled data across the SPOTLIGHT, GLOW and CheckMate-649 studies. For both PFS and OS restricted cubic spline models with three knots were used. The chemotherapy arm was used as a reference arm, with outcomes in the zolbetuximab plus chemotherapy arm projected by applying time varying hazard ratios from the non-proportional NMA. An assumption was made from the NMA that nivolumab, pembrolizumab and zolbetuximab have equal efficacy in their respective eligible subgroups, therefore, the same hazard ratios for zolbetuximab plus chemotherapy were applied to nivolumab plus chemotherapy and pembrolizumab plus chemotherapy. DoT for the chemotherapy arm was extrapolated separately using a gamma distribution and the time varying hazard ratios from the NMA for PFS were applied to estimate DoT for zolbetuximab plus chemotherapy (and by assumption, for nivolumab plus chemotherapy and pembrolizumab plus chemotherapy).
Quality of life	Utilities were sourced from EQ-5D-5L data collected in SPOTLIGHT and GLOW studies, pooled across treatment arms, then mapped to ED-5D-3L. To estimate health state utilities, the company applied a generalised estimating equation (GEE) model to the EQ-5D data. The model produced mean utility values for pre-progression and post-progression health states, which were applied equally to all treatment arms. AE disutilities were drawn from published sources and applied as one off decrements.
Costs and resource use	Costs included medicine acquisition for both pre-progression treatment and post-progression treatment, AEs, disease management, testing and terminal care.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. SMC would wish to present the with-PAS cost-effectiveness results that were used for decision-making. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

6.2. Results

The base case economic modelling estimated that zolbetuximab plus chemotherapy was associated with higher costs and better health outcomes than chemotherapy alone. SMC is unable to present economic results used for decision-making as they were considered commercial in confidence (CiC) by the submitting company.

The submitting company considered the primary comparator to be chemotherapy alone, and SMC experts confirmed that few patients suitable for nivolumab plus chemotherapy or pembrolizumab plus chemotherapy would receive zolbetuximab plus chemotherapy. Given this, the results of subgroup analysis are not discussed further within this, or the following, section but were made available to SMC Committee Members during their decision-making.

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

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in Table 6.3 below

Table 6.3: Sensitivity and scenario analysis results

#	Parameter	Base case	Scenario	ICER (£/QALY)
	Base case			*CiC*
1	Chemotherapy regimen	All patients assumed to receive CAPOX as chemotherapy	80% of patients receive CAPOX and 20% receive FOLFOX.	*CiC*
2	Time horizon	40 years	10 years	*CiC*
3	Survival outcomes with chemotherapy	OS and PFS data: pooled from SPOTLIGHT, GLOW and CheckMate-649 studies OS extrapolation: 3-knot hazard spline PFS extrapolation: 3-knot odds spline for PFS	OS and PFS data: SPOTLIGHT and GLOW studies OS extrapolation: log-logistic PFS extrapolation: log-logistic	*CiC*
4	Survival outcomes with zolbetuximab + chemotherapy	Modelling approach: HRs applied to chemotherapy reference arm OS and PFS data: N/A OS extrapolation: N/A PFS extrapolation: N/A	Modelling approach: Independently fitted curves OS and PFS data: pooled SPOTLIGHT and GLOW studies OS extrapolation: log-logistic for zolbetuximab plus chemotherapy, gamma for chemotherapy PFS extrapolation: log-logistic for both zolbetuximab plus chemotherapy and chemotherapy	*CiC*
5			Modelling approach: Independently fitted curves OS and PFS data: pooled SPOTLIGHT and GLOW studies OS extrapolation: Weibull for both zolbetuximab plus chemotherapy and chemotherapy PFS extrapolation: log-logistic for both zolbetuximab plus chemotherapy and chemotherapy	*CiC*
6	Duration of treatment	Chemotherapy: Gamma curve fitted to data from GLOW study	Chemotherapy: As base case Zolbetuximab plus chemotherapy:	*CiC*

#	Parameter	Base case	Scenario	ICER (£/QALY)
		Zolbetuximab plus chemotherapy: PFS relative efficacy from NMA applied to chemotherapy reference arm.	Gamma curve fitted to data from GLOW study	
7			Chemotherapy: Gamma curve fitted to pooled data from SPOTLIGHT and GLOW studies Zolbetuximab plus chemotherapy: Gamma curve fitted to pooled data from SPOTLIGHT and GLOW studies	*CiC*
8	Utilities by health states	Utilities based on GEE utility model from EQ-5D data from GLOW and SPOTLIGHT studies	Utilities based on mixed-effects utility model from EQ-5D data from GLOW and SPOTLIGHT studies	*CiC*
9			Utilities based on the literature (ToGA study):[16, 17]	*CiC*
10	Combination	Combined scenarios of 5 and 10		*CiC*
11	Combination	Combined scenarios of 3 and 16		*CiC*
12	Combination	Combined scenarios of 5 and 13		*CiC*

Abbreviations: GEE= generalised estimating equation; Incr. = incremental; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS= progression-free survival; QALYs =quality-adjusted life years

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

6.4. Key strengths

- A partitioned survival model was appropriate and this structure is commonly used in other oncology submissions.
- There was direct evidence from two phase III studies (SPOTLIGHT and GLOW) against a relevant comparator.
- The key comparator contained within the economic analysis was confirmed as the treatment most likely to be displaced by Scottish clinical experts consulted by SMC.
- Adverse event rates were sourced directly from SPOTLIGHT and GLOW for zolbetuximab plus chemotherapy, and chemotherapy alone.

6.5. Key uncertainties

- In the base case, the submitting company pooled data from SPOTLIGHT, GLOW and CheckMate-649 studies for the chemotherapy alone reference arm. The inclusion of CheckMate-649 introduced uncertainty: its population differed from the zolbetuximab studies, the generalisability to the appraisal was felt limited, and outcomes for chemotherapy alone appeared poorer than in SPOTLIGHT and GLOW. Given that checkpoint inhibitor comparisons were not seen as relevant comparators in Scotland, reliance on CheckMate-649 may have undermined the robustness of the base case.
- The company applied hazard ratios from the NMA to extrapolate the long-term outcomes for zolbetuximab plus chemotherapy. However, direct head-to-head evidence was available from SPOTLIGHT and GLOW studies. The approach employed in the base case was identified as introducing unnecessary uncertainty. Alternative scenarios (see Scenarios 4 and 5, Table 6.3) explored applying parametric curves directly to the pooled GLOW and SPOTLIGHT study data for the zolbetuximab plus chemotherapy arm. These analyses

suggest higher incremental cost-effectiveness ratios (ICERs) relative to the base case, particularly when more conservative parametric curves are used in extrapolation.

- In the base case DoT for the chemotherapy reference arm was based on the GLOW study. For zolbetuximab, DoT was modelled by applying PFS hazard ratios from the NMA to DoT the chemotherapy reference arm. This approach was viewed as highly uncertain given the imperfect link between progression and treatment discontinuation, and because direct evidence on DoT for both chemotherapy and zolbetuximab was available from SPOTLIGHT and GLOW. An alternative scenarios where pooled data from SPOTLIGHT and GLOW were used and independent gamma curves were used to model DoT in both the chemotherapy and zolbetuximab plus chemotherapy arm led to an increase in the ICER (Scenario 7).

7. Conclusion

The Committee considered the benefits of zolbetuximab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as zolbetuximab 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 accepted zolbetuximab for use in NHSScotland.

8. Guidelines and Protocols

National Institute for Health and Care Excellence NICE (NG83) Oesophago-gastric cancer: assessment and management in adults, published in 2018 (last updated in 2023).[18]

European Society for Medical Oncology (ESMO) guidelines, Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Published in 2022.[2]

9. Additional Information

9.1. Product availability date

14 August 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per dose (£)
zolbetuximab	**800 mg/m^2 via intravenous infusion on cycle 1, day 1 (the cycle duration of zolbetuximab is determined based on the respective chemotherapy backbone). The recommended maintenance doses of zolbetuximab are either 600 mg/m^2 every 3 weeks or 400 mg/m^2 every 2 weeks.**	**Loading dose: £6,150** **600 mg/m^2: £4,510** **400 mg/m^2: £3,280**

Costs BNF online on 08 September 2025. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. Costs assume a body surface

area of 1.8 m^2. Zolbetuximab is used in combination with fluoropyrimidine- and platinum-containing chemotherapy, the costs of which have not been included in this table.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 67 patients eligible for treatment with zolbetuximab in each year.

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*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 **17 October 2025**.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.