Medicinrådet

Bilag til Medicinrådets vurdering af zolbetuximab i kombination med kemoterapi til 1. linjebehandling af adenokarcinom i mavesæk eller mavemund

Til patienter med lokalavanceret, ikke-resektabel eller metastatisk HER2-negativ, claudin 18.2-positiv adenokarcinom – i kombination med fluoropyrimidin- og platinbaseret kemoterapi

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. zolbetuximab i kombination med kemoterapi
2. Forhandlingsnotat fra Amgros vedr. zolbetuximab i kombination med kemoterapi
3. Ansøgers endelige ansøgning vedr. zolbetuximab i kombination med kemoterapi

Notat til Medicinrådets vurderingsrapport for Vyloy (zolbetuximab)

Astellas takker for muligheden for at komme med bemærkninger til Medicinrådets udkast til vurderingsrapport vedrørende zolbetuximab i kombination med kemoterapi til 1. linje behandling af adenokarcinom i mavesæk eller mavemund.

Indledningsvist vil vi gerne takke for et godt samarbejde med sekretariatet og en konstruktiv dialog undervejs i processen.

Vi er enige i og ser positivt på Medicinrådets kliniske vurdering af Vyloy. Dog ønsker vi at henlede Rådets opmærksomhed på at den økonomiske analyse for de patienter som i dag ikke har adgang til targeteret behandling (CPS <5) ikke er konsistent med den kliniske vurdering.

Den kliniske vurdering opdeles i to populationer baseret på den nuværende behandlingsalgoritme og konkluder sammefatningsvis:

- *Patienter med CPS* < 5: Zolbetuximab i kombination med kemoterapi er forbundet med forbedret progression-free survival (PFS) og overall survival (OS) sammenlignet med kemoterapi alene. Der er en højere frekvens af bivirkninger overordnet set, men en sammenlignelig frekvens af svære bivirkninger.
- *Patienter med CPS* ≥ 5: Zolbetuximab har en sammenlignelig effekt med PD-(L)1-hæmmere. Frekvensen og sværhedsgraden af bivirkninger er også sammenlignelige, men tolerabilitetsprofilen adskiller sig. Mens zolbetuximab er forbundet med gastrointestinale bivirkninger, er behandling med PD-(L)1 forbundet med en højere risiko for immunrelaterede bivirkninger, som kan være langvarige og potentielt fatale.

Den kliniske vurdering finder endvidere at effekten af zolbetuximab er uafhængig af CPS udtryk.

I den sundhedsøkonomiske vurdering af zolbetuximab i kombination med kemoterapi sammenlignet med kemoterapi alene (CPS<5) er ICER'en væsentligt højere end i Astellas' hovedanalyse (ca. 1 mio. kr/QALY til forskel). Medicinrådet har foretaget en række ændringer, men forskellen er drevet af en enkelt ændring: valg af ekstrapoleringskurve for OS i zolbetuximab-armen, som mere end halverer QALY-gevinsten sammenlignet med Astellas indsendte analyse. Astellas mener ikke, at ændringen fra log-log til Gompertz kan understøttes af data og ej heller er en klinisk plausibel beskrivelse af behandlings-effekten. Desuden er ændringen ikke konsistent med at zolbetuximabs effekt er sammenlignelig med PD-(L)1-hæmmerne.

Den log-logistiske funktion blev i Astellas' model valgt på baggrund på statistisk tilpasning, visuel inspektion af de ekstrapolerede kurver samt de udglattede hazard-funktioner. Gompertz-kurven antager, at hazard stiger eller falder, men ikke kan ændre retning, mens den log-logistiske er fleksibel nok til at tillade, at hazardraterne har et vendespunkt.

I den integrerede analyse af SPOTLIGHT og GLOW synes hazardraterne indledningsvist at stige og derefter falde, hvilket understøtter valget af den log-logistiske fordeling. Dette understøtter, at de patienter, der bidrager til KM-kurvens hale, er dem, der har haft det bedste behandlingsrespons og derfor har en aftagende mortalitetsrisiko. Gompertz-modellen antager derimod stigende en hazard – dvs mortalitetsraten er konstant stigende over tid (se Figur 1). Medicinrådet antager, at blot 4 % af

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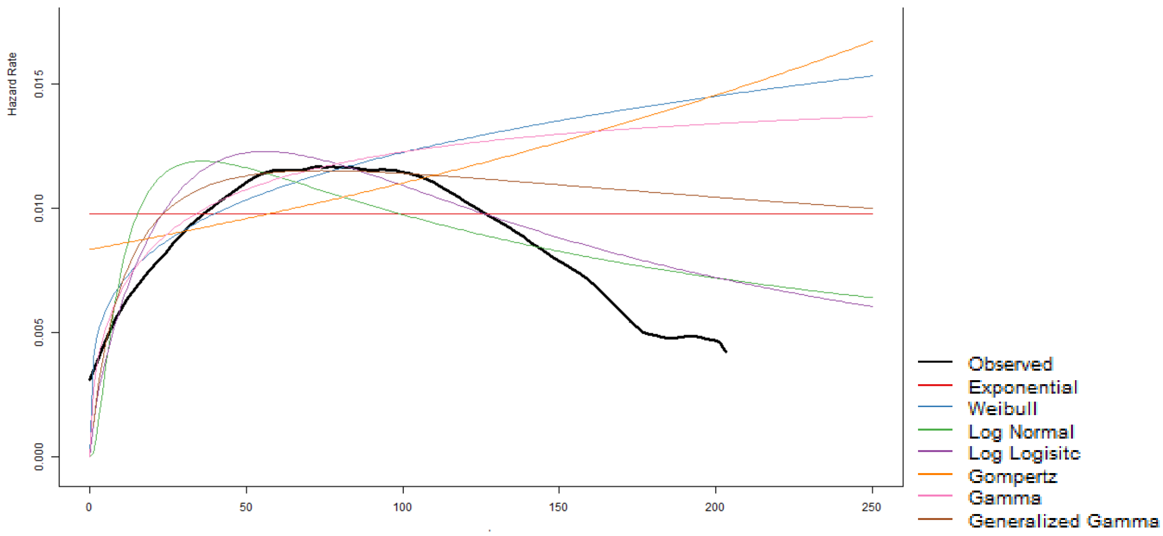
patienterne i zolbetuximab-armen vil være i live efter 5 år, hvilket må betragtes som værende yderst konservativt, når 15% er i live efter fire år i den integretede analyse af SPOTLIGHT/GLOW (Tabel 1) og mortalitetsrisikoen her er aftagende (Figur 1).

Figur 1. Udglattede hazard-funktioner for OS (observeret data og standard parametriske funktioner) (zolbetuximab + chemo)



Tabel 1. Sammenligning af OS-rater for zolbetuximab fra SPOTLIGHT/GLOW og ekstapolering med hhv Gompertz og log-log funktionen.

Kilde	6	12	24	36	48	60
SPOTLIGHT/GLOW (Observeret)	na	62%	34%	20%	15%	NA
Gompertz(estimeret)	79,8%	62,7%	36,5%	19,6%	9,5%	4.1%
Log-log (estimeret)	84,1%	62,2%	33,8%	20,5%	13,7%	9.8%

I et scenarie, hvor OS for zolbetuximab modelleres med log-log fremfor Gompertz ændres den samlede QALY genvinst fra 0,27 til 0,57 i Medicinrådets hovedanalyse. Dette syntes mere plusibelt givet at Medicinrådet konkluderer at zolbetuximab og PD-(L)1-hæmmerne er sammenlignelige. I Medicinrådets vurdering af nivolumab til samme patientgruppe var QALY-genvinsten i Medicinrådets sundheds-økonomiske analyse 0,64. Hvis OS for zolbetuximab modelleres med log-log sænkes ICER'en med 900.000-1.000.000 kr/QALY og ved vores tilbudte pris (SAIP) resulterer dette i en ICER på [redacted] kr/QALY.

Vi har ingen kommentarer til omkostningsminimeringsanalysen, hvor zolbetuximab sammenlignes med henholdvis nivolumab og pembrolizumab. Astellas har til hensigt at tilbyde zolbetuximab til en pris, der er sammenlignelig med omkostningsniveauet for PD-(L)1-hæmmere. Ved denne pris bør zolbetuximab også kunne anses som værende omkostningseffektiv sammenlignet med kemoterapi i en justeret sundhedsøkonomisk analyse.

En positiv anbefaling vil give en begrænset patientgruppe med CLDN18.2 positiv adenokarcinom i mavesæk eller mavemund mulighed for et targeteret behandlingsalternativ, som er lige så effektivt som PD-(L)1-hæmmerne og med en anden bivirkningsprofil.

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14.11.2025

KLE og DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	17.12.2025
Leverandør	Astellas Pharma
Lægemiddel	Vyloy (zolbetuximab)
Ansøgt indikation	Zolbetuximab i kombination med fluoropyrimidin- og platinbaseret kemoterapi til førstelinjebehandling af voksne patienter med lokalt avanceret inoperabel eller metastatisk HER2-negativ adenokarcinom i ventrikel eller den gastroøsofageale overgang (GEJ), hvis tumorer er Claudin (CLDN) 18.2-positive
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Vyloy (zolbetuximab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (Paknings-størrelse)	AIP (DKK)	Forhandlet SAIP, (DKK)	Forhandlet rabat ift. AIP
Vyloy	100 mg, pulver til koncentrat til infusionsvæske, opl. (1 stk.)	3.543,30	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder at hvis Medicinrådet ikke anbefaler Vyloy, indkøbes lægemidlet til AIP.

[redacted]

Konkurrencesituationen

Medicinrådet vurderer at Vyloy + kemoterapi er klinisk ligeværdig med PD(L)1-hæmmerne for patienter med PD-L1 CPS ≥ 5. I tabel 2 vises lægemiddeludgifterne for den gennemsnitlige behandlingstid pr. patient på 7,6 måneder for Vyloy, Keytruda (pembrolizumab) og Opdivo (nivolumab).

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling* (SAIP, DKK)
Vyloy**	100 mg (1 stk, pulver til konc. til infusionsvæske, opl)	Opstartsdosis på 800 mg/m^2, derefter 600 mg/m^2 hver 3. uge, i.v.	[redacted]	[redacted]
Keytruda***	25 mg/ml (4 ml, konc. til infusionsvæske, opl)	2 mg/kg hver 3. uge, i.v.	[redacted]	[redacted]
Opdivo***	120 mg/12 ml (1 stk, konc. til infusionsvæske, opl.)	4,5 mg/kg hver 3. uge, i.v.	[redacted]	[redacted]

*) Behandlingsvarigheden er i gennemsnit 7,6 måneder pr. patient, jf. tabel 21, s. 62 i Medicinrådets vurderingsrapport
**) Baseret på en BSA på 1,81
***) Baseret på en legemsvægt på 68 kg

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Ikke anbefalet	Link til anbefaling
Sverige	Under vurdering	

Opsummering

[redacted]

Application for the assessment of Vyloy (zolbetuximab) for first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
[redacted]	Confidential information

Contact information

Contact information	
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Table of contents

Tables and Figures

Tables

Figures

Abbreviations

Abbreviation	Definition	Abbreviation	Definition
5-FU	Fluorouracil	IHC	Immunohistochemistry
AE	Adverse event	IRC	Independent review committee
BSA	Body surface area	IVDR	In vitro diagnostic regulation
CAPOX	Capecitabine oxaliplatin	mFOLFOX6	Modified 5-fluorouracil, folinic acid and oxaliplatin
CI	Confidence interval	NMA	Network Meta Analysis
CLDN	Claudin	OG25-Pain	European Organisation for Research and Treatment of Cancer Quality of Life Oesophago-Gastric
CPS	Combined positive score	ORR	Objective response rate
CR	Complete response	OS	Overall survival
CUA	Cost utility analysis	QALY	Quality adjusted life year
DCR	Duration of treatment	PD	Post-progression
DECG	Dansk Esophago-Gastrisk Cancergruppe	PD-(L)1	Programmed death(-ligand) 1
DKK	Danske kroner	PF	Pre-progression
DOR	Duration of response	PICO	Patients, intervention, comparison and outcome
DMC	Danish Medicines Agency	PR	Partiel response
EC	European Commission	PRO	Patient reported outcome
ECOG PS	Eastern Cooperative Oncology Group Performance Status	RECIST	Response Evaluation Criteria in Solid Tumours
EFS	Event free survival	RR	Relative risk
EMA	European Medicines Agency	SAE	Serious adverse event
EQ-5D-5L	EuroQOL Five Dimensions Questionnaire 5L	SD	Standard deviation
ESMO	European Society for Medical Oncology	SmPC	Summary of Product Characteristics
FOLFOX	Folinic acid, fluorouracil, and oxaliplatin	TEAE	Treatment-emergent adverse event
G	Gastric	TTCD	Time to clinical deterioration
GC	Gastric cancer	TTDD	Time to first definitive deterioration
HER2	Human epidermal growth factor 2		

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Vyloy
Generic name	zolbetuximab
Therapeutic indication as defined by EMA	Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive
Marketing authorization holder in Denmark	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden The Netherlands
ATC code	L01FX31
Combination therapy and/or co-medication	Yes (combination with chemotherapy)
Date of EC approval	September 19, 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes (EU/3/10/803) by EC decision of 26/11/2010 (Reevaluated and approved by EMA July 16, 2024)
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	No. The timelines for HTA submissions and launch in the four Nordic countries will not be the same and disease management is not completely comparable across the Nordics. Therefore, a tailored approach for each country is considered more appropriate.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Vyloy 100 mg powder for concentrate for solution for infusion. Each vial contains 100 mg zolbetuximab. Pack size: one carton containing 1 vial.

2. Summary table

Summary	
Indication relevant for the assessment	The submission considers the approved indication for Vyloy: Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive
Dosage regiment and administration	The recommended dose should be calculated according to body surface area (BSA) for the Vyloy loading dose and maintenance doses. Single loading dose: 800 mg/m2 intravenously, Cycle 1, Day 1. Maintenance dose: 600 mg/m2 intravenously every 3 weeks or 400 mg/m2 intravenously every 2 weeks* *The cycle duration of Vyloy is determined based on the respective chemotherapy backbone Intravenous infusion
Choice of comparator	The following relevant comparators have been identified: • In patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive, the relevant comparator is chemotherapy (typically fluoropyrimidine- and platinum-containing chemotherapy) *(Patients with CLDN18.2 positivity)* • In a subgroup of patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive, with a CPS≥5 the relevant comparator is a PD-(L)1 inhibitor given in addition to chemotherapy (i.e. nivolumab or pembrolizumab *(Patients with CLDN18.2 positivity and PD-(L)1 expression (CPS≥5))*
Prognosis with current treatment (comparator)	Locally advanced unresectable or metastatic HER2-negative gastric (G) or gastro-oesophageal junction (GEJ) adenocarcinoma is a progressive disease leading to premature death and a significantly reduced quality of life. Treatment is palliative. According to the assessment of nivolumab in G/GEJ cancer by the Medicines Council, the median OS for patients treated with nivolumab given in addition to chemotherapy is 14.4 months and 11.1 months for patients on chemotherapy (median diff: 3.3 months). [1] According to the recent assessment of pembrolizumab in G/GEJ, only approximately 40% of Danish patients with advanced G/GEJ/E cancer who have started palliative treatment are alive 1 year after initial systemic treatment in 2022. [2]

Summary	
Type of evidence for the clinical evaluation	The comparison vs chemotherapy is based on integrated analysis of two pivotal clinical trials (head-to-head data). The comparisons vs PD-(L)1 inhibitors are based on two separate Bucher analyses.
Most important efficacy endpoints (Difference/gain compared to comparator)	Integrated efficacy analysis (SPOTLIGHT and GLOW): Median OS was 16.39 months in the zolbetuximab + chemo arm and 13.7 months in the chemo arm (HR: 0.774 [0.672; 0.892]; p=0.0002). Median PFS was 9.17 months in the zolbetuximab + chemo arm and 8.18 months in the chemo arm (HR: 0.712 [0.610; 0.831]; p <0.00001).
Most important serious adverse events for the intervention and comparator	The frequency of adverse events/reactions is overall comparable for zolbetuximab given in addition to chemotherapy vs chemotherapy alone. The most frequent and severe toxicities related to the treatment with zolbetuximab in combination with chemotherapy are gastrointestinal disorders such as nausea and vomiting and these are the only serious adverse events that occur with a frequency of ≥ 5%.
Impact on health-related quality of life	All health-related quality of life (HRQoL) instruments document that patients receiving zolbetuximab given in addition to chemotherapy experience comparable QoL as patients receiving chemotherapy alone [3]. Similar trends were observed in the zolbetuximab versus placebo arms for LSM changes from baseline in key PRO domains, with no clinically meaningful deterioration. Nausea/vomiting worsened during the first few zolbetuximab cycles but later returned to baseline levels. Overall TTCD and time to first definitive deterioration (TTDD) results were similar between arms in both studies. [3] Health economic model: Gain in QALYs based on increased life expectancy and distribution of time pre-/ post progression.
Type of economic analysis that is submitted	Cost-utility model vs chemotherapy (partitioned survival). For subgroup of patients with l CLDN18.2 positivity and PD-(L)1 expression (CPS≥5), cost-minimization was applied (separate Excel model).
Data sources used to model the clinical effects	GLOW/SPOTLIGHT (zolbetuximab pivotal registration trial trials)
Data sources used to model the health-related quality of life	GLOW/SPOTLIGHT (zolbetuximab pivotal registration trial trials)
Life years gained	0.7 years compared to chemotherapy alone. 0 compared to PD-(L)1 inhibitors
QALYs gained	0.62 QALY compared to chemotherapy alone 0 compared to PD-(L)1 inhibitors
Incremental costs	519,320 DKK/patient compared to chemotherapy alone -21,462 DKK/patient compared to pembrolizumab 153,119 DKK/patient compared to nivolumab

Summary	
ICER (DKK/QALY)	841,129 DKK/QALY compared to chemotherapy alone
Uncertainty associated with the ICER estimate	The results were mainly sensitive to parameters determining the long-term survival of patients in chemotherapy only (standard of care) arm in the model, followed by parameters of the zolbetuximab OS extrapolation and discount rate
Number of eligible patients in Denmark	In Denmark, approximately 800 pt are yearly diagnosed with G/GEJC (incidence) and the prevalence of G/GEJC is approx. 3,000 pt. There is limited information available about the number of patients receiving palliative treatment for G/GEJC in Denmark. Based on the assessment report for Opdivo in G/GEJC, we assume that 300 patients with newly diagnosed adenocarcinoma are candidates for chemotherapy and that 240 of these patients are HER2 negative. Approximately 90 patients are expected to be candidates for zolbetuximab each year based on the incidence of CLDN18.2 positivity (38.4%) across the two clinical trials, SPOTLIGHT and GLOW.
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Gastric/gastro-oesophageal junction cancer (G/GEJC) comprises cancer that occurs in the lining of the stomach and the gastro-oesophageal junction (GEJ; between the stomach and the oesophagus), respectively. Adenocarcinoma is the most common type of G/GEJC and affects approximately 95% of patients with the disease. There are several known risk factors associated with G/GEJC including increased age (≥ 70 years), obesity [4, 5], smoking, diet and being male. [4, 5] As gastric cancer (GC) and gastro-oesophageal junction cancer (GEJC) are similar, both histologically and in terms of treatment response, patients with GC and GEJC are commonly the combined target population in clinical trials. [6, 7]

G/GEJC are often asymptomatic in early disease stages and hence patients are often first diagnosed at a late disease stage and hence with a poor prognosis.

Locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma is a progressive disease leading to premature death and a significantly reduced quality of life. Treatment is palliative.

According to the assessment of nivolumab in G/GEJC by the Medicines Council, the median OS for patients treated with nivolumab given in addition to chemotherapy is 14.4 months and 11.1 months for patients on chemotherapy (median diff: 3.3 months). [1] According to the recent assessment of pembrolizumab in G/GEJC, only approximately 40% of Danish patients with advanced G/GEJ/E cancer, who have started palliative oncological treatment, are alive 1 year after initial systemic treatment in 2022.[2, 8]

3.2 Patient population

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.

Astellas anticipate that Vyloy (zolbetuximab) will be used in patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive *(Patients with CLDN18.2 positivity)*. In this patient population current standard of care is chemotherapy (typically fluoropyrimidine- and platinum-containing chemotherapy) and hence chemotherapy is considered the most relevant comparator. In a subgroup of patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive, patients will be eligible for treatment with a PD-(L)1 inhibitor given in addition to chemotherapy (i.e. nivolumab or pembrolizumab) (patients with a CPS≥5) *(Patients with CLDN18.2 positivity and PD-(L)1 expression)*

In Denmark, approximately 800 patients are yearly diagnosed with G/GEJC (Table 1).

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark[9]*	716	734	889	776	NA
Prevalence in Denmark[9]**	2391	2556	2824	2909	NA
Global prevalence * **	NA	NA	NA	NA	NA

* Gastric cancer in Nordcan include C16.0 (Cardia) (most of GEJ). This definition is a slightly different definition from the DECG yearly report (where GEJ and Gastric cancer is reported separately)**all stages *** For small patient groups, also describe the worldwide prevalence.

Zolbetuximab is only indicated to be used in patients whose tumours are Claudin (CLDN) 18.2 positive.

Global clinical studies as well as a retrospective study have documented that a substantial proportion (38.4–47.2%) of patients with HER2 negative G/CEJ adenocarcinoma have CLDN18.2-positive tumours (defined as moderate-to-strong membrane expression in ≥75% of tumour cells) [10-13]. According to our knowledge, there is no data on the share of patients with CLDN18.2 positive tumours in Denmark. It is expected that the share of patients with CLDN18.2 positive tumours will be comparable to that observed in other countries.

There is limited information available about the number of patients receiving palliative treatment for G/GEJC in Denmark. Based on the assessment report for Opdivo in G/GEJC, we assume that 300 patients with newly diagnosed adenocarcinoma are candidates for chemotherapy and that 240 of these patients are HER2 negative (HER2-). Approximately 90 patients are expected to be candidates for zolbetuximab each year based on the incidence of CLDN18.2 positivity (38.4%) across the two clinical trials, SPOTLIGHT and GLOW (Table 2).

Table 2 Estimated number of patients eligible for treatment

Year	2025	2026	2027	2028	2029
G/GEJC patients in Denmark who are eligible for 1st line palliative treatment[1]	300	300	300	300	300
Patients with no HER2 expression (HER2-)[1]	240	240	240	240	240
Patients with positive CLDN18.2 expression[10, 11]	**90**	**90**	**90**	**90**	**90**

3.3 Current treatment options

The most recent treatment guideline from Dansk Esophago Gastrisk Cancergruppe (DECG) originates from February 2025. All patients with advanced gastric or gastro-oesophageal junction cancer (G/GEJC) eligible for treatment will in Danish clinical practice be tested for Programmed death-ligand 1 (PD-(L)1 score) (using the combined positive score, CPS), mismatch repair (MMR) status and Human epidermal growth factor receptor 2 (HER2) status before treatment is initiated. Zolbetuximab is included in the guidelines as a treatment option as according to the indication approved by EMA.[14]

First line treatment for patients with advanced G/GEJC who are HER2- is chemotherapy, typically fluoropyrimidine- and platinum-containing chemotherapy. [15]

According to the guideline, first line treatment for patients with advanced G/GEJC who are HER2- and who are eligible for treatment with a PD-(L)1 inhibitor, treatment with pembrolizumab is recommended in patients with CPS≥10 (GEJC) and treatment with nivolumab is recommended in patients with CPS≥5 (G/GEJC). PD-(L)1 inhibitors are given in combination with fluoropyrimidine- and platinum-containing chemotherapy.[15] Recently, pembrolizumab has been approved by EMA for a broader patient group (gastric cancer is now also included and approval is for patients with CPS≥1). In June 2024, pembrolizumab was nationally recommended by the DMC in patients with CPS≥5 (G/GEJ). [2]

Hence, current first line treatment in Danish clinical practice for patients with advanced G/GEJ who are HER2 negative (HER2-) and with CPS<5 is chemotherapy (typically fluoropyrimidine- and platinum-containing chemotherapy). For patients with a CPS≥5, first line treatment with a PD-(L)1 inhibitor (nivolumab or pembrolizumab) given in addition to chemotherapy is used in Danish clinical practice.

According to the most recently updated ESMO guideline (September 2024), first line treatment in patients with advanced G/GEJC is chemotherapy, where a platinum and fluoropyrimidine is recommended. Oxaliplatin is preferred, especially for older patients. [3, 16] For patients with CPS≥5, the addition of a PD-(L)1 inhibitor is recommended and for patients with CPS1-4, the addition of a PD-(L)1 inhibitor can be considered. For patients who are CLDN18.2 positive, addition of zolbetuximab is recommended. [3, 16]

Locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma is a progressive disease leading to premature death and a significantly reduced quality of life.

According to the assessment of nivolumab in G/GEJC by the Medicines Council, the median OS for patients treated with nivolumab given in addition to chemotherapy is 14.4 months and 11.1 months for patients on chemotherapy (median diff: 3.3 months). [1] According to the recent assessment of pembrolizumab in G/GEJC, only approximately 40% of Danish patients with advanced G/GEJ/E cancer who have started palliative oncological treatment are alive 1 year after initial systemic treatment in 2022.[2, 8]

3.4 The intervention

Overview of intervention	
Indication relevant for the assessment	Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive
ATMP	No
Method of administration	Intravenous infusion
Dosing	The recommended dose should be calculated according to body surface area (BSA) for the Vyloy loading dose and maintenance doses. Single loading dose: 800 mg/m2 intravenously, Cycle 1, Day 1. Maintenance dose: 600 mg/m2 intravenously every 3 weeks or 400 mg/m2 intravenously every 2 weeks* *The cycle duration of Vyloy is determined based on the respective chemotherapy backbone
Dosing in the health economic model (including relative dose intensity)	Dosing as per SmPC. [17] RDI was estimated separately from GLOW (96%) and SPOTLIGHT (92%) and weighted in the cost analysis. [18]

Overview of intervention	
Should the medicine be administered with other medicines?	Zolbetuximab should be given in addition to chemotherapy (see indication)
Treatment duration / criteria for end of treatment	Until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	Monitoring for hypersensitivity, infusion related reactions and nausea and vomiting is required in association with infusions.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	CLDN18.2 positivity (defined as ≥ 75% of tumour cells demonstrating moderate-to-strong membranous CLDN18 IHC staining) should be determined by a validated test. Cost of a CDLN18.2 is included in the economic evaluation as the cost per patient found to be eligible for treatment.
Package size(s)	Pack size: one carton containing 1 vial.

3.4.1 Description of ATMP

NA

3.4.2 The intervention in relation to Danish clinical practice

Vyloy (zolbetuximab) is a new treatment option indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive. A substantial proportion (38.4-47.2%) of patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma have CLDN18.2-positive tumours (defined as moderate-to-strong membrane expression in ≥75% of tumour cells).

Current standard of care in Denmark for patients with HER2-negative locally advanced unresectable or metastatic G/GEJC eligible for palliative treatment, is chemotherapy (typically fluoropyrimidine- and platinum-containing chemotherapy). [14] For patients eligible for treatment with a Programmed death-ligand 1 (PD-(L)1) inhibitor, nivolumab or pembrolizumab will be given in addition to chemotherapy (patients with a CPS≥5).

Hence, the relevant comparators to zolbetuximab in a Danish clinical practice are:

- In patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive, the relevant comparator is *chemotherapy* (typically fluoropyrimidine- and platinum-containing chemotherapy) *(Patients with CLDN18.2 positivity)*

- In a subgroup of patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive, with a CPS≥5 the relevant comparator is a *PD-(L)1 inhibitor given in addition to chemotherapy* (i.e. nivolumab or pembrolizumab) *(Patients with CLDN18.2 positivity and PD-(L)1 expression (CPS≥5))*

CLDN18.2 positivity (defined as ≥ 75% of tumour cells demonstrating moderate-to-strong membranous CLDN18 IHC staining) should be determined by a validated test. On October 7, 2024, CE certification was issued by the EU Notified Body, TUV SÜD, under the in vitro diagnostic regulation (IVDR) for the CLDN18 CDx assay.

3.5 Choice of comparator(s)

The relevant comparator in the current submission is chemotherapy (mFOLFOX6/CAPOX) and for a subgroup of patients with CPS≥5, PD-(L)1 inhibitor given in addition to chemotherapy is a relevant comparator (nivolumab and pembrolizumab). In the following, an overview of the comparators is provided. The choice of comparators reflects current clinical practice in Denmark.

Overview of comparator.: mFOLFOX6	
Generic name	Chemotherapy regimen: Modified 5-fluorouracil, folinic acid and oxaliplatin (mFOLFOX6)
ATC code	Fluorouracil: L01BC02 Folinic acid: V03AF03 Oxaliplatin: L01XA03
Mechanism of action	Cytotoxic therapy
Method of administration	Concentrate for solution for infusion
Dosing	*mFOLFOX6*: folinic acid 400 mg/m², or optionally in Japan, levofolinate 200 mg/m²; fluorouracil 400 mg/m² bolus followed by 2400 mg/m² in a 46-h to 48-h infusion; and oxaliplatin 85 mg/m²; on days 1, 15, and 29)
Dosing in the health economic model (including relative dose intensity)	*mFOLFOX6* is not used in the base case analysis [1] but is available in the model for scenario analysis. Dosing as above with oxaplatin given for 8 cycles. RDI (based on data on file from SPOTLIGHT): Oxaplatin 87% Flouracil: bolus 94% infusion pump 93% Lecuvorin 91%
Should the medicine be administered with other medicines?	Pre-medication with a combination of antiemetics [17]
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Fluorouracil (50 mg/ml): 10, 50 and 100 ml Folinic acid (10 mg/ml), 10, 35, 100ml, 10×10, 10×35 and 10×100 ml: Oxaliplatin (5 mg/ml): 10, 20 and 40 ml

Overview of comparator: CAPOX	
Generic name	Chemotherapy regimen: capecitabine and oxaliplatin (CAPOX)
ATC code	Capecitabine: L01BC06 Oxaliplatin: L01XA03
Mechanism of action	Cytotoxic therapy
Method of administration	Oxaliplatin: concentrate for solution for infusion; Capecitabine: orally
Dosing	*CAPOX*: oral capecitabine, 1,000 mg/m2, twice daily on days 1–14 of each cycle; intravenous infusion of oxaliplatin, 130 mg/m2, day 1 of each cycle) for eight 21-day cycles
Dosing in the health economic model (including relative dose intensity)	*CAPOX*: oral capecitabine, 1,000 mg/m2, twice daily on days 1–14 of each cycle (RDI 83%); intravenous infusion of oxaliplatin, 130 mg/m2, day 1 of each cycle) for nine 21-day cycles (RDI 95%). [1] RDI from GLOW (data on file)
Should the medicine be administered with other medicines?	Pre-medication with antiemetics [19, 20]
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Capecitabine: 150 mg (60 pack), 300 mg (60 pack), 500 mg (120 pack) Oxaliplatin (5 mg/ml): 10, 20 and 40 ml

Overview of comparator: nivolumab	
Generic name	Nivolumab
ATC code	L01FF01
Mechanism of action	Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor
Method of administration	Intravenous infusion
Dosing	360 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine and platinum-based chemotherapy administered every 3 weeks or 240 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine, leucovorin and platinum-based chemotherapy administered every 2 weeks

Overview of comparator: nivolumab	
Dosing in the health economic model (including relative dose intensity)	4.5 mg/kg Q3W or 3mg/kg Q2W RDI 100% (According to the EMA safety assessments of nivolumab[21] the accumulated average dose divided by the average number of cycles was above target dose for both patients treated with 240 mg Q2W and patients treated with 360 mg Q2W).
Should the medicine be administered with other medicines?	Nivolumab should be given in addition to chemotherapy for the G/GEJC indication (see indication)
Treatment duration/ criteria for end of treatment	Until disease progression, unacceptable toxicity, or up to 24 months
Need for diagnostics or other tests (i.e. companion diagnostics)	PD-(L)1 CPS test
Package size(s)	1 vial×40mg/4ml, 1 vial×100mg/10ml, 1 vial×120 mg/12ml, 1vial×240mg/24ml

Overview of comparator: pembrolizumab	
Generic name	Pembrolizumab
ATC code	L01FF02
Mechanism of action	pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2
Method of administration	Intravenous administration
Dosing	The recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes
Dosing in the health economic model (including relative dose intensity)	2mg/kg Q3W or 4mg/kg Q6W RDI =100% (assumed same as nivolumab)
Should the medicine be administered with other medicines?	Pembrolizumab should be given in addition to chemotherapy for the G/GEJC indication (see indication)
Treatment duration/ criteria for end of treatment	Until disease progression, unacceptable toxicity, or up to 24 months
Need for diagnostics or other tests (i.e. companion diagnostics)	PD-L1 CPS test
Package size(s)	4 ml× 25 mg/ml

3.6 Cost-effectiveness of the comparator(s)

Both nivolumab and pembrolizumab have been assessed and recommended by the DMC within G/GEJC. [1, 2] In the assessment of nivolumab, a cost-utility analysis was conducted comparing nivolumab given in addition to chemotherapy to chemotherapy as monotherapy. The assessment concluded that nivolumab was cost-effective in Denmark and nivolumab was nationally recommended in patients with CPS≥5.

Pembrolizumab was recently nationally recommended in patients with CPS≥5 via a fast track process. The assessment by the Medicine Council concluded that the efficacy of pembrolizumab was comparable to that of nivolumab in patients with a CPS≥5.

The chemotherapy regimens (mFOLFOX6 and CAPOX) have not been formally assessed by the DMC. However, previous assessments of new treatments for G/GEJC have used platin based chemotherapy regimens as comparators.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In the application, the following efficacy outcomes are assessed: overall survival (OS) and progression free survival (PFS) (primary efficacy endpoint). Furthermore, duration of response (DOR) and objective response rate (ORR) is included in appendix B but not in the main application. The application also considers health related quality of life (HRQoL). This is described in section 14 and appendix F.

For a subgroup of patients, treatment with PD-(L)1 inhibitor is a relevant comparator (nivolumab and pembrolizumab). The two efficacy endpoints that are considered for nivolumab and pembrolizumab are OS and PFS. These endpoints are defined in a comparable manner in the CheckMate-649 and KEYNOTE-859 studies. [22, 23]

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression free survival (PFS) [SPOTLIGHT and GLOW]	SPOTLIGHT: 8/9-2023; GLOW: 12/1-2024. The median follow-up for PFS was 18.2 months zolbetuximab group and 17.9 months in the placebo group.	Time from the date of randomization until the date of radiological progressive disease (per RECIST 1.1 by Independent Review Committee (IRC)) or death from any cause, whichever is earliest	Per RECIST 1.1 by Independent Review Committee (IRC)) or death from any cause, whichever is earliest. Kaplan-Meier (KM) estimates were used for analysis
Overall survival (OS)	SPOTLIGHT: 8/9-2023; GLOW: 12/1-2024. The	Time from the date of randomization until the	Kaplan-Meier (KM) estimates were used for analysis

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
[SPOTLIGHT and GLOW]	median follow-up for overall survival was 32.7 months in the zolbe-tuximab group and 31.8 months in the placebo group	date of death from any cause	
Objective response rate (ORR) [SPOTLIGHT and GLOW]	SPOTLIGHT: 8/9-2023; GLOW: 12/1-2024.	The proportion of participants who have a best overall response of Complete Response (CR) or Partial Response (PR) as assessed by IRC)	Per RECIST v1.1 by ICR
Duration of response (DOR) [SPOTLIGHT and GLOW]	SPOTLIGHT: 8/9-2023; GLOW: 12/1-2024.	Time from the date of the first response (CR/PR) until the date of progressive disease as assessed by IRC per RECIST 1.1 or date of death from any cause, whichever is earliest)	Per RECIST v1.1 by ICR. KM estimates were used for analysis

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

OS, PFS, and HRQoL (measured by EQ-5D) are relevant outcomes in this application. These outcomes have been previously deemed relevant by the DMC in the assessment of G/GEJC. DOR and ORR are reported in appendix B. These outcomes have also earlier been deemed relevant by the DMC in the assessment of new treatments for G/GEJC.

4. Health economic analysis

Separate methods were used for the two populations.

- Overall population of CDLN18.2 positive: A cost-utility analysis was established to compare the net-present value of costs and QALY for patients treated with zolbetuximab, and patients treated with chemotherapy *(Patients with CLDN18.2 positivity)*.
- Subgroup with l CDLN18.2 positivity and PD-(L)1 expression (CPS≥5): A cost-minimisation analysis was established to compare per patient cost of treatment with zolbetuximab compared to nivolumab and pembrolizumab, respectively *(Patients with CLDN18.2 positivity and PD-(L)1 expression)*.

4.1 Model structure

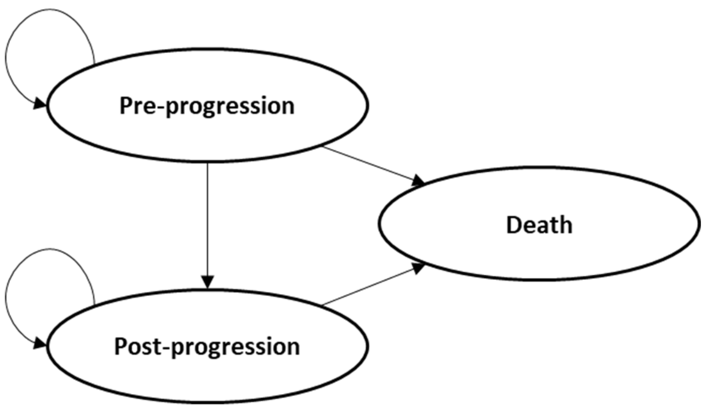
4.1.1 Overall population: cost-utility model

Zolbetuximab in combination with chemotherapy has been shown to improve time to progression and death for any cause in two RCTs. Therefore, cost-effectiveness approach was chosen for the economic evaluation.

The CEA model used a three-state partitioned survival modelling approach. The model structure is presented in Figure 1. The model is comprised of three mutually exclusive health states. A description of each health state and the calculation for the proportion of patients in each state in each cycle is given below:

- Pre-progression (PF): These patients are classified as disease-free and receive first-line treatment for as long as their treatment regimen dictates, and the state membership is defined by the proportion of patients who are progression-free at any given time point based on the PFS curve
- Post-progression (PD): These patients have experienced disease progression, and their state membership is defined as the proportion of patients who are alive at any given time point minus the proportion of patients who have not progressed at the same time point (%OS - %PFS).
- Death: This is set as an absorbing state and the proportion of patients in this health state is defined as 1 minus the proportion of patients alive (1 - %OS) at a given time point.

Figure 1. Model structure



4.1.2 Subgroup with CLN18.2 positivity and PD-(L)1 expression (CPS≥5): cost-minimization model

For patients with CLDN18.2 positivity and PD-(L)1 expression (CPS ≥ 5), zolbetuximab in combination with chemotherapy and PD-(L)1 inhibitor in combination with chemotherapy are clinically equivalent treatment options (see section 7). Hence, the purpose of the economic evaluation is to establish a framework for comparing the cost of treatment with zolbetuximab in comparison to both pembrolizumab and nivolumab (irrespective of backbone chemotherapy).

The model structure consists of a calculation of net-present cost per patient for the three treatment options and includes the following cost-elements

- Cost of intervention (zolbetuximab, pembrolizumab and nivolumab)
- Cost of premedication
- Cost of CLDN18.2 test

Intervention cost is calculated based on SMPC posology and applied for the same duration of treatment across all three treatment options.

All interventions are to be combined with chemotherapy administrated Q2W or Q3W as IV infusions. Cost of chemotherapy and cost of drug administration will therefore be the same irrespective of whether the chemotherapy is combined with zolbetuximab or a PD-L()1 inhibitor.

Cost of side-effect management have been omitted since the AE profiles are similar across treatments (see section 13).

Cost of testing required before initiation of treatment has been included. CPS is assumed to be known at the time of considering choice of treatment. Hence, no cost of quantifying PD-(L)1 expression is included, but – as a new treatment option – the cost of CDLN18.2 tests are.

Cost of subsequent treatment has been omitted as the choice of first line treatment is not expected to affect subsequent lines of treatment.

4.2 Model features

Table 4A provides an overview of the model features for the CUA of zolbetuximab in combination with chemotherapy in patients with CLDN18.2 positivity compared to chemotherapy alone.

Table 4B presents the features of the cost-minimization applied in the subgroup-analysis comparing zolbetuximab in combination with chemotherapy to PD-(L)1 inhibitor in combination with chemotherapy (patients with CDLN18.2 positivity and PD-(L)1 expression (CPS ≥ 5)).

Table 4A Features of the economic model (analysis of cost-utility of zolbetuximab plus chemotherapy compared to chemotherapy)

Model features	Description	Justification
Patient population	Adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive	Patients indicated to first-line treatment with zolbetuximab (see section 3.2)
Perspective	Limited societal cost	According to DMC method guide v 1.2
Time horizon	40 years	Life-time (until age of ~100 years)
Cycle length	1 week	Short cycle length chosen to enable modelling of both Q3W and Q2W dosing

Model features	Description	Justification
Half-cycle correction	Yes	Time in state calculated using half-cycle correction
Discount rate	3.5%	The DMC applies a discount rate of 3.5 % for all years
Intervention	Zolbetuximab 800mg/m^2 loading dose +600mg/m^2 Q3W (400mg/m^2 Q2W) in combination with platin-based chemotherapy Q3W or Q2W. The main intervention is Zolbetuximab plus CAPOX Q3W	In line with treatment guideline and Vyloy SmPC
Comparators	Platin-based chemotherapy (Q3W or Q2W). Cost of comparator is based on CAPOX (Q3W)	According to DMC previous assessments in G/GEJC
Outcomes	Model outcomes include cost, LY gained, and QALY gained Model outcomes are estimated using extrapolation of OS, PFS from integrated analysis of GLOW and SPOTLIGHT. Time to treatment discontinuation (TTD) extrapolated from GLOW and SPOTLIGHT and weighted Health state utility values estimated from integrated analysis of GLOW and SPOTLIGHT	Standard outcomes in partitioned-survival model

Table 4B Features of the economic model (cost-minimization vs PD-(L)1 inhibitors)

Model features	Description	Justification
Patient population	Adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive and with a PD-(L)1 expression of CPS≥5	Subgroup of indicated patients who have CDLN18.2 positivity and PD-(L)1 expression with CPS≥5 (see section 3.2)
Perspective	Limited societal perspective	DMC preferred perspective
Time horizon	8 Months	Average treatment duration across clinical trials identified for the indirect comparison of efficacy
Cycle length	Not applicable	The model does not have dynamic elements

Model features	Description	Justification
Half-cycle correction	Not applicable	The model does not have dynamic elements
Discount rate	Not applicable	All cost compared within first year of treatment
Intervention	Zolbetuximab 800mg/m^2 loading dose +600mg/m^2 Q3W	Dosing according to SmPC.
Comparators	Pembrolizumab and nivolumab	According to DMC decisions.
Outcomes	Per-patient cost of antibody treatment based on average treatment duration in clinical trials informing the indirect treatment comparison	Cost-minimisation analysis

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) was conducted by Astellas in order obtain the most up to date information about the published evidence on efficacy and safety of different treatments in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction cancer. Below, find a brief description of the SLR. Details are available in appendix H and in the full SLR report. [24] The objective was to identify published evidence on efficacy and safety of treatments for patients with locally advanced unresectable or metastatic G/GEJC.

The data sources used to identify the relevant studies included:

- Electronic databases (via the OVID platform on 22nd September 2020 in the original review. An update of the search was conducted on 9th August 2022 to identify relevant papers published post-September 2020. A second update was conducted in October 2023. Third update of searches was conducted on 4th March 2024 to identify studies published after the update review in October 2023)
- Hand-searching of conference proceedings, HTA submissions, and reference lists of included studies

Outcomes in included studies:

- Baseline characteristics: Patient and study characteristics (including age, race, country, % males, CLDN18.2 status etc.)
- Efficacy: overall survival (OS), progression free survival (PFS), time to progression (TTP), duration of response (DoR), event free survival (EFS), response rates (complete response, partial response, stable disease), objective response rate (ORR), duration of response (DCR), duration of treatment; duration of treatment beyond progression
- Safety: All-grade treatment related adverse events (AE), treatment related Grade 3 or 4 AEs, treatment related serious adverse events (SAEs), tolerability: dose reductions and interruptions, discontinuation (all-cause; due to AEs)

The SLR prepared by Astellas included all treatment regimens for G/GEJC (various chemo regimens and PD-(L)1 inhibitors). The most relevant comparators to zolbetuximab in Denmark in this assessment are pembrolizumab, nivolumab, CAPOX and mFOLFOX6. Since the comparison of zolbetuximab given in addition to chemotherapy vs chemotherapy is based on the pivotal trials for zolbetuximab (GLOW and SPOTLIGHT), the Danish adaptation of the global SLR only includes phase 3 clinical trials of studies of zolbetuximab, nivolumab and pembrolizumab (all given in addition to chemotherapy and compared to chemotherapy alone). Furthermore, the Danish adaptation excluded (see appendix H for details).

- references where the patient population considered was non-caucasian (e.g. study was conducted in Asia only or the publication only presented data for a subgroup of patients from Asia),
- studies were the treatment considered was irrelevant for the Danish assessment,
- references where only irrelevant endpoint were included

After the global SLR was conducted, a hand search was conducted where additional references for zolbetuximab was identified. [25, 26] Furthermore, the EPAR assessment reports were included for the Danish adaptation and the DMC assessment of Keytruda in G/GEJC was added after the global SLR was completed.

The following four pivotal clinical trials and key references are included in the Danish adaptation:

- Zolbetuximab:

SPOTLIGHT/NCT03504397 reported by Shitara et al 2023 (phase 3 study)[11]
GLOW/NCT03653507 reported by Shah et al 2023 (Phase 3 study)[10]. Results from the integrated efficacy and safety analysis of GLOW and SPOTLIGHT were sourced from Shitara et al. (2024)[26] and the EMA Public Assessment Report. [18]. Health related quality of life data was sourced from Lordick et al (2024)[25]

- Nivolumab

CheckMate-649/NCT02872116 (phase 3 study) reported by Janjigian et al 2021, Shitara et al 2024, and the EMA Public Assessment report [27-29] and DMC assessment of Opdivo in G/GEJ [1]. Health related quality of life data was sourced from Moehler et al (2024).[30]

- Pembrolizumab

KEYNOTE-859/NCT03675737 (phase 3 study) reported by Rha et al 2022, [31], EMA Public Assessment report.[32], and DMC Assessment of Keytruda in G/GEJC[2]

Hence, the included trials for zolbetuximab are the two pivotal clinical trials SPOTLIGHT and GLOW. The included trials for nivolumab and pembrolizumab are the pivotal trials CheckMate 649 and KEYNOTE 859. This study selection for nivolumab and pembrolizumab align with the recent assessment of nivolumab and pembrolizumab in G/GEJC by DMC. [1, 2] Details regarding the methodology and the search is available in appendix H. In the following the included studies are presented briefly.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Shitara K, Lordick F, Bang Y-J, Enzinger P, Ilson D, Shah MA, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. The Lancet. 2023;401(10389):1655-68. [11] Shitara K, Shah MA, Lordick F, Van Cutsem E, Ilson DH, Klempner SJ, et al. Zolbetuximab in Gastric or Gastroesophageal Junction Adenocarcinoma. N Engl J Med. 2024;391(12):1159-62[26] Lordick F, Van Cutsem E, Shitara K, Xu RH, Ajani JA, Shah MA, et al. Health-related quality of life in patients with CLDN18.2-positive, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma: results from the SPOTLIGHT and GLOW clinical trials. ESMO open. 2024;9(8):103663[25]	SPOTLIGHT	NCT03504397	Start: 21-06-2018 Primary efficacy and interim OS: 09 Sep 2022 Final OS analysis: 08 Sep 2023	Zolbetuximab given in addition to chemotherapy vs chemotherapy (mFOLFOX6) in patients HER2-negative advanced/metastatic G/GEJC
Shah MA, Shitara K, Ajani JA, Bang YJ, Enzinger P, Ilson D, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nature medicine. 2023;29(8):2133-41.[10] Shitara K, Shah MA, Lordick F, Van Cutsem E, Ilson DH, Klempner SJ, et al. Zolbetuximab in Gastric or Gastroesophageal Junction Adenocarcinoma. N Engl J Med. 2024;391(12):1159-62[26] Lordick F, Van Cutsem E, Shitara K, Xu RH, Ajani JA, Shah MA, et al. Health-related quality of life in patients with CLDN18.2-positive, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma: results from the SPOTLIGHT and GLOW clinical trials. ESMO open. 2024;9(8):103663[25]	GLOW	NCT03653507	Start: 28-11-2018 Primary efficacy and Interim OS analysis based on data-cut: 07 Oct 2022 Final analysis of OS: 12 Jan 2024	Zolbetuximab given in addition to chemotherapy vs chemotherapy (CAPOX) in patients HER2-negative advanced/metastatic G/GEJC
Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27-40. [27]	Checkmate-649	NCT02872116	Start: 12-10-2016 At the latest data cut, efficacy inputs were based on data with minimum follow-up time	Zolbetuximab given in addition to chemotherapy vs nivolumab given in addition to chemotherapy in patients HER2-negative advanced/metastatic G/GEJC with a CPS≥5

Reference	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Shitara K, Moehler M, Ajani JA, Shen L, Garrido M, Gallardo C, et al. Nivolumab plus chemotherapy vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: 4-year follow-up of the CheckMate 649 study. ASCO Gastrointestinal Cancers Syposium. San Francisco, CA: US; 2024[29] Moehler MX, H.; Blum, S. I.; Elimova, E.; Cella, D.; Shitara, K.; Ajani, J. A.; Janjigian, Y. Y.; Garrido, M.; Shen, L.; Yamaguchi, K.; Liu, T.; Schenker, M.; Kowalyszyn, R.; Bragagnoli, A. C.; Bruges, R.; Montesarchio, V.; Pazo-Cid, R.; Hunter, S.; Davenport, E.; Wang, J.; Kondo, K.; Li, M.; Wyrwicz, L. Health-Related Quality of Life With Nivolumab Plus Chemotherapy Versus Chemotherapy in Patients With Advanced Gastric/Gastroesophageal Junction Cancer or Esophageal Adenocarcinoma From CheckMate 649. Journal of Clinical Oncology. 2023;41:5388-99[30] EMA. Opdivo. CHMP Assessment report (Variation) EMEA/H/C/003985/II/0096. 2021 Sept 16.[28] Medicinrådet. Medicinrådets anbefaling vedrørende nivolumab i kombination med kemoterapi til 1. linjebehandling af fremskredent HER2-negativ adenokarcinom i mavesæk, mavemund eller spiserør og PD-L1 CPS ≥ 5.; 2022. [1]			of 4 years, reported in Shitara 2024	
Rha SY, Oh DY, Yanez P, Bai Y, Ryu MH, Lee J, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2023;24(11):1181-95. [31] EMA. Keytruda. CHMP Assessment report (variation). EMEA/H/C/003820/II/0135. 2023 Oct 12[32] Medicinrådet. Medicinrådets anbefaling vedr. pembrolizumab i kombination med kemoterapi til behandling af HER2-negativ adenokarcinom i mavesæk eller mavemund. Patienter med PD-L1CPS ≥ 1. 2024[2]	KEYNOTE-859	NCT03675737	Start: 8-11-2018 Interim analysis: 03 Oct022 Final analysis not published	Zolbetuximab given in addition to chemotherapy vs pembrolizumab given in addition to chemotherapy in patients with HER2-negative advanced/metastatic G/GEJC with a CPS≥5

5.2 Literature used for the assessment of health-related quality of life

The CUA comparing zolbetuximab + chemotherapy to chemotherapy alone, included disutility of side-effects from the literature. Given the low impact of side-effects on incremental QALY in partitioned survival models, the estimates were pragmatically sourced from a published CUA and NICE assessments of pembrolizumab.

Reference	Health state/Disutility	Reference in dossier
NICE. ID1465 Committee Papers. 2022. [33]	Vomiting, Nausea	Section 14.3.1
Shah et al. Cost-Effectiveness of KTE-X19 for Adults with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia in the United States. Advances in therapy. 2022;39(8):3678-95 [34]	Neutropenia, Neutrophil count decreased, Decreased appetite, Hypokalaemia, Diarrhoea	Section 14.3.1
Lloyd et al. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683–90.[35]	Asthenia	Section 14.3.1

5.3 Literature used for inputs for the health economic model

No further literature inputs were used for the health economic model. In order to validate the extrapolation of OS, Astellas commissioned an analysis of time to overall death in patients treated with chemotherapy from the national registry "*Nationella registret för esofagus- och magcancer*" (NREV). This source is applied in Appendix D.3.7.

6. Efficacy vs chemotherapy

6.1 Efficacy

6.1.1 Relevant studies

In the following the two pivotal phase 3 clinical trials of zolbetuximab given in addition to chemotherapy vs chemotherapy alone are presented. Additional information is available in the peer reviewed publications [10, 11] (interim data cuts), in a recent publication of final data from the two pivotal trials (and integrated analysis hereof)[26], as well as in the EPAR assessment report. [18]

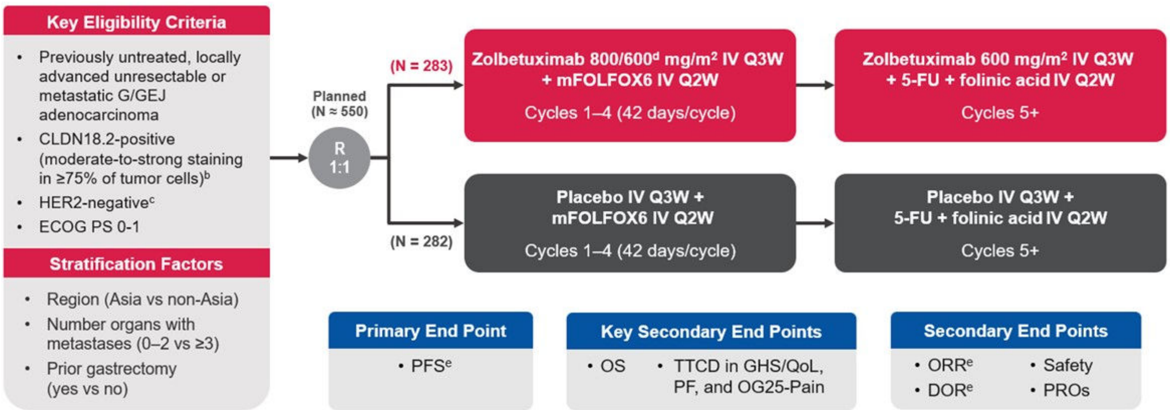
SPOTLIGHT
SPOTLIGHT is a global, randomised, placebo-controlled, double-blind, phase 3 trial that enrolled patients from 215 centres in 20 countries. Eligible patients were aged 18 years

or older with CLDN18.2-positive (defined as ≥75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative (based on local or central evaluation), previously untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma, with radiologically evaluable disease (measurable or non-measurable) according to Response Evaluation Criteria in Solid Tumors version 1.1; an Eastern Cooperative Oncology Group performance status score of 0 or 1; and adequate organ function. Patients were randomly assigned (1:1) to zolbetuximab + mFOLFOX6 or placebo + mFOLFOX6, and stratified according to region, number of organs with metastases, and previous gastrectomy [11].

Patients received either an intravenous infusion of zolbetuximab 800 mg/m² (cycle 1, day 1) followed by 600 mg/m² (cycle 1, day 22, and days 1 and 22 of subsequent cycles) plus intravenous infusion of mFOLFOX6 (folinic acid 400 mg/m², or optionally in Japan, levofolinate 200 mg/m²; fluorouracil 400 mg/m² bolus followed by 2400 mg/m² in a 46-h to 48-h infusion; and oxaliplatin 85 mg/m²; on days 1, 15, and 29) or placebo plus mFOLFOX6, for four 42-day cycles. Patients without disease progression continued beyond four cycles with zolbetuximab or placebo, plus, at the investigator's discretion, folinic acid (or optionally in Japan, levofolinate) and fluorouracil. 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.

The study consisted of six periods: screening, treatment, safety follow-up, post-treatment follow-up for progression-free survival (PFS), long-term follow-up for PFS following subsequent anticancer treatment (PFS2), and OS. The SPOTLIGHT trial design is presented below.

Figure 2. SPOTLIGHT study design



Abbreviations: 5-FU fluorouracil; CLDN18.2 claudin 18.2; DOR duration of response; ECOG PS Eastern Cooperative Oncology Group Performance Status; G/GEJ gastric/gastro-oesophageal junction; GHS global health status; HER2 human epidermal growth factor receptor 2; IHC immunohistochemistry; IRC independent review committee; IV intravenous; mFOLFOX6 modified folinic acid in combination with fluorouracil and oxaliplatin; OG25-Pain European Organisation for Research and Treatment of Cancer Quality of Life Oesophago-Gastric; ORR objective response rate; OS overall survival; PFS progression-free survival; PRO patient-reported outcome; Q2W every 2 weeks; Q3W every 3 weeks; QoL quality of life; R randomised; RECIST Response Evaluation Criteria in Solid Tumours; TTCD time to confirmed deterioration

The primary efficacy endpoint of SPOTLIGHT was PFS (time from the date of randomization until the date of radiological progressive disease (per RECIST 1.1 by Independent Review Committee (IRC)) or death from any cause, whichever is earliest).

Key secondary endpoints included OS (time from the date of randomization until the date of death from any cause) and time to confirmed deterioration (TTCD) (time from randomization to first clinically meaningful deterioration). Other secondary endpoints included objective response rate (ORR) (the proportion of participants who have a best overall response of Complete Response (CR) or Partial Response (PR) as assessed by Independent Review Committee), duration of response (DoR) (time from the date of the first response (CR/PR) until the date of progressive disease as assessed by IRC per RECIST 1.1 or date of death from any cause, whichever is earliest) and HRQoL.

HRQoL was measured using EORTC-QLQ-C30 (a cancer-specific instrument consisting of 5 functional domain scales: physical, role, emotional, social and cognitive), the EORTC-QLQ-OG25 instrument (evaluates Gastric and GEJ cancer-specific symptoms such as stomach discomfort, difficulties eating and swallowing and indigestion), the Global Pain (GP) questionnaire and the EuroQOL Five Dimensions Questionnaire 5L (EQ-5D-5L).

In SPOTLIGHT, the final overall survival analysis was planned when 396 patients had died. The final database lock for the SPOTLIGHT trial took place on 8th of September 2023. The following presentation focus on the final data cut. Additional data provided for interim data cut is published (interim data cut 9th of September 2022)[11].

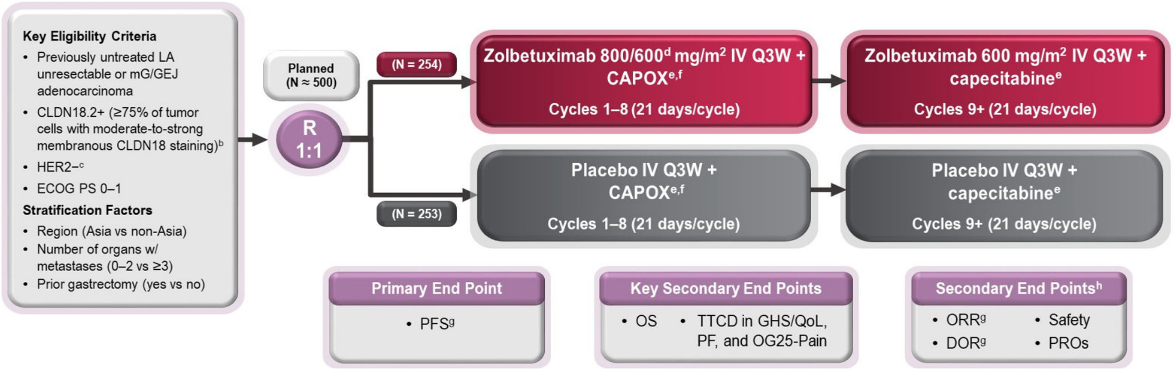
At the final data cut, median follow-up time was 33.28 months in the zolbetuximab+ FOLFOX arm and 31.38 months in the placebo + FOLFOX arm.[26]

GLOW

GLOW is a Phase 3, multicentre, double-blind RCT designed to evaluate the efficacy and safety of zolbetuximab + CAPOX versus placebo + CAPOX as first-line treatment in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJC. Patients (n = 507) were randomized 1:1 to zolbetuximab plus CAPOX or placebo plus CAPOX.

Randomisation of patients was stratified by region (Asia versus non-Asia), number of organs with metastatic sites (0–2 versus ≥ 3) and prior gastrectomy (yes or no).

Figure 3. GLOW study design



Abbreviations: BID twice daily; CAPOX capecitabine and oxaliplatin; CLDN18.2 claudin 18 isoform 2; DOR duration of response; ECOG PS Eastern Cooperative Oncology Group performance status; FISH fluorescent in situ hybridization; GHS global health status; HER2 human epidermal growth factor receptor 2; IHC immunohistochemistry; IV intravenous; LA locally advanced; mG/GEJ metastatic gastric/gastroesophageal junction; OG25-Pain European Organisation for Research and Treatment of Cancer Quality of Life Oesophago-Gastric; ORR objective response rate; OS overall survival; PFS progression-free survival; PRO patient-reported outcome; Q3W every 3 weeks; QoL quality of life; R randomised; RECIST Response Evaluation Criteria In Solid Tumours version 1.1; TTCD time to confirmed deterioration.

Notes: a) Study was conducted at 166 sites in 18 countries across Asia, Europe, North America, and South America. b) By central IHC using the VENTATA CLDN18.2 (43-14A) RxDx. C) By central or local HER2 testing (IHC 0–1, or IHC2/FISH-). d)800 mg/m2 on Day 1 of subsequent cycles. e)1,000 mg/m2 capecitabine orally BID on Days 1–14 of each cycle. f) 130 mg/m2 oxaliplatin IV on Day 1 of each cycle. g) RECIST V 1.1 per IRC assessment

For inclusion in GLOW, patients were ≥ 18 years of age with CLDN18.2-positive (defined as ≥ 75% of tumour cells with moderate-to-strong membranous CLDN18 staining, determined by central IHC using the investigational VENTANA CLDN18 [43-14A] RxDx Assay), HER2-negative, previously untreated, locally advanced unresectable or metastatic G/GEJC, with radiologically evaluable disease according to RECIST version 1.1, an ECOG performance status score of 0 or 1, and adequate organ function.

The primary efficacy endpoint of GLOW is PFS per RECIST 1.1 by IRC. Key secondary endpoints include OS and time to confirmed deterioration (TTCD); other secondary endpoints include ORR, DoR and HRQoL. Definitions of endpoint were comparable to SPOTLIGHT (see above).

In GLOW, the final overall survival analysis was planned when 386 patients had died. The following presentation of key results from the GLOW trial is based on final data cut (12th of January 2024) which was recently published by Shitara and colleagues [26]. This data hence differs from the initial peer reviewed publication by Shah and colleagues [10], which is based on an earlier data cut (interim data cut: 7th October 2022).

At the final data cut the median duration of follow-up (months) was 31.70 months in the zolbetuximab + CAPOX arm and 32.95 months in the placebo+ CAPOX arm.[26]

Table 6 Overview of study design for studies included in the comparison (SPOTLIGHT and GLOW)

Study design	Study duration	Patient population	Intervention	
Phase 3, double-blind RCT	Start: 21/06/2018 Median follow-up time at final data cut was 33.28 months in the zolbetuximab+ FOLFOX arm and 31.38 months in the placebo + FOLFOX arm	Adults with CLDN18.2-positive*, HER2-, previously untreated, locally advanced unresectable or metastatic G/GEJ adenocarcinoma. ECOG 0 or 1 and adequate organ function	Zolbetuximab (800 mg/m² loading dose followed by 600 mg/m² every 3 weeks) plus mFOLFOX6 (every 2 weeks).	Placebo plus mFOLFOX6 (every 2 weeks)
Phase 3, double-blind RCT	Start: 28/11/2018 Median duration of follow-up (months) 31.70 months in the zolbetuximab + CAPOX arm and 32.95 months in the placebo+ CAPOX arm	Adults with CLDN18.2-positive*, HER2-, previously untreated, locally advanced unresectable or metastatic G/GEJ adenocarcinoma. ECOG 0 or 1 and adequate organ function	Zolbetuximab (800 mg/m² loading dose followed by 600 mg/m² every 3 weeks) plus CAPOX	Placebo (loading dose plus every 3 weeks) + CAPOX

* defined as ≥75% of tumour cells showing moderate-to-strong membranous CLDN18 staining

6.1.2 Comparability of studies

SPOTLIGHT and GLOW were simultaneously planned and homogenous in terms of PICO (patients, intervention, comparison and outcome) criteria, with patient populations selected based on similar inclusion/exclusion criteria. Thus, a combined efficacy and safety analysis was conducted on the results from the trials. In the assessment by EMA, the integrated analysis was also considered relevant and included as part of the assessment of zolbetuximab.

The chosen chemotherapy regimen differs between the two studies. However, both chemotherapy regimens are platinum based and the HRs for SPOTLIGHT and GLOW (for zolbetuximab + chemotherapy versus chemotherapy) were very similar, despite different chemotherapy backbone (i.e. CAPOX in GLOW and FOLFOX in SPOTLIGHT).

6.1.2.1 Comparability of patients across studies

The inclusion and exclusion criteria for the SPOTIGHT and GLOW trial were comparable and the baseline characteristics of the patients included in the SPOTLIGHT and GLOW trials are comparable as reflected in Table 7.

Table 7 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (SPOTLIGHT, GLOW and integrated analysis of SPOTLIGHT and GLOW)

	SPOTLIGHT		GLOW		Integrated (SPOTLIGHT/GLOW)[26]	
	Zolbetuximab + mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbetuximab + CAPOX (n = 254)	CAPOX (n = 253)	Zolbetuximab + chemotherapy (n = 537)	Placebo + chemotherapy (n = 535)
Age (years), median	62	60	61	59	61	60
Male gender, %	62	62	63	62	62	62
Race						
White, %	54	53	37	36	46	45
Asian, %	37	38	63	64	50	51
Other, %	10	9	0	0	5	4
ECOG, %						
0	44	41	43	43	44	42
1	55	59	57	57	NA	NA
2	0	0	0	0	NA	NA
Tumour location %						
Oesophagus	0	0	0	0	0	0
GEJ	23	26	14	17	18	22

	SPOTLIGHT		GLOW		Integrated (SPOTLIGHT/GLOW)[26]	
	Zolbetuximab + mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbetuximab + CAPOX (n = 254)	CAPOX (n = 253)	Zolbetuximab + chemotherapy (n = 537)	Placebo + chemotherapy (n = 535)
GC	77	74	86	83	82	78
HER2 status, %						
positive	0	0	0	0	0	0
negative	100	100	100	100	100	100
unknown	0	0	0	0	0	0

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

In the health economic model, the mean age applied in the model is 58.5 years based on the mean age at baseline in the pivotal clinical trials (SPOTLIGHT and GLOW). According to our knowledge, no information is available on the mean age for in a Danish patient population with advanced G/GEJC. According to the recent assessment of nivolumab, a median age of 64.6 years was assumed to reflect Danish patients with advanced G/GEJC. Based on this, the median age for nivolumab and pembrolizumab in the pivotal clinical trials (CheckMate 649 and KEYNOTE 859) were assumed to reflect a Danish patient population by DMC. As can be seen from Table 20, the median age in the pivotal trials for zolbetuximab is comparable to that in the pivotal trials for nivolumab and pembrolizumab. Hence, the median age for patients included in the SPOTLIGHT/GLOW studies seem to reflect the median age for a Danish patient population.

Table 8 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age (years)	64.6 years*[2]	58.5 (SPOTLIGHT/GLOW mean age at baseline)
BSA (m^2)	NA	1.81 (SPOTLIGHT baseline) †

*median age is based on information from DMC in the assessment of pembrolizumab[1] † BSA was estimated for the Asian/non-Asian strata in the study and reweighted by the proportion of Danes with Asian heritage. [36]

6.1.4 Efficacy – results per SPOTLIGHT and GLOW (Integrated analysis)

As SPOTLIGHT and GLOW were simultaneously planned and homogenous in terms of PICO (patients, intervention, comparison and outcome) criteria, with patient populations selected based on similar inclusion/exclusion criteria, a combined efficacy and safety analysis was conducted on the results from the trials. In the following the key findings from the integrated efficacy analysis are presented. Additional information is available in appendix B, where detailed results are presented for the combined analysis as well as for SPOTLIGHT and GLOW, respectively.

Interim results from SPOTLIGHT and GLOW respectively are presented in peer reviewed publications [10, 11] as well as in the EPAR assessment report.[18] In addition, the recent publication by Shitara and colleagues (2024) reports final results both for the individual studies separately as well as for the integrated analysis. [26]

The data cutoff date in SPOTLIGHT was September 8, 2023. The data cutoff date in GLOW was January 12, 2024 (final data cut off).

It should be noted that while the hazard ratios (HR) and confidence intervals (CI) for PFS and OS reported in GLOW and SPOTLIGHT are similar, differences between studies in PFS and OS in active and control arm were observed. Baseline characteristics were balanced between the zolbetuximab and control arms in SPOTLIGHT, and no selection biases were identified among the randomized patients, including time to randomization. However, there were differences in the median PFS and OS, particularly in the control arms of the trials. In the control arm of SPOTLIGHT, median (95% CI) PFS and OS were 8.9 months (8.2-10.4) and 15.6 months (13.7-16.9), respectively. In comparison, the median (95% CI) PFS and OS in the GLOW trial were 6.8 months (6.1-8.1) and 12.2 months (10.3-13.7) [26].

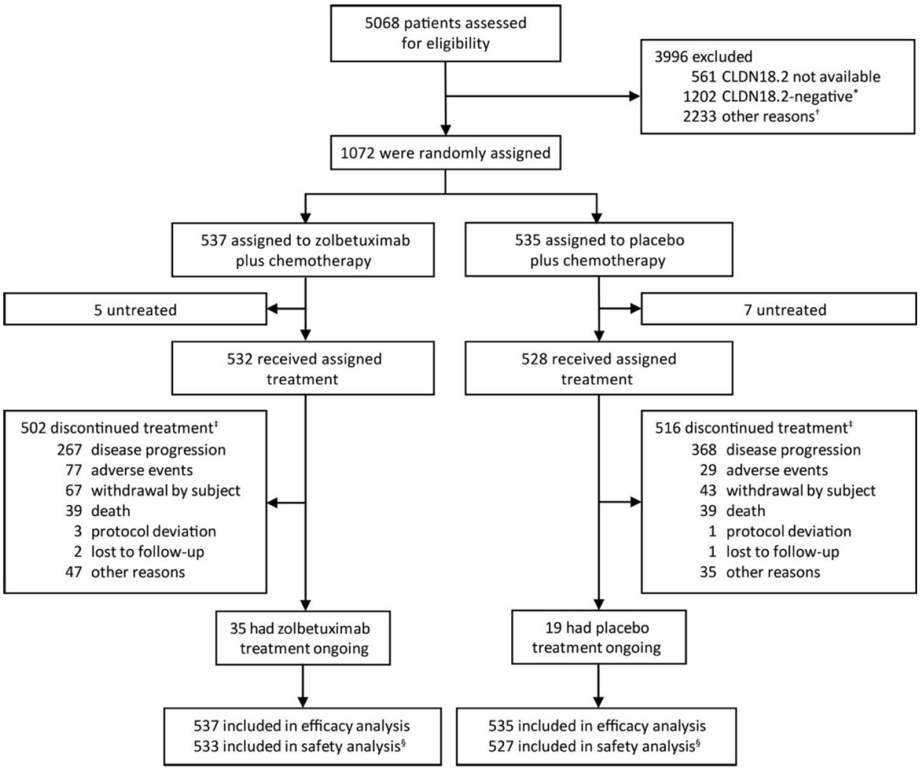
Longer median PFS and OS were also observed in the zolbetuximab treatment arm of the SPOTLIGHT trial compared to the GLOW trial (PFS: 11 vs 8.2 months; OS: 18.2 vs 14.3 months). This suggests the observed differences may be linked to the chemotherapy regimen used in combination with zolbetuximab or placebo, and it is notable that patients in both arms of SPOTLIGHT were exposed to oxaliplatin for a longer duration compared to patients in GLOW.

Note that the comparison to chemotherapy (patients not eligible for PD-(L)1 treatment in Denmark) was based on results in ITT population of the integrated analysis. There is no known biological mechanism by which PD-(L)1 CPS could affect zolbetuximab's mechanism of action. Furthermore, the trials were not designed to collect - nor analyse result by - CPS. Post-hoc analysis of results in patients with known baseline CPS indicate that the treatment effect of zolbetuximab is independent of CPS status. The relative effect of zolbetuximab given in addition to chemo compared to chemo alone was comparable for the ITT population and for patients with a CPS<5 suggesting that the treatment effect of zolbetuximab is independent of CPS status. This supports using the full population to evaluate relative efficacy. In the economic model, however, a sensitivity analysis was included using efficacy data from the subgroup of patients with known baseline CPS and CPS <5 (subgroup data are presented in Appendix D.4)

Patient disposition

A total of 1072 patients were randomly assigned to the zolbetuximab group (n=537 patients) or the placebo group (n=535). A total of 532 received treatment with zolbetuximab and 528 received the assigned treatment with chemotherapy. Discontinuation and reason for discontinuation is presented in Figure 4.

Figure 4. Randomization, Treatment, and Follow-Up in the integrated analysis [26]



*CLDN18.2-positive was defined as ≥75% of tumor cells with moderate-to-strong membranous CLDN18 staining determined by central immunohistochemistry using the VENTANA CLDN18 (43-14A) RxDx Assay (for investigational Use Only; VMSI/Roche). †Patients excluded for "other reasons" represents patients whose tumors were CLDN18.2-positive but who failed screening for reasons including laboratory findings, HER2 expression status, Eastern Cooperative Oncology Group performance status score, other exclusion criteria, or withdrawal by patient. ‡If patients discontinued from both zolbetuximab or placebo and chemotherapy on the same day, all reasons for discontinuation were summarized; therefore, the sum of values for individual reasons for discontinuation is more than the total patients who discontinued treatment. §In GLOW, one patient assigned to the placebo group received one dose of zolbetuximab as a protocol deviation and was moved to the zolbetuximab group for the safety analysis set.

Abbreviations: CLDN18, claudin 18; CLDN18.2, claudin 18 isoform 2; HER2, human epidermal growth factor receptor 2.

Progression free survival (PFS) and overall survival (OS) (integrated analysis) (ITT)

At the final data cut off patients treated with zolbetuximab + chemotherapy (CAPOX or mFOLFOX6) showed a significant reduction (29%) in the risk of progression or death (as assessed by an IRC) compared with patients treated with placebo + chemotherapy (HR=0.712 [95% CI: 0.61; 0.831], p<0.0001). When looking at the two individual trials, the HR was comparable for the two trials (SPOTLIGHT: 0.73; GLOW: 0.69) (see appendix B).

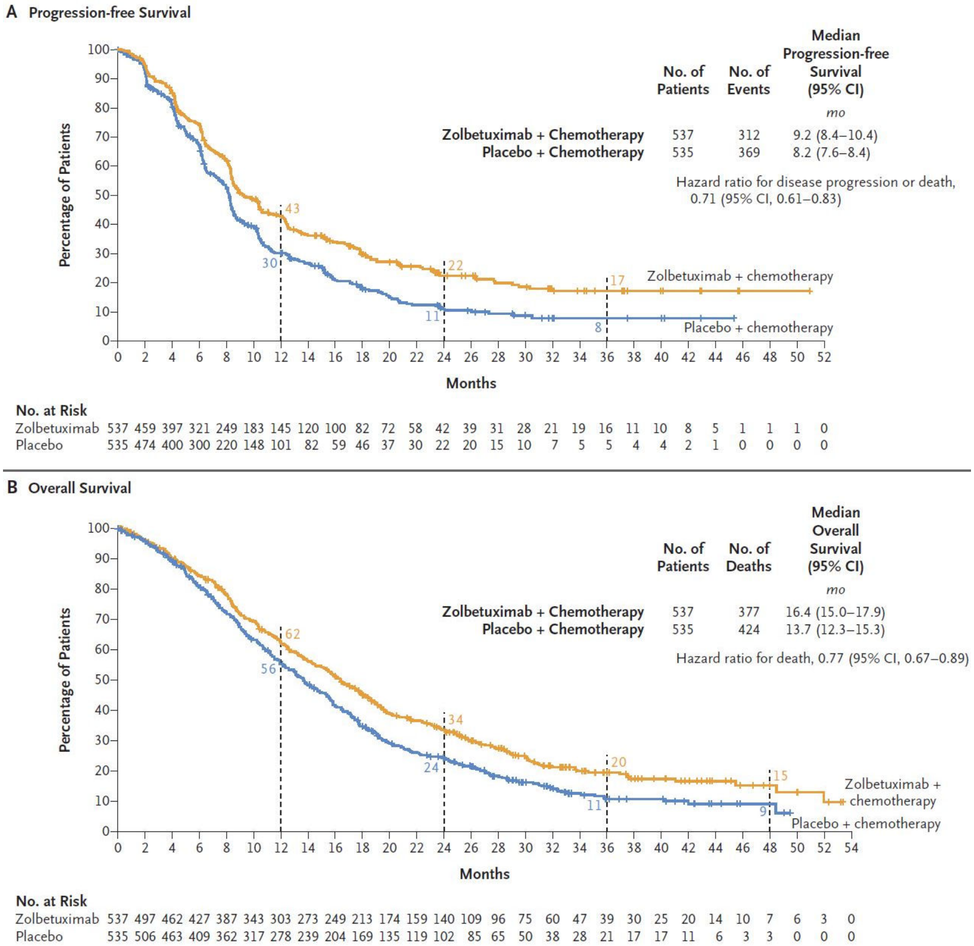
As of the final data cut, patients who received zolbetuximab in addition to chemotherapy (CAPOX or mFOLFOX6) had improved OS compared with chemotherapy alone (HR 0.774 [95% CI: 0.672; 0.892], p=0.0002). A total of 377 patients had died in the zolbetuximab + chemotherapy arm (70.2%) and 424 patients had died in the chemotherapy arm (79.3%). Median OS was 16.39 months [95% CI: 14.9; 17.87] in the zolbetuximab + chemotherapy arm and 13.70 months [95% CI: 12.32; 15.28] in the placebo + chemotherapy arm. When looking at the two individual trials, the HR was comparable for the two trials (SPOTLIGHT: 0.78; GLOW: 0.76) (see appendix B).

Table 9. Integrated efficacy analysis (SPOTLIGHT and GLOW) (final data cuts) [26]

	Integrated efficacy analysis	
	Zolbetuximab + mFOLFOX6 or CAPOX (n =537)	Placebo + mFOLFOX6 or CAPOX (n=535)
PFS (Assessed by IRC)		
Events, n (%)	312 (58.1%)	369 (69.0%)
Median duration, months (95% CI)†	9.17 [8.44; 10.41]	8.18 [7.59; 8.38]
HR (95% CI)‡	0.712 [0.610; 0.831]	
P value§	<0.0001	
OS		
Deaths, n (%)	377 (70.2%)	424 (79.3%)
Median duration, months (95% CI)†	16.39 [14.98; 17.87]	13.70 [12.32; 15.28]
HR (95% CI)‡	0.774 [0.672; 0.892]	
P value§	0.0002	

Notes: †Based on Kaplan-Meier estimate. ‡Based on Cox proportional hazards model with treatment, region, number of organs with metastatic sites, prior gastrectomy and study ID in the integrated analysis as the explanatory variables. Assuming proportional hazards, a HR <1 indicates a reduction in hazard rate in favour of the treatment group. §Based on 1-sided log-rank test.
Abbreviations: HR hazard ratio; mFOLFOX6: modified 5-fluorouracil leucovorin (or folinic acid) and oxaliplatin; OS overall survival; PFS progression-free survival

Figure 5. Kaplan Meier plot of Progression free survival (PFS) and overall survival (OS) (integrated analysis)[26]



Shown are results from a combined analysis of two placebo-controlled trials of zolbetuximab. Panel A shows the Kaplan–Meier plot for progression-free survival, and Panel B the Kaplan–Meier plot for overall survival. The data cutoff date in SPOTLIGHT was September 8, 2023. The data cutoff date in GLOW was January 12, 2024. The median follow-up for progression-free survival was 18.2 months (95% CI, 15.4 to 20.9) in the zolbetuximab group and 17.9 months (95% CI, 14.8 to 23.7) in the placebo group. The median follow-up for overall survival was 32.7 months (95% CI, 29.5 to 34.3) in the zolbetuximab group and 31.8 months (95% CI, 29.7 to 34.3) in the placebo group. In both panels, tick marks indicate censored data.
Abbreviations: CI: confidence interval, mo: months

Hence, the integrated analysis based on the final data for SPOTLIGHT and GLOW clinical trials demonstrated that zolbetuximab plus chemotherapy resulted in longer progression-free survival and overall survival than placebo plus chemotherapy among patients with HER2-negative, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors were positive for claudin 18.2.

Patient reported outcomes are presented in section 14.

7. Comparative analyses of efficacy

The comparison of zolbetuximab given in addition to chemotherapy to chemotherapy alone is based on the pivotal head-to-head clinical trials (SPOTLIGHT and GLOW).

7.1.1 Differences in definitions of outcomes between studies

NA

7.1.2 Method of synthesis

NA

7.1.3 Results from the comparative analysis

See section 6.1.4 above.

8. Modelling of efficacy in the health economic analysis

Separate methods were used for the two populations.

- Overall population: A cost-utility analysis was established to compare the net-present value of costs and QALY for patients treated with zolbetuximab and patients treated with chemo-therapy *(Patients with CLDN18.2 positivity)*.
- Subgroup with CDLN18.2 positivity and PD-(L)1 expression (CPS≥5): A cost-minimisation analysis was established to compare per patient cost of treatment with zolbetuximab compared to pembrolizumab and nivolumab, respectively *(Patients with CLDN18.2 positivity and PD-(L)1 expression)*.

Sections 8.1 through 8.5 present the modeling of efficacy in the cost-utility model comparing zolbetuximab given in addition to chemotherapy to chemotherapy.

8.1 Presentation of efficacy data from the clinical documentation used in the health economic analysis vs chemotherapy

8.1.1 Extrapolation of efficacy data

Extrapolations of PFS and OS (as well as time to treatment discontinuation) were carried out using data from the integrated clinical dataset (data-cut for final OS analyses). Data from the FAS population were used (see section 6.1.4). In a sensitivity analysis, extrapolations of PFS and OS were conducted using data from the subgroup of patients with known baseline PD-(L)1 status with CPS< 5 (see appendix D4).

8.1.1.1 Extrapolation of overall survival

Below find a summary of assumptions associated with extrapolation of OS.

Table 10 Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	Integrated efficacy analysis of GLOW and SPOTLIGHT
Model	Exponential, Weibull, Log-Logistic, Lognormal, Gompertz, Gamma, Generalized Gamma
Assumption of proportional hazards between intervention and comparator	No a'priori assumptions on proportionality were made
Function with best AIC fit	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Gamma
Function with best BIC fit	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Gamma
Function with best visual fit	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Gamma
Validation of selected extrapolated curves (external evidence)	The predicted OS for the chemo only arm was compared to long-term follow-up in the Royal Marsden study [37] and Ontario Cancer Registry [38].
Function with the best fit according to external evidence	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Gamma
Selected parametric function in base case analysis	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Gamma
Adjustment of background mortality with data from Statistics Denmark	Yes. Hazards capped at age-specific hazard from general population mortality (gender weighted using Medicinrådet's calculation)
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No.
Assumptions of cure point	No a'priori assumptions of cure-point was made.

Figure 6 Extrapolations of OS compared to KM (by arm and week)

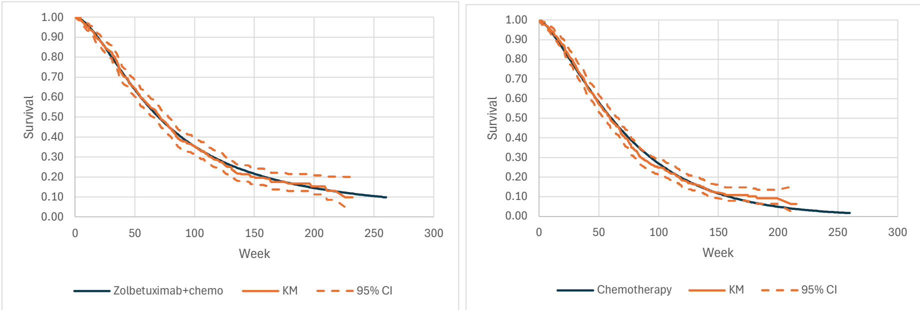
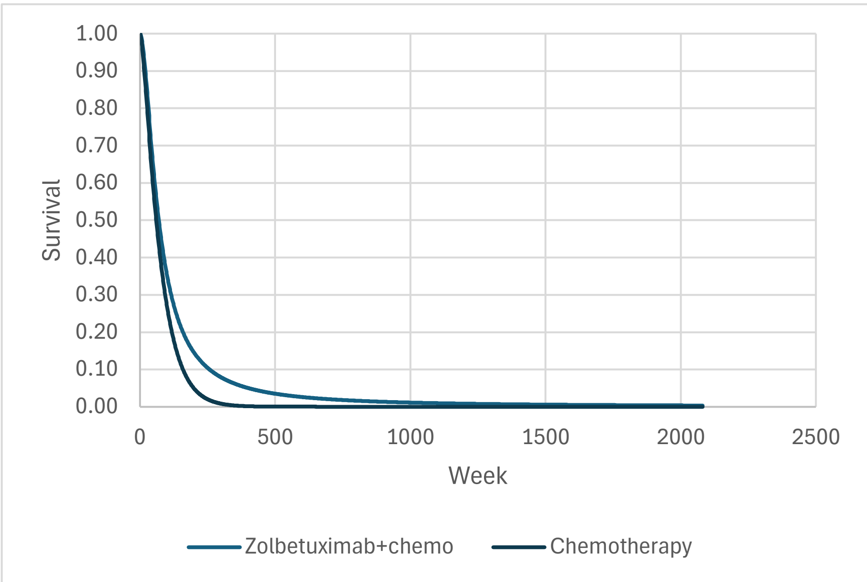


Figure 7 Overall survival in base case analysis before correction for general mortality by arm and week



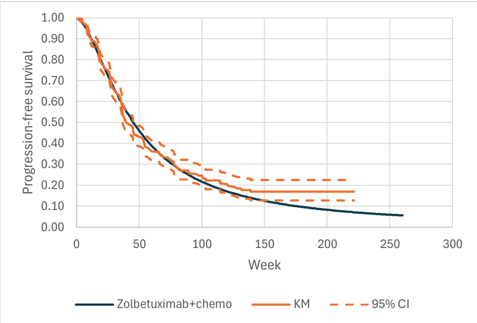
8.1.1.2 Extrapolation of progression-free survival

Table 11 Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	Integrated efficacy analysis of GLOW and SPOTLIGHT
Model	Exponential, Weibull, Log-Logistic, Lognormal, Gompertz, Gamma, Generalized Gamma
Assumption of proportional hazards between intervention and comparator	No a'priori assumptions on proportionality were made
Function with best AIC fit	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Log-logistic

Method/approach	Description/assumption
Function with best BIC fit	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Log-logistic
Function with best visual fit	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Log-logistic
Validation of selected extrapolated curves (external evidence)	Not attempted
Function with the best fit according to external evidence	Not attempted
Selected parametric function in base case analysis	Zolbetuximab plus chemotherapy: Log-logistic Chemotherapy alone: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	PFS can – by construction of traces – not exceed OS which is adjusted for general population morality
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No.
Assumptions of cure point	No a'priori assumptions of cure-point were made.

Figure 8 Extrapolations of PFS compared to KM (by arm and week)



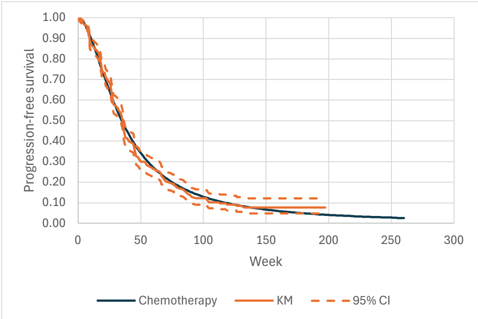
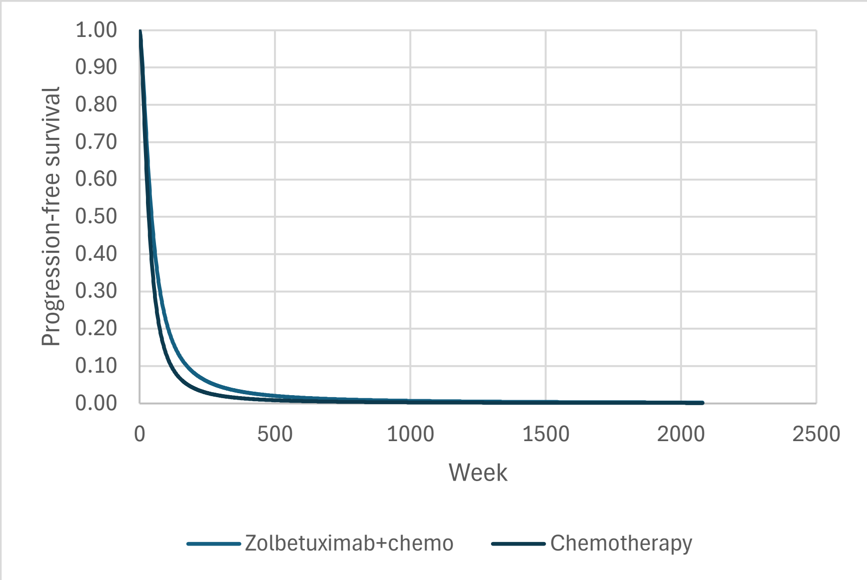


Figure 9 PFS in base case analysis before correction for general mortality by arm and week



8.1.1.3 Extrapolation of time to treatment discontinuation (TTD)

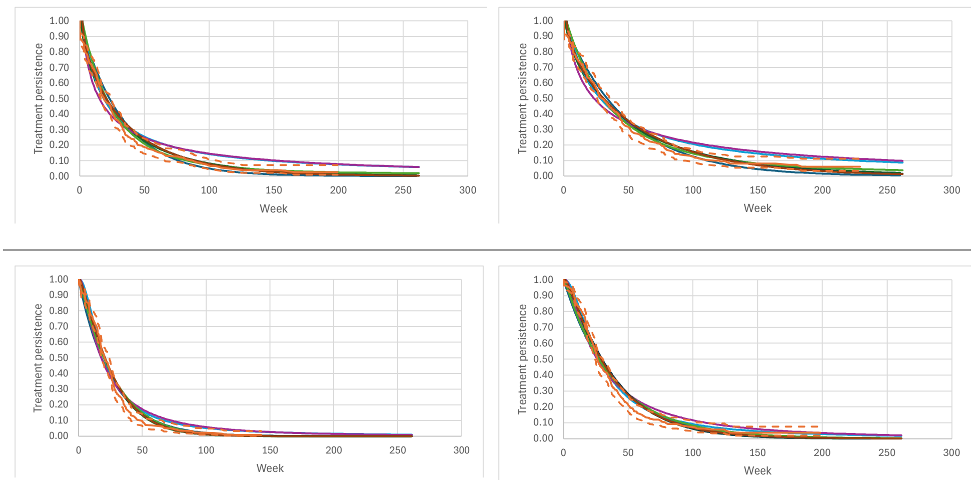
Table 12 Summary of assumptions associated with extrapolation of TTD

Method/approach	Description/assumption	
Data input	TTD from GLOW and SPOTLIGHT, respectively	
Model	Exponential, Weibull, Log-Logistic, Lognormal, Gompertz, Gamma, Generalized Gamma	
Assumption of proportional hazards between intervention and comparator	No a'priori assumptions on proportionality were made	
	GLOW	**SPOTLIGHT**
Function with best AIC fit	Zol+CAPOX: Gamma Capox: Gamma	Zol+FOLFOX: Gamma FOLFOX: Log-normal
Function with best BIC fit	Zol+CAPOX: Gamma Capox: Gamma	Zol+FOLFOX: Gamma FOLFOX: Log-normal
Function with best visual fit	Zol+CAPOX: Gamma Capox: Gamma	Zol+FOLFOX: Gamma FOLFOX: Log-normal
Function with best fit according to evaluation of smoothed hazard assumptions	Zol+CAPOX: Gamma Capox: Gamma	Zol+FOLFOX: Gamma FOLFOX: Log-normal
Validation of selected extrapolated curves (external evidence)	Not attempted	Not attempted
Function with the best fit according to external evidence	Not attempted	Not attempted

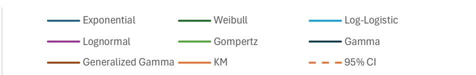
Method/approach	Description/assumption	
Selected parametric function in base case analysis	Zol+CAPOX: Gamma Capox: Gamma	Zol+FOLFOX: Gamma FOLFOX: Log-normal
Adjustment of background mortality with data from Statistics Denmark	TTD can – by construction of traces – not exceed PFS or OS which is adjusted for general population morality	
Adjustment for treatment switching/cross-over	No	
Assumptions of waning effect	No.	
Assumptions of cure point	No a'priori assumptions of cure-point were made.	

Figure 10 Estimated failure-time models and KM curves (with 95% CI) for TTD. Upper panels: Zolbetuximab plus chemo. Lower panels: placebo plus chemotherapy

GLOW SPOTLIGHT



Legend



8.1.2 Calculation of transition probabilities

Transition between health states in the partitioned survival model is determined by the estimated hazards for TTD, PFS and OS. When applying the extrapolated time to event curves in the patient traces, the following adjustments were made

- TTD in the patient traces cannot exceed PFS in any given cycle
- PFS in the patient traces cannot exceed OS in any given cycle
- Probability of death in any given cycle cannot be lower than the weekly probability of death in the gender-weighted Danish population at the same age

Table 13 Transitions in the health economic model

Not applicable

8.2 Presentation of efficacy data from other sources

Not applicable

8.3 Modelling effects of subsequent treatments

Subsequent treatment following progression was assumed to be the same whether patients have been treated with zolbetuximab plus chemotherapy or chemotherapy alone. No (additional) effect of subsequent treatment was modelled, however, the cost of next line of therapy was included as a lump-sum event cost at the time of progression. In this implementation of subsequent treatment, only the discounting effect of prolonging time to initiating the subsequent treatment will influence the net-present cost. Therefore, a pragmatic approach was taken to subsequent treatment, assuming that only docetaxel will be used as subsequent treatment. The relevance of docetaxel as the main subsequent treatment in Danish clinical practice is supported by the DMC assumptions in the assessment of nivolumab in G/GEJC.[2]

8.4 Other assumptions regarding efficacy in the model

Not applicable

8.5 Overview of modelled average treatment length and time in model health state

Table 14 provide the modelled efficacy outcomes in the model compared to observed median time to event. Average time to event in the model is calculated from model survival curves without discounting and using standard trapezoid calculation of mean survival (area under curve). Median time is calculated using linear interpolation of week closest to 50% percentiles on the survival curves. Means and medians were recalculated from cycles to months in the time-definition of the model (1 month = 1/12 year = 12/52 cycles).

Table 14 Estimates in the model compared to observed median time to event

	Modelled average	Modelled median	Observed median GLOW/SPOTLIGHT
OS (Sheet 'Partitioned Survival Model' cells O21:O24)			
Zolbetuximab plus chemotherapy	29 months	16.1 months	16.4 months
Chemotherapy alone	17.6 months	13.9 months	13.7 months

	Modelled average	Modelled median	Observed median GLOW/SPOTLIGHT
PFS (Sheet 'Partitioned Survival Model' cells N21:N24)			
Zolbetuximab plus chemotherapy	20.1 months	10.5 months	9.2 months
Chemotherapy alone	13.8 months	8.0 months	8.2 months

Table 15 presents the modelled average treatment length and time in model health state. Average time to discontinuation or event in the model was calculated from model survival curves without discounting and using standard trapezoid calculation of mean time to discontinuation or event (area under curve). Means were recalculated from cycles to months in the time-definition of the model (1 month = 1/12 year = 12/52 cycles).

Table 15 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Duration of treatment (mean)	PF	PD	OS
Zolbetuximab plus chemotherapy	7.8 months	1.7 years	0.7 year	2.4 years
Chemotherapy alone	6.0 months	1.0 year	0.4 years	1.5 years

9. Safety vs chemotherapy

9.1 Safety data from the clinical documentation

As SPOTLIGHT and GLOW were simultaneously planned and homogenous in terms of PICO (patients, intervention, comparison and outcome) criteria, with patient populations selected based on similar inclusion/exclusion criteria, a combined efficacy and safety analysis was conducted on the results from the trials. EMA assessed safety of zolbetuximab based on the integrated safety analysis. The integrated safety analysis for SPOTLIGHT and GLOW was undertaken to identify potential safety signals that may not have been identified from either Phase 3 study alone. Safety outcomes were generally consistent between SPOTLIGHT and GLOW [18] and with that reported in previous clinical studies of zolbetuximab. Importantly, no new safety signals were observed in the integrated safety analysis.

The integrated safety analysis is based on interim data cuts for SPOTLIGHT and GLOW (SPOTLIGHT: 09 Sep 2022; GLOW:07 Oct 2022). The safety population (all participants who received at least 1 dose of any study drug (zolbetuximab or chemotherapy)) included 533 patients in the zolbetuximab + chemo arm (SPOTLIGHT: 279; GLOW: 254) and 527 in the placebo + chemo arm (SPOTLIGHT: 278; GLOW: 249). [18] In SPOTLIGHT, the median study follow-up time (defined as the duration from the first dosing of zolbetuximab/placebo to the date of completion of the 90-day follow-up period, date of discontinuation from the 90-day follow-up period, date of death or date of CSR cutoff in case of ongoing participants) was 8.61 months in the zolbetuximab group and 8.87 months in the placebo group. In GLOW, the median study follow-up time was 6.97 months in the zolbetuximab group and 7.16 months in the placebo group. [18]

The frequency of adverse events/reactions is overall comparable for zolbetuximab given in addition to chemotherapy vs chemotherapy alone. However, more patients treated with zolbetuximab had dose reduction compared to that observed in patients treated with chemotherapy alone (Table 16).

Table 16 Overview of safety events (integrated safety analysis) (interim data cuts: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022) (Safety analysis set)

	Zolbetuximab + mFOLFOX6 or CAPOX (N=533) [18]	placebo + mFOLFOX6 or CAPOX (N=527) [18]	Difference, %-points (95 % CI)
Number of adverse events, n	NA	NA	NA
Number and proportion of patients with ≥1 adverse events, n (%)	529 (99.2%)	521 (98.9%)	0.4 (-0.8; 1.6)
Number of serious adverse events*, n	NA	NA	NA
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	245 (46.0%)	245 (46.5%)	-0.5 (-6.5; 5.5)
Number of CTCAE grade ≥ 3 events, n	NA	NA	NA
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	427 (80.1)	390 (74.0)	6.1 (1.1; 11.2)
Number of adverse reactions, n	NA	NA	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	523 (98.1%)	502 (95.3%)	2.9 (0.7; 5)
Number and proportion of patients who had a dose reduction, n (%)	409 (76.7%)	284 (53.9%)	22.8 (17.3; 28.4)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)†	502 (93.5%)	516 (96.4%)	-3.0 (-5.6; -0.4)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	199 (37.3%)	169 (32.1%)	5.3 (-0.5; 11)

Source: EPAR Public Assessment report [18] Data cuts: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022

§ CTCAE v. 5.0 must be used if available. † Denominator are the ITT population for each arm

The most frequent and severe toxicities related to the treatment with zolbetuximab in combination with chemotherapy are gastrointestinal disorders such as nausea and vomiting and these are the only SAE that occur with a frequency of ≥ 5% (Table 17). In order to limit the impact on the quality of life of patients and the tolerability of other standard treatment with chemotherapy risk mitigation measures have been implemented in the SmPC to optimize the toxicity management and improve the tolerability in clinical practice. Furthermore, these events most frequently occur during the early course of treatment and are acceptable in the context of advanced or metastatic gastric or GEJ cancer.

Table 17 Serious adverse events (integrated safety analysis, safety analysis set) with a frequency of ≥ 5%

Adverse events	Zolbetuximab + mFOLFOX6 or CAPOX (N=533)		Placebo + mFOLFOX6 or CAPOX (N=527)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Vomiting	38 (7.1%)	NA	24 (4.6%)	NA
Nausea	30 (5.6%)	NA	17 (3.2%)	NA
By system organ class				
Blood and Lymphatic System Disorders	29 (5.4%)	NA	24 (4.6%)	NA
Gastrointestinal Disorders	109 (20.5%)	NA	92 (17.5%)	NA
General Disorders and Administration Site Conditions	42 (7.9%)	NA	35 (6.6%)	NA
Infections and Infestations	54 (10.1%)	NA	44 (8.3%)	NA
Metabolism and Nutrition Disorders	31 (5.8%)	NA	24 (4.6%)	NA
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	24 (4.5%)	NA	34 (6.5%)	NA
Respiratory, Thoracic and Mediastinal Disorders	23 (4.3%)	NA	37 (7.0%)	NA
Blood and Lymphatic System Disorders	29 (5.4%)	NA	24 (4.6%)	NA
Gastrointestinal Disorders	109 (20.5%)	NA	92 (17.5%)	NA

Source: EPAR Public Assessment report [18] Data cuts: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022

Below find an overview of the adverse events used in the cost-effectiveness model.

Table 18 Adverse events used in the health economic model

Adverse events	Zolbetuximab plus chemotherapy	Chemotherapy	
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source / Justification
Neutropenia	18.2%	13.7%	Grade ≥3 adverse events with incidence ≥5% Integrated safety analysis. EPAR public assessment report [18]
Neutrophil count decreased	17.8%	17.6%	
Vomiting	14.3%	4.7%	
Nausea	12.6%	4.6%	
Anaemia	9.6%	10.2%	
Decreased appetite	6.2%	2.5%	
Hypokalaemia	5.6%	4.9%	
Asthenia	5.1%	1.9%	
Diarrhoea	5.1%	5.1%	

9.2 Safety data from external literature applied in the health economic model

Not applicable

10. Efficacy vs PD-(L)1 inhibitors

10.1 Efficacy

10.1.1 Relevant studies

Two relevant studies were identified, CheckMate-649 and KEYNOTE-859, where the efficacy and safety of PD-(L)1 inhibitors were documented in a subgroup of patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma and with a CPS≥5 (Appendix H). Efficacy data for PD-(L)1 inhibitor (nivolumab and pembrolizumab) is not available for patients who are CLDN18.2 positive. However, it has been demonstrated that CLDN18.2 expression have no impact on treatment outcomes with chemotherapy or PD-(L)1 inhibitors [39] (see appendix C).

CheckMate-649 and KEYNOTE-859 are presented in the following. It should also be noted that a detailed presentation of the studies and comparability of the studies was recently presented to and assessed by DMC in the assessment of pembrolizumab.[2]

The studies of zolbetuximab are presented in section 6.

Table 19 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
CheckMate-649 [27, 40] **NCT02872116**	Phase 3, multi-centre, randomised, open-label, active-controlled study	Start: 12-10-2016 At the latest data cut, efficacy inputs were based on data with minimum follow-up time of 4 years, reported in Shitara 2024[29]	Previously untreated, unresectable advanced or metastatic HER2-negative, G/GEJ, or oesophageal adenocarcinoma, regardless of PD-(L)1 expression	Nivolumab 360 mg plus XELOX every 3 weeks or nivolumab 240 mg plus FOLFOX every 2 weeks	Placebo + XELOX every 3 weeks or FOLFOX every 2 weeks	Dual primary endpoint: OS in PD-L1 positive (CPS ≥5) patients based on the PD-L1 immunohistochemistry (IHC) 28-8 pharmDX and PFS (per BICR) in PD-L1 positive (CPS ≥5) patients Secondary endpoints: OS in PD-L1 positive (CPS ≥1) patients and in all randomised patients (hierarchically tested) OS in PD-L1 positive (CPS ≥10) patients PFS (per BICR) in PD-L1 positive (CPS ≥1, ≥10) patients or all randomised patients ORR (per BICR) in PD-L1 positive (CPS ≥1, ≥5, ≥10) patients or all randomised patients. Safety and tolerability Exploratory: DRR by BICR and by investigator DOR by BICR and by investigator TTSD using GaCS of FACT-Ga PFS and ORR by investigator in subjects with different PD-L1 CPS cutoffs PFS2 or TSST PFS and ORR by BICR and by investigator and OS in subjects with different PD-L1 CPS cutoffs Incidence of death, AEs, SAEs, IMAEs and select AEs OS, PFS, and ORR in subjects with different MSI status Nivolumab ADA and characterization of Nab EQ-5D-3L descriptive system and VAS FACT-Ga including GaCS and FACT-G7 4 year follow up data exists for PFS and OS
KEYNOTE-859 [31] **NCT03675737**	Multicentre, double-blind, placebo-controlled, randomised, phase 3 trial	Start: 08-11-2018 Median duration of follow up 13 months (Interim analysis: Oct 3, 2022)[31]. Final analysis not published	patients with locally advanced or metastatic HER2-negative gastric or gastro-esophageal junction adenocarcinoma.	Pembrolizumab 200 every 3 weeks + FP every 3 weeks or CAPOX every 3 weeks	Placebo + FP every 3 weeks or CAPOX every 3 weeks	Primary: Overall Survival (OS) in All Participants, OS In Participants With PD-L1 Combined Positive Score (CPS) ≥1, OS In Participants With PD-L1 Combined Positive Score (CPS) ≥10. OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the analysis were censored at the date of the last follow-up. OS was estimated using the product-limit (Kaplan-Meier) method for censored data. Progression Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Assessed by Blinded Independent Central Review (BICR) in All

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						Participants, PFS in Participants With PD-L1 Combined Positive Score (CPS) ≥1, PFS in Participants With PD-L1 Combined Positive Score (CPS) ≥10 Median duration of follow up 13 months for OS and PFS at the interim analysis: Oct 3, 2022 [31]. Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Assessed by Blinded Independent Central Review (BICR) in All Participants, ORR in Participants With PD-L1 Combined Positive Score (CPS) ≥1, ORR in Participants With PD-L1 Combined Positive Score (CPS) ≥10 Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Assessed by Blinded Independent Central Review (BICR) in All Participants, DOR in Participants With PD-L1 Combined Positive Score (CPS) ≥1, DOR in Participants With PD-L1 Combined Positive Score (CPS) ≥10 [Time Frame: Up to 49.5 months] Number of Participants Who Experienced an Adverse Event (AE) Number of Participants Who Discontinued Study Treatment Due To an Adverse Event (AE).

10.1.2 Comparability of studies

The Medicine Council have in the recent assessment of pembrolizumab, where nivolumab was a relevant comparator, assessed the CheckMate-649 and KEYNOTE-859 studies and concluded that the design of the clinical studies and patient populations included are comparable. [2] In the following, the baseline characteristics for the CheckMate-649 and KEYNOTE-859 studies are compared to the patient population in SPOTLIGHT and GLOW.

10.1.2.1 Comparability of patients across studies

Baseline characteristics from the clinical trials for zolbetuximab, pembrolizumab and nivolumab in patients with advanced/metastatic G/GEJ adenocarcinoma are presented in Table 20 below.

The median age is comparable across trials (59-62 years) and the share of male patients included is 62-71% across the clinical trials. The clinical trials, however, included a varying proportion of white patients; in the clinical trials of zolbetuximab approximately half of all included patients were white, whereas the single included clinical study of nivolumab included 75% of patients being white. Distribution of ECOG score was comparable across trials and tumour location was fairly comparable across trials. All patients were HER2 negative in the clinical trials.

A fundamental difference is that the zolbetuximab trials only included patients with claudin 18.2 positivity while the PD-(L)1 trials did not collect CLDN18.2 status. This is discussed in section 11.

Table 20 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (ITT)

	SPOTLIGHT		GLOW		CheckMate 649		KEYNOTE-859	
	Zolbe+ mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbe + CAPOX (n = 254)	CAPOX (n = 253)	Nivo+ CAPOX/ FOLFOX (n = 789)	CAPOX/ FOLFOX (n = 792)	Pembro+ CF/CAPOX (n = 790)	CF/CAPOX (n = 789)
Age (years), median	62	60	61	59	62	61	61	62
Male gender, %	62	62	63	62	68	71	67	69
Race, %								
White	54	53	37	36	70	68	54	55
Asian	37	38	63	64	24	24	34	34
ECOG, %								
0	44	41	43	43	41	42	36	38
1	55	59	57	56	59	57	64	62
2	0	0	0	0	< 1	< 1	NR	NR

	SPOTLIGHT		GLOW		CheckMate 649		KEYNOTE-859	
	Zolbe+ mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbe + CAPOX (n = 254)	CAPOX (n = 253)	Nivo+ CAPOX/ FOLFOX (n = 789)	CAPOX/ FOLFOX (n = 792)	Pembro+ CF/CAPOX (n = 790)	CF/CAPOX (n = 789)
Tumour location, %								
Oesophagus	0	0	0	0	13	14	NR	NR
GEJ	23	26	14	17	17	16	19	23
G	77	74	86	83	70	70	81	76
Oesophagus	0	0	0	0	13	14	NR	NR
HER2 status, %								
Positive	0	0	0	0	0	0	0	0
Negative	100	100	100	100	NR	NR	100	100
Unknown	0	0	0	0	~40	~40	0	0

Abbreviations: CAPOX, capecitabine and oxaliplatin; CF, fluorouracil + cisplatin; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJ, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; SmPC, summary of product characteristics.
Source: Shitara et al., 2024[26] ; Sahin et al. 2021[41]; Janjigian et al. 2023;[40]; Nivolumab EPAR [28]; Pembrolizumab EPAR. [32]

10.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

In the health economic model, the mean age applied in the model is 58.5 years based on mean age at baseline in the pivotal clinical trials (SPOTLIGHT and GLOW). According to our knowledge, no information is available on the mean age for the relevant patient population in a Danish patient population. According to the recent assessment of nivolumab, a median age of 64.6 years was assumed to reflect Danish patients with advanced G/GEJC. Based on this, the median age for nivolumab and pembrolizumab in the pivotal clinical trials (CheckMate 649 and KEYNOTE 859) were assumed to reflect a Danish patient population. As can be seen from Table 20, the median age in the pivotal trials for zolbetuximab is comparable to that in the pivotal trials for nivolumab and pembrolizumab. Hence, the median age for patients included in the SPOTLIGHT/GLOW studies seem to reflect the median age for a Danish patient population.

The average weight in the Danish population is assumed to be 68 kg based on the assessment of Opdivo by DMC. However, no weight data is available from the pivotal trials of zolbetuximab. To our knowledge, no data is available on BSA for a Danish patient population with advanced G/GEJC. BSA in the pivotal trials of zolbetuximab was 1.7 m^2 (integrated analysis) and 1.73 m^2 in SPOTLIGHT. SPOTLIGHT data was used in the economic model because it had the highest number of Caucasians but BSA data by race strata (Asian vs non-Asians) were reweighting so that the Asian strata data were weighted by the percentage of Danes with Asian heritage (Table 21).

Table 21 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	64.6 years*[2]	58.5 (GLOW/SPOTLIGHT mean age at baseline)
Weight	68 kg**[1]	Not specified
BSA	NA	1.81 (SPOTLIGHT baseline†)

*Median age is based on information from DMC in the assessment of pembrolizumab; **Information about average weight in relevant Danish population is not available. An average weight of 68 kg has been applied since this was accepted by DMC in the assessment of nivolumab. † BSA was estimated for the Asian/non-Asian strata in the study and reweighted by the proportion of Danes with Asian heritage. [36]

10.1.4 Efficacy – results per CheckMate-649

CheckMate-649 is a phase 3 randomized controlled trial in adults with previously untreated, unresectable advanced, or metastatic G/GEJC/E. A total of 1581 patients were randomized to treatment (nivolumab given in addition to chemotherapy n=789; chemotherapy n=792). Randomized patients received nivolumab (360 mg Q3W or 240 mg Q2W) + chemo (XELOX Q3W or FOLFOX Q2W) or placebo + chemo. [27, 40]. In patients with CPS≥5, the median OS for patients treated with nivolumab + chemo was 14.4 months [13.1;16.2] and for patients treated with chemo alone 11.1 months [10.1;12.1] (HR 0.70 [0.61;0.81] [29]. This is in line with previous OS data reported for nivolumab in patients with CPS≥5 (Figure 11; Table 22)

Table 22. Overall survival (OS) in patients with CPS≥5 (interim analyses, final analysis and 4 year) (CheckMate-649) (subgroup: patients with CPS≥5) [1, 29]

	Nivolumab + chemo (n=473)	Placebo + chemo (n=482)
Overall survival (OS)		
Number of events	309 (65.3%)	362 (75.1%)
Median OS (95% CI)	14.39 (95% CI: 13.11; 16.23)	11.10 (95% CI: 10.02; 12.09)
Interim analysis HR for OS (95% CI), P value	0.71 (98,4% CI: 0.56; 0.81), <0.0001	
Final analysis of OS HR for OS (95% CI), P value	0.70 (0.61; 0.81), <0.0001	
4 year analysis, HR for OS (95% CI), P value	0.70 (0.61; 0.81), <0.0001	
Progression free survival (PFS)		
Number of events	328 (69,3%)	350 (72,6%)
Median PFS (95% CI)	7.69 (7.03; 9.17)	6.05 (5.55; 6.90)
Final PFS analysis HR for PFS (95% CI), P value	0.68 (98% CI: 0.56; 0.81), < 0.0001	
4 year analysis HR for PFS (95% CI), P value	0.71 (0.61; 0.82), < 0.0001	

Recently, 4 year data for the CheckMate 649 study was published. In patients with CPS≥5, the median PFS for patients treated with nivolumab + chemo was 8.3 months [7.0;9.3] and for patients treated with chemo alone 6.1 months [5.6;6.9] (HR 0.71 [0.61;0.82]. In all randomized patients the median PFS for patients treated with nivolumab + chemo was 7.7 months [7.1;8.6] and for patients treated with chemo alone 6.9 months (6.7-7.2) (HR 0.80 [0.71;0.89] (4 years follow up [29]).

Below Kaplan Meier curves for OS and PFS is provided. These are provided for earlier data cuts than the most recent 4 year analysis since Kaplan Meier curves for the 4 year analysis is not available to Astellas.

Figure 11. Kaplan Meier curve: OS in patients with CPS ≥5 (CheckMate 649) (data cut of May 2022) (subgroup: patients with CPS≥5) [42]

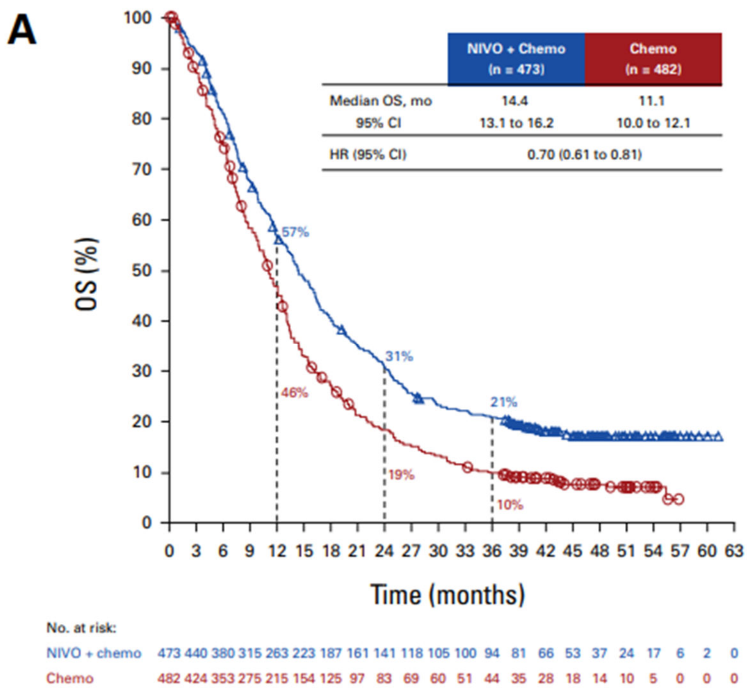
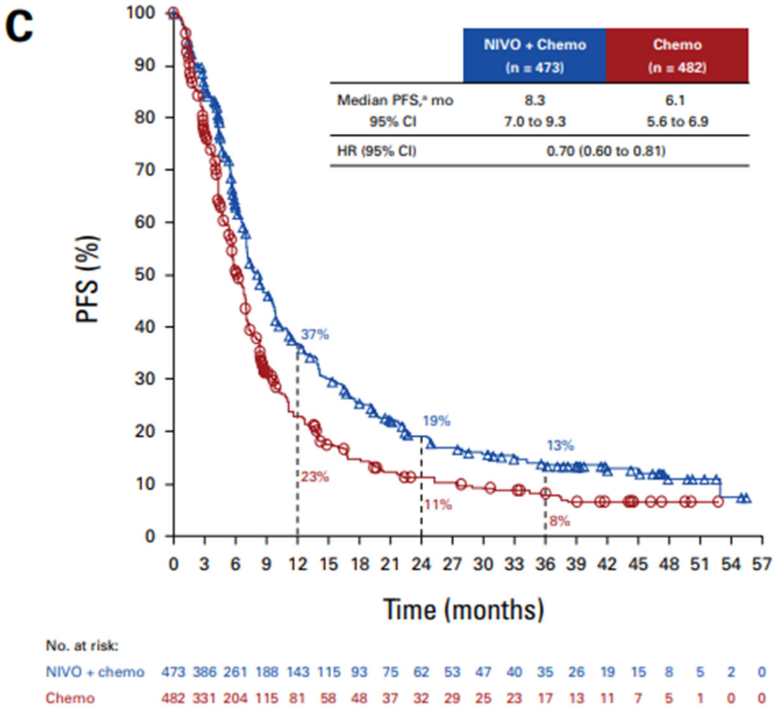


Figure 12. Kaplan Meier curve: PFS in patients with CPS≥5 (CheckMate 649) (final PFS analysis)) (subgroup: patients with CPS≥5) [42]



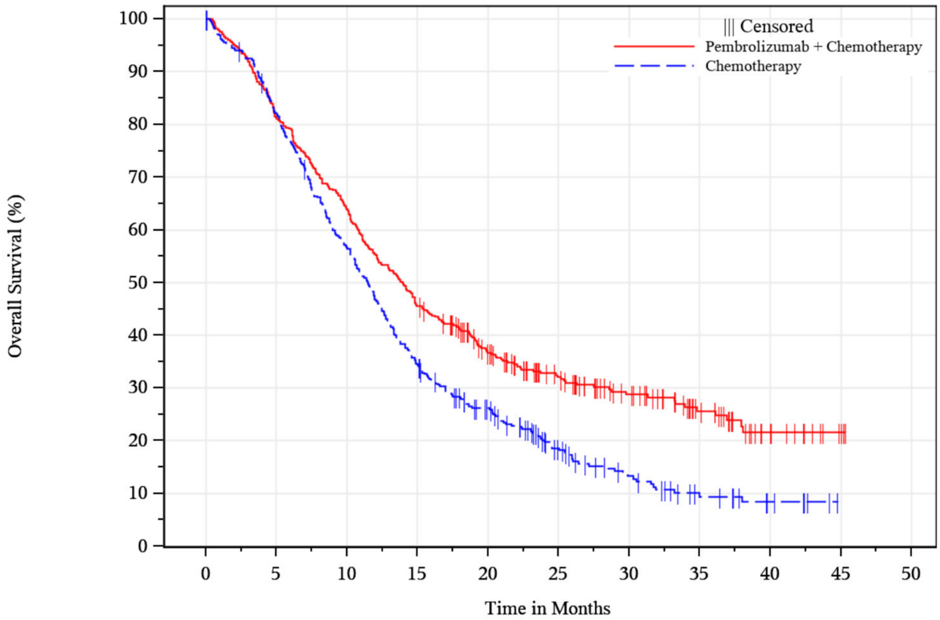
10.1.5 Efficacy – results per KEYNOTE-859

KEYNOTE-859 is a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. Included patients were previously untreated locally advanced or metastatic HER2-negative G/GEJ. Patients were randomly assigned (1:1) to receive pembrolizumab plus chemotherapy (pembrolizumab group; n=790) or placebo plus chemotherapy (placebo group; n=789); chemotherapy in both arms consisted of FP (Q3W) or CAPOX (Q3W); pembrolizumab dosing was 200mg Q3W. Backbone chemotherapy was chosen by investigators prior to randomization [31]

At the data cut October 3 2022 (median follow up 13 months (0.2-45.9 months), median overall survival was longer in the pembrolizumab + chemo group than in the placebo + chemo group in patients with a PD-(L)1 CPS of 5 or higher (14.0 months [12.1;15.4] vs 11.5 months [10.3;12.5]; HR 0.70 [0.60;0.82]; p<0·0001).[2, 21]

Among patients with a CPS≥5, median PFS was 7.1 months [95% CI: 6.1;8.3] in the pembrolizumab group compared with 5.6 months [5.4;5.9] in the placebo group (HR 0.69 [95% CI:0.58;0.81]; p<0.0001). [21]

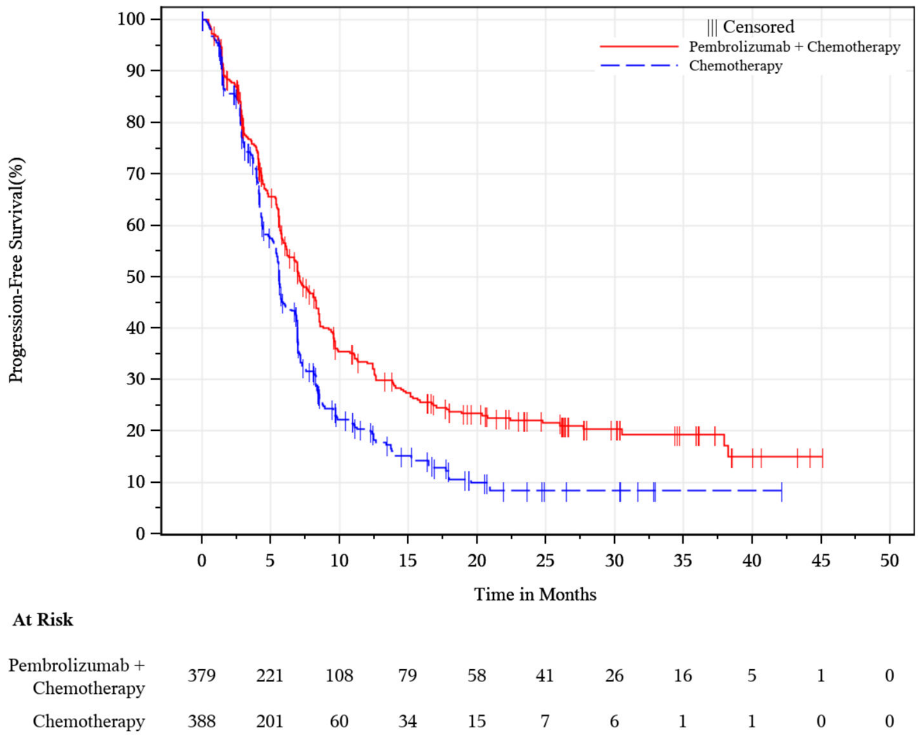
Figure 13. Kaplan Meier curve of OS in patients with CPS≥5 (KEYNOTE-859) (interim analysis, data cut Oct 3 2022) (subgroup: patients with CPS≥5) [2]



At Risk

Pembrolizumab + Chemotherapy	379	308	242	173	122	86	59	34	13	3	0
Chemotherapy	388	315	216	132	88	47	27	13	6	0	0

Figure 14. Kaplan Meier curve of PFS in patients with CPS≥5 (KEYNOTE-859) (interim analysis, data cut Oct 3 2022) (subgroup: patients with CPS≥5) [2]



11. Comparative analyses of efficacy

The comparison of zolbetuximab to chemotherapy is based on the pivotal trials for zolbetuximab (integrated data) where zolbetuximab given in addition to chemotherapy is compared to chemotherapy. For the subgroup of patients with a CPS≥5, where current standard of care is a PD-(L)1 inhibitor given in addition to chemotherapy, there are no head-to-head clinical trials. Therefore, an indirect comparison of clinical effect was performed using Bucher analysis where zolbetuximab given in addition to chemotherapy is compared to nivolumab given in addition to chemotherapy and pembrolizumab given in addition to chemotherapy, respectively (see Appendix C for details).

No quantitative comparison of health-related quality of life was attempted. A narrative comparison of EQ-5D VAS results is available in section 11.1.5.

11.1.1 Differences in definitions of outcomes between studies

OS and PFS were defined in a comparable manner in the SPOTLIGHT, GLOW, CheckMate-649 and KEYNOTE-859 studies.

11.1.2 Method of synthesis

The SLR (described in Appendix H) identified a total of 4 clinical trials. [24] All studies compared two treatment regimens: one of zolbetuximab, nivolumab or pembrolizumab in addition to chemotherapy, compared to chemotherapy alone (placebo given in addition to chemotherapy).

Under the assumptions that the new regimens' relative efficacy is similar irrespective of the chemotherapy backbone and irrespective of the chemotherapy comparator, the relative efficacy can be established using chemotherapy as a common comparator arm.

Randomization in both KEYNOTE-859 and CheckMate-649 was stratified for PD-(L)1 expression. In KEYNOTE-859 the primary endpoint was assessed in the intention-to-treat (ITT) population, and the populations with CPS≥ 1, and CPS ≥10. In CheckMate 649 the predefined primary analysis was in patients with CPS≥ 5. Since the recommended use of pembrolizumab in Denmark is restricted to a subgroup of the approved indications, data from the CPS≥5 was used for both pembrolizumab and nivolumab.

For zolbetuximab, data from the ITT population was considered since the relative effect of zolbetuximab given in addition to chemo compared to chemo alone was comparable for the ITT population and for patients with a CPS<5 (see section 6.1.4).

Outcomes considered were OS and PFS. OS and PFS was measured in all trials. In the indirect treatment comparison, hazard ratios were used a measure of treatment effects from the individual trials.

Clinical efficacy (OS and PFS) was compared using separate *Bucher analysis* (zolbetuximab compared to pembrolizumab and zolbetuximab compared to nivolumab, respectively). DMC have previously concluded that the two PD-(L)1 antibodies are clinically equivalent for patients with CPS ≥ 5. [2], however, the indirect comparisons were performed without any a'priori assumptions on relative effects between the PD-(L)1 comparators.

The following key assumptions were made (these are discussed in detail in appendix C):

- Backbone chemo therapies are comparable across the included pivotal trials
- Efficacy of the backbone, platinum-based chemotherapy appears independent of both PD-(L)1 status and CDLN18.2 status in HER2- locally advanced or metastatic G/GEJ cancer [32]
- Efficacy of PD-(L)1 inhibitors depend on tumour PD-(L)1 expression as measured by CPS.[34, 35] but not of CDLN18.2 status [32]
- On the other hand, efficacy of zolbetuximab is independent of PD-(L)1 status (see section 6.1.4).

It was hence concluded that the chemo-therapy backbone was sufficiently similar to allow indirect comparison via chemotherapy as the common comparator and, furthermore, that relative efficacy estimates from the two zolbetuximab trials (comparing to mFOLFOX6 and CAPOX, respectively) could be sourced from the integrated analysis (pooled dataset).

Furthermore, comparison of relative treatment effect from the trials was performed despite the selection of patients was based on different biomarkers in the two zolbetuximab studies and the PD-(L)1 inhibitor studies due to the lack of head-to-head studies in the population with CDLN18.2 positivity and PD-(L)1 expression.

11.1.3 Results from the comparative analysis

Table 23 presents the relative treatment effects applied in the Bucher analyses.

Table 23. Summary of relative effects by outcomes used for clinical studies considered for indirect treatment comparison

	Zolbetuximab + chemo vs chemo		Pembrolizumab + chemo vs chemo	Nivolumab + chemo vs chemo
	SPOTLIGHT	GLOW	KEYNOTE-859	CheckMate 649
Overall survival (HR [95% CI])				
By study	0.78 [0.64; 0.95][a]	0.76 [0.62; 0.94][a]	HR [95%CI by CPS group)	HR [95%CI by CPS group)
Pooled	0.77 [0.67; 0.89][a]		≥1: 0.74 [0.65; 0.84][b] ≥5: 0.70 (0.60; 0.82)[c] 5-10: 0.94 (0.71; 1.25)[c] ≥ 10: 0.65 [0.53; 0.79][c]	≥5: 0.70 [0.61; 0.81][d] 5-10: 0.92 [0.66; 1.28][d] ≥ 10: 0.66 [0.57; 0.77]
Progression free survival (HR [95% CI])				
By study	0.73 [0.59, 0.91][a]	0.69 [0.55, 0.86][a]	HR [95%CI by CPS group)	HR [95%CI by CPS group)
Pooled	0.71 [0.61; 0.83][a]		≥1: 0.72 [0.63; 0.82][b] ≥5: 0.69 (0.58; 0.81)[c] 5-10: 0.93 (0.69; 1.25)[c] ≥ 10: 0.62 [0.51; 0.76][c]	≥5: 0.71 [0.61; 0.82][d] 5-10: Not reported ≥ 10: Not reported

Key: CLDN18.2, claudin 18.2; CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-(L)1, programmed death-ligand 1.
Notes: HR reported with 95% CI for each intervention (in combination) vs chemotherapy alone. HR < 1 indicates lower event rate for each treatment versus chemotherapy.
a) All analyses used the ITT population of the final SPOTLIGHT datacut (dated 8 September 2023), final GLOW datacut (dated 12 January 2024). Shitara et al. (2024)[26]
b) KEYNOTE-859 efficacy inputs were based on data cutoff date of October 3, 2022, reported in Rha 2023
c) Medicinrådet (2024)[2]
d) CheckMate 649 efficacy inputs were based on data with minimum follow-up time of 4 years, reported in Shitara 2024.[29]

11.1.4 Efficacy – results per OS and PFS

Below the results from the base case analyses of indirect treatment effect comparing zolbetuximab + chemotherapy to pembrolizumab + chemotherapy and zolbetuximab + chemotherapy to nivolumab + chemotherapy.

The analyses show that there are no statistically significant differences in OS or PFS of zolbetuximab and PD-(L)1 inhibitors (95% confidence intervals cross 1). Compared to pembrolizumab (patients with CPS≥5), HR for OS was XXXXXXXXXXXXX and for PFS [redacted]. Compared to nivolumab (patients with CPS≥5), HRs were [redacted] and [redacted] for OS and PFS, respectively.

Table 24. Results of Bucher indirect comparison (HR with 95%CI)

	Zolbetuximab + chemo compared to pembrolizumab + chemo[a]	Zolbetuximab + chemo compared to nivolumab + chemo[b]
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: CI confidence interval; HR hazard ratio; OS Overall survival; PFS progression free survival

a) Analysis based on patients in KEYNOTE-859 with CPS≥ 5
b) Analysis based on patients in CheckMate-649 with CPS ≥ 5

Table 25 provides the estimated implied absolute difference in effect. The estimation was based on assumed comparator median estimated as the mid-point observed in the active arms in CheckMate-649 and KEYNOTE-859 and assumed 12-month survival estimated from the active arm of the CheckMate-649 study. The absolute differences are small and the confidence intervals support that they are not statistically significant.

Table 25 Implied absolute differences from the indirect comparison

	Zolbetuximab + chemo compared to pembrolizumab + chemo[a]	Zolbetuximab + chemo compared to nivolumab + chemo[b]
OS		
Difference median OS (months)[a]	[redacted]	[redacted]
Difference in 12-month survival (%-points)[b]	[redacted]	[redacted]
PFS		
Difference median OS (months)[c]	[redacted]	[redacted]
Difference in 12-month event-free survival (%-points)[d]	[redacted]	[redacted]

Abbreviations: CI confidence interval; HR hazard ratio; OS Overall survival; PFS progression free survival

a) Assumed median OS based on mid-point OS from active arms in CheckMate-649 and KEYNOTE-859
b) Assumed 12-month OS rate based on nivolumab arm CheckMate-649
c) Assumed median PFS based on mid-point OS from active arms in CheckMate-649 and KEYNOTE-859
d) Assumed 12-month PFS rate based on nivolumab arm CheckMate-649

Below the results from sensitivity analyses with respect to CPS subgroups for the PD-(L)1 inhibitors are presented. The analyses show that numerically the HRs of zolbetuximab are lower when compared to PD-(L)1 inhibitors in populations with less PD-(L)1 expression, and higher in populations with higher PD-(L)1 expression. All confidence intervals cross 1 suggesting that the estimated differences in treatment effect are not statistically significant.

Table 26. Sensitivity analysis. Results of Bucher indirect comparison by CPS score

	Zolbetuximab + chemo compared to pembrolizumab + chemo[a]	Zolbetuximab + chemo compared to nivolumab + chemo[a]
Overall survival (HR [95% CI])		
Base case	[redacted]	[redacted]
5 ≤ CPS <10	[redacted]	[redacted]
≥ 10	[redacted]	[redacted]
Progression free survival (HR [95% CI])		
Base case	[redacted]	[redacted]
5≤ CPS <10	[redacted]	[redacted]
≥ 10	[redacted]	[redacted]

11.1.5 Health related quality of life

With respect to HRQoL, EQ-5D VAS data have been collected in both SPOTLIGHT, GLOW, CheckMate 649 and KEYNOTE 859. While EQ-5D VAS data for nivolumab for the relevant subgroup of patients with CPS≥5 is published by Moehler and colleagues (2023) [30] and presented in the recent assessment of pembrolizumab by DMC, EQ-5D VAS data for the relevant subgroup of patients with CPS≥5 is not publicly available for pembrolizumab. [2] However, data for CPS≥1 is available. [2]

Based on the assessment by DMC of pembrolizumab, where HRQoL is compared for nivolumab and pembrolizumab based on EQ-5D VAS, it is concluded by DMC that there is no statistically significant change in QoL over time when compared to baseline (change from baseline) and there is no difference between treatment arms. [2] This is aligned with the EQ-5D VAS data on change from baseline from zolbetuximab (see section 14.1.3).

A summary of the change from baseline in EQ-5D VAS (CFB) is presented below for KEYNOTE 859, SPOTLIGHT and GLOW. Data for CheckMate 649 is not available as CFB. However, the most recent assessment of pembrolizumab in Denmark conclude that treatment with both pembrolizumab and nivolumab did not lead to statistically significant changes in EQ-5D VAS from baseline or between treatment arms. [2] This aligns with the findings for zolbetuximab.

Table 27. Change from baseline in EQ-5D VAS (KEYNOTE 859; SPOTLIGHT and GLOW)

KEYNOTE 859 (CPS≥1)			
	Pem + chemo	**PBO + Chemo**	**Pem + chemo vs PBO + chemo**
Change from baseline (w18) [2] LS mean (95% CI)	-0.91 (-2.50;0.68)	-1.21 (-2.79;0.30)	0.30 (-1.78;2.30)
SPOTLIGHT (ITT)			

	Zolbe + chemo	PBO + Chemo	Zolbe + chemo vs PBO + chemo
Change from baseline (w48) LS mean (SE)	[redacted]	[redacted]	[redacted] [redacted]
GLOW (ITT)			
	Zolbe + chemo	**PBO + Chemo**	**Zolbe + chemo vs PBO + chemo**
Change from baseline (w48) LS mean (SE)	[redacted]	[redacted]	[redacted] [redacted]

12. Modelling of efficacy in the health economic analysis

Not applicable: For the subgroup population of patient with CDLN18.2 positivity and PD-(L)1 (CPS≥5) expression, a cost-minimisation analysis was established to compare per patient cost of treatment with zolbetuximab compared to nivolumab and pembrolizumab, respectively. The comparisons are based on the assumption of equal efficacy, safety, and treatment duration. Hence, extrapolation of clinical data was not performed.

13. Safety vs PD-(L)1 inhibitors

13.1 Safety data from the clinical documentation

An overview of the safety profile for PD-(L)1 inhibitors (nivolumab and pembrolizumab) is provided below based on the regulatory documents.

Safety data for nivolumab in G/GEJC is sources from the EMA assessment report (variation report) and is based on the CheckMate-649 study [28]. Safety results are provided for all patients that were randomised and treated in the nivolumab given in addition to chemo and chemo arms in CheckMate-649 (N=1549). Data cut-off date June 2020. Safety data for pembrolizumab in G/GEJC is source from EMA assessment report (variation report) and is based on the KEYNOTE-859 study. Safety analyses were based on all randomised participants who received at least 1 dose of study intervention [32]. Data cut-off date of 03-OCT-2022, with approximately 12 months of follow-up after last participant was randomised.

Table 28 Overview of safety events (nivolumab) (June 2020) (CheckMate-649)[28]

	Nivolumab+ chemotherapy (N=782)	chemotherapy (N=767)	Difference, % (95 % CI)
Number of adverse events, n	NA	NA	NA
Number and proportion of patients with ≥1 adverse events, n (%)	776 (99.2%)	752 (98.0%)	1.2 (0; 2.3)
Number of serious adverse events*, n	NA	NA	NA
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	423 (54.1%)	335 (43.7%)	10.4 (5.5; 15.4)
Number of CTCAE grade ≥ 3 events, n	NA	NA	NA
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	540 (69.1%)	456 (59.5%)	9.6 (4.9; 14.4)
Number of adverse reactions, n	NA	NA	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	738 (94.4%)	679 (88.5%	5.8 (3.1; 8.6)
Number and proportion of patients who had a dose reduction, n (%)	NA	NA	0 (0; 0)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	698 (89.3%)	728 (94.9%)	-3.5 (-6.4; -0.5)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	284 (36.3%)	181 (23.6%)	12.7 (8.2; 17.2)

§ CTCAE v. 5.0 must be used if available.

Table 29 Overview of safety events (pembrolizumab) (03OCT2022) (KEYNOTE-859 study)[2, 32]

	Pembro + chemo (N=785)	Placebo+ chemo (N=787)	Difference, % (95 % CI)
Number of adverse events, n	NA	NA	NA
Number and proportion of patients with ≥1 adverse events, n (%)	776 (98.9%)	771 (98.0%)	0.9 (-0.3; 2.1)
Number of serious adverse events*, n	NA	NA	NA
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	355 (45.2%)	316 (40.2%)	5.1 (0.2; 10)
Number of CTCAE grade ≥ 3 events, n	NA	NA	NA

	Pembro + chemo (N=785)	Placebo+ chemo (N=787)	Difference, % (95 % CI)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	591 (75.3%)	548 (69.6%)	5.7 (1.2; 10.1)
Number of adverse reactions, n	NA	NA	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	751 (95.7%)	736 (93.5%)	2.1 (-0.1; 4.4)
Number and proportion of patients who had a dose reduction, n (%)	679 (86.5%)	660 (83.9%)	2.6 (-0.9; 6.1)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	529 (86.0%)	586 (95.1%)	-5.6 (-8.6; -2.5)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	257 (32.7%)	204 (25.9%)	NA

§ CTCAE v. 5.0 must be used if available.

Serious adverse events reported in ≥5% of subjects is not reported for pembrolizumab or nivolumab in the EPAR assessment reports. In appendix E, a presentation of serious adverse events with an incidence ≥ 1% is reported for pembrolizumab and adverse events with an incidence ≥ 2% is reported for nivolumab based on the regulatory documents.

Comparison of safety profile for zolbetuximab and PD-(L)1 inhibitors

A comparison of the safety profile for zolbetuximab vs PD-(L)1 inhibitors is based on the estimated difference vs chemotherapy from Table 16, Table 28 and Table 29 (see summary table below).

Table 30. Difference (%, 95% CI) for zolbetuximab, nivolumab and pembrolizumab vs chemotherapy

	Integrated SPOTLIGHT/GLOW (zolbe vs chemo)	CheckMate-649 (nivo vs chemo)	KEYNOTE-849 (pembro vs chemo)
	Difference, % (95 % CI)	Difference, % (95 % CI)	Difference, % (95 % CI)
Number and proportion of patients with ≥1 adverse events, n (%)	0.4 (-0.8; 1.6)	1.2 (0; 2.3)	0.9 (-0.3; 2.1)
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	-0.5 (-6.5; 5.5)	10.4 (5.5; 15.4)	5.1 (0.2; 10)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	6.1 (1.1; 11.2)	9.6 (4.9; 14.4)	5.7 (1.2; 10.1)

Number and proportion of patients with ≥ 1 adverse reactions, n (%)	2.9 (0.7; 5)	5.8 (3.1; 8.6)	2.1 (-0.1; 4.4)
Number and proportion of patients who had a dose reduction, n (%)	22.8 (17.3; 28.4)	NA	2.6 (-0.9; 6.1)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	-3 (-5.6; -0.4)	-3.5 (-6.4; -0.5)	-5.6 (-8.6; -2.5)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	5.3 (-0.5; 11)	12.7 (8.2; 17.2)	6.8 (2.3; 11.3)

95% confidence interval for difference (%-points) to chemotherapy arm calculated from published incidences for each product

As can be seen from Table 30, the difference in the proportion with adverse events is comparable for the zolbetuximab, nivolumab and pembrolizumab when compared to chemotherapy. The only differences between treatments are observed for serious adverse events (SAE) and the number of patients needing dose reduction. The difference in the proportion of patients with ≥1 SAE is higher for nivolumab vs chemo than for zolbetuximab vs chemo (difference: 10.4% vs -0.5% (zolbetuximab vs chemo)) and 5.1% (pembrolizumab vs chemo). With respect to the proportion of patients requiring dose reduction, the frequency is higher vs chemotherapy for patients treated with zolbetuximab than that seen for pembrolizumab. It should be noted that dose reductions of pembrolizumab and placebo were not permitted in the KEYNOTE 859 clinical trial [31].

A comparison of the safety profile per organ class is not possible since this data is not available for pembrolizumab. When comparing the incidence of serious adverse events per organ class for nivolumab and zolbetuximab, the incidence of serious “gastrointestinal disorders” adverse events is fairly comparable (CheckMate 649: nivo 17%, chemo 16.2%; Integrated SPOTLIGTH/GLOW: zolbe 20.5%, chemo 17.5%) whereas the incidence of serious “Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps”) is higher for nivolumab than for zolbetuximab CheckMate 649: nivo 15.7%, chemo 13%; Integrated SPOTLIGTH/GLOW: zolbe 4.5%, chemo 6.5%). The incidence of serious “Infections and Infestations” is 10.1% for patients treated with zolbetuximab vs 8.3% for patients treated with chemo and 9.2% for patients treated with nivolumab vs 4.3% for patients treated with chemo (see 0 for details).

Based on the above, it is assumed that the tolerability profile of zolbetuximab is fairly comparable to that of PD-(L)1 inhibitors and safety is hence not included in the cost minimization analysis.

13.2 Safety data from external literature applied in the health economic model

Not applicable

14. Documentation of health-related quality of life (HRQoL)

Table 31 summaries all measuring quality of life instruments included

Table 31 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	Integrated SPOTLIGHT/GLOW	EQ-5D-5L data was collected to inform health state utilities in the cost-effectiveness model vs chemotherapy
GHS/QoL	Integrated SPOTLIGHT/GLOW	Time to Confirmed Deterioration
PF	Integrated SPOTLIGHT/GLOW	Time to Confirmed Deterioration
OG25-pain	Integrated SPOTLIGHT/GLOW	Time to Confirmed Deterioration

14.1 Presentation of the health-related quality of life

14.1.1 Study design and measuring instrument

The health-related quality of life (HRQoL) of zolbetuximab was assessed in SPOTLIGHT and GLOW using the following instruments:

- EQ-5D-5L
- Time to Confirmed Deterioration (TTCD) for GHS/QoL, physical functioning and OG25-Pain

TTCD was defined as the time from randomisation to first clinically meaningful deterioration that is confirmed at the next scheduled visit using physical functioning, OG25-Pain, and GHS/QoL scores as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) and the Quality of Life Oesophago-Gastric (QLQ-OG25).

In summary all HRQoL instruments document that patients receiving zolbetuximab given in addition to chemotherapy experience comparable QoL as patients receiving chemotherapy alone. Recently, Lordick and colleagues published detailed HRQoL results from the SPOTLIGHT and GLOW studies. The authors concluded that compliance rates were similar between treatment arms. Similar trends were observed in the zolbetuximab versus placebo arms for LSM changes from baseline in key PRO domains, with no clinically meaningful deterioration. Nausea/vomiting worsened during the first few zolbetuximab cycles but later returned to baseline levels. Overall TTCD and time to first definitive deterioration (TTDD) results were similar between arms in both studies. [3] Detailed HRQoL results are published by Lordick and colleagues (2024). [3]

In this section only the results for EQ-5D-5L will be presented since this is the data DMC prefer for the assessment and this is in line with previous assessments of products for

G/GEJC. [1, 2] For EQ-5D-5L, both the utility index and the visual analogue scale (VAS) was used to collect HRQoL.

14.1.2 Data collection

All PRO measures were administered on Day 1 and 22 of each treatment cycle, at the study treatment discontinuation visit, and at 30-day and 90-day safety follow-up visits following their last dose of zolbetuximab/placebo.

EQ-5D VAS was analysed separately for GLOW and SPOTLIGHT at the primary data-cuts. Due to the repeated measurements of EQ-5D over a long time period in SPOTLIGHT and GLOW, data is in the following presented as illustration (Figure 15) and for selected time points (Table 32, Table 33, Table 34, and Table 35). Additional data is available in appendix F.

In Figure 15, missing data and completion rates are illustrated for GLOW and SPOTLIGHT. For both GLOW and SPOTLIGHT, the completion rates match the expected numbers at each timepoint. For SPOTLIGHT, the illustration reflects that while EQ-5D was measured every 3 weeks, patient responses were only provided at the hospital every 6 weeks since the administration of zolbetuximab and chemotherapy did not fully match the timepoints for EQ-5D measurements. Data collected at the remaining time points were collected via e-diary. Thus, this was reflected in the response rates.

Figure 15. Pattern of missing data and completion (EQ-5D VAS at primary data-cut) by study: GLOW (left panel) and SPOTLIGHT (right panel)

[redacted]

Table is available in Appendix F Table 86 (SPOTLIGHT) and Table 87 (GLOW)

EQ-5D Utility index was analysed based on the integrated data set from GLOW and SPOTLIGHT based on the final OS data-cuts.

Pattern of completion is illustrated below per visit (Figure 16 left panel) and by visit and health state in Figure 16 right panel (used in the model). Overall response rates were acceptable except for patients who had experienced progression where – towards the end of the study – completion rates were low. This pattern is seen in other GEJ/G cancer studies.

Figure 16. Pattern of missing data and completion (EQ-5D Index (DK) at final OS data-cut: per visit (left panel) and per health state and visit (right panel)

[redacted]

Table is available in Appendix F Table 91

14.1.3 HRQoL results

Baseline EQ-5D questionnaire index score and EQ-VAS (visual analogue scale) scores were comparable between treatment arms. No significant differences were observed for either treatment arm for the EQ-5D questionnaire index score and EQ-VAS during the treatment and follow-up periods.

The EQ-5D VAS data from GLOW and SPOTLIGHT have not been integrated, but identical statistical analyses have been conducted. The primary analysis of change from baseline consisted of a mixed model of repeated measures (MMRM) with the primary objective of comparing change from baseline to cycle 9 day 1 in SPOTLIGHT (after 48 weeks of treatment) and cycle 17 day 1 (48 weeks). Patients were included in the analyses if they had a measurement at baseline and at least 1 follow-up. Follow-up measures were included as observed without any measurements carried forward. No imputation of missing data was attempted. The MMRM model included Treatment am, Time point as categorical variable, baseline VAS score, Region (China vs rest of world), Number of metastatic sites (0-2 vs 3 or more) and prior gastrectomy (yes vs no) as fixed effects and baseline VAS score × time and treatment arm × time as interaction terms. In addition, overall change from baseline across visits were estimated. The analysis only considered on-treatment assessments.

In SPOTLIGHT the compliance rate was ≥71.0% [range 71.0%- 100%] (GLOW ≥ 85.3% [range 85.3%-100%]) for any treatment visits where there were more than 50 participants remaining on the study. The compliance rates were similar between the treatment arms during the treatment and follow-up periods of the study.

In SPOTLIGHT, EQ-5D VAS improved in both arms, but no significant differences were observed between the treatment arms. EQ VAS at Cycle 9 Day 1 (LS mean [SE] was XXXXXXXXXX in the zolbetuximab arm and [redacted] in the placebo arm; difference zolbetuximab vs placebo [redacted]. Similar results were observed in GLOW. Difference in LS mean change from baseline over 17 cycles for zolbetuximab compared to placebo was -[redacted]. LS mean changes from baseline at each cycle is shown in Figure 17.

Figure 17 Longitudinal analysis of change from baseline in EQ VAS – MMRM analysis (Upper panel SPOTLIGHT, Lower panel GLOW)

[redacted]

Abbreviations: CI: Confidence interval; EQ-5D-5L: EuroQoL 5-level EQ-5D; LS: Least-squares; MMRM: Mixed model repeated measures; VAS: Visual analog scale.

Data was from primary data-cut (SPOTLIGHT 9 Sept 2022; GLOW 7 Oct 2022) Only patients with a baseline and at least one post-baseline score are included in the analysis. The analysis includes only the on-treatment assessments.

EQ-5D summary statistics for SPOTLIGHT and GLOW are presented for selected time points (every 8th cycle until last visit) due to the extensive number of measurements. In appendix F measurements for all timepoints are presented.

Table 32 HRQoL EQ-5D VAS summary statistics (SPOTLIGHT, FAS primary-data-cut)

	Zolbetuximab + mFOLFOX6 N = 283		Placebo + mFOLFOX6 N = 282		Zolbetuximab vs Placebo
Analysis Visit	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 days safety follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90 days follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SPOTLIGHT FAS. Primary data-cut (09 Sep 2022)

Table 33 HRQoL EQ-5D VAS summary statistics (GLOW, FAS primary-data-cut)

	Zolbetuximab + CAPOX		Placebo + CAPOX		Zolbetuximab vs
	N = 254		N = 253		Placebo
Analysis Visit	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 24 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 days safety follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90 days follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

GLOW (FAS) Primary data-cut (07October2022)

Measurements for each time point is available in appendix F Table 88 (SPOTLIGHT) and Table 89 (GLOW)

In conclusion, HrQoL as measured by EQ-5D VAS was maintained for patients in SPOTLIGHT and GLOW while on treatment with zolbetuximab in combination with chemotherapy in comparison to patients on treatment with chemotherapy alone.

For the EQ-5D Index, a descriptive analysis of mean change from baseline was conducted for the integrated efficacy dataset (at final OS data-cuts) using Danish weight set. Data from the two studies were merged based on week of study (rather than cycles). Figure 18 presents the results for each study week where EQ-5D was collected (mean change from baseline with 95% CI and number of observations by arm and week). The analysis shows that in general patients on the zolbetuximab plus chemotherapy arm had positive change from baseline, but with confidence intervals crossing 0. In section 14.2, results are shown in an analysis taking into account the health state of patients at the time of responding to the EQ-5D instrument.

Figure 18 EQ-5D index (Danish utility weights). Mean change from baseline (95% CI). Descriptive analysis

[redacted]

Abbreviations: CFB Change from baseline; CI: Confidence interval; EQ-5D-5L: EuroQoL 5-level EQ-5D; PBO placebo + chemotherapy arm; Zol zolbetuximab + chemotherapy arm

Integrated data from final OS data-cut (SPOTLIGHT: 8 September 2023; GLOW 12 January 2024) Time series for each arm were truncated at first visits with fewer than 5 CFB observations.

Below summary statistics are presented for EQ-5D index. Data is presented for selected time points (every 24w until week 187) due to the extensive number of measurements. Details for all time points are available in in Table 93 in appendix F.

Table 34 HRQoL EQ-5D Index (DK) summary statistics (FAS Final OS data-cut)

Analysis	Zolbetuximab + chemotherapy		Placebo + chemotherapy		Zolbetuximab vs PBO
visit*	N	Mean (95%CI)	N	Mean (95%CI)	Mean (95%CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 121	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 145	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 169	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 187	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 D SFU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90 D FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations 30 D SFU 30-days safety follow-up; 90 D FU 90-days follow-up; CI confidence interval
* Week in table refers in day one of each cycle in GLOW and day one or day 22 of each cycle in SPOTLIGHT.
Mean only calculated for visits with 5 or more complete questionaires

14.2 Health state utility values (HSUVs) used in the health economic model

This section only applies to the cost-utility model (comparison to chemotherapy).

14.2.1 HSUV calculation

The EQ-5D-5L instrument used to measure patients' health related quality of life in the GLOW and SPOTLIGHT trials were used to estimate EQ-5D utility index values based on Danish weights. The utility index was estimated using the pooled data from GLOW and SPOTLIGHT for the health states considered in the model. Each EQ-5D elicitation was classified as a pre-progression measurement if was done before the patients' date of progression, death or PFS censoring and a post-progression measurement otherwise.

The analysis considered health state utilities to be independent of treatments and therefore data were pooled among all treatment arms. All completed EQ-5D-5L measures from the GLOW and SPOTLIGHT trials were included in the utility analysis. No attempts were made to adjust for missing observations or missing items. Instrument completions rates by week and study arm and by week and health state are available in appendix F (Table 92).

Data was summarized descriptively. Furthermore, two methods were used to account for repeated measurement (see appendix F). First a generalized equation estimation he (GEE) model was estimated using a robust variance estimator was used to account for correlation within patients' repeated assessments. Additionally, a mixed effects model was estimated including both random intercept and slopes. The patient effects were included as random effects to account for unobserved, patient characteristics and repeated measurement. In both analyses utilities from all included patients were used. The dependent variable was EQ-5D-5L utilities, and the independent variable was the health state at time of measurement (with pre-progression as the reference group). The estimates per health state were calculated as the averages of individual subject results.

Table 35. Utility index[c] per health state

	N. Patients (observations[a])	Descriptive statistics		GEE		Mixed effects model	
		Mean	SE	Mean	SE	Mean	SE
Pre-progression[b]	994 (11 249)	0.875	0.002	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression[b]	350 (1243)	0.820	0.007	[redacted]	[redacted]	[redacted]	[redacted]
Difference	-	0.054	-	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GEE Generalized estimation equation model; SE Standard error
a No imputation was performed for missing observations and thus a subject who did not have an evaluation on a scheduled visit would be excluded from the analysis for that visit
b Pre-progression health state is defined as the period for subjects treated with the study drug who have not experienced disease progression, or death due to any cause. Pre-progression utility was estimated among EQ-5D assessments occurred during the pre-progression health state.
Post-progression health state is defined as the period for subjects who have experienced disease progression and are still alive. Post-progression utility was estimated among EQ-5D assessments occurred during the pre-progression health state.
c Estimated using Danish EQ-5D weights

14.2.1.1 Mapping

Not applicable

14.2.2 Disutility calculation

Not applicable. Disutility associated with adverse events were sourced from literature.

14.2.3 HSUV results

Table 36 summaries the HSUV applied in the model (estimated from the pivotal trials as described in section 14.2.1) using the descriptive results as base case as this method is more conventionally used for health-state based utility valuation in GEJ/GC (see e.g. Medicinrådet (2022) [1]), and because its simpler methodology is more transparent and less sensitive to methodological choices. However, GEE and mixed effect model results are available in the model

Table 36 Overview of health state utility values

State	N/ n	Results [SE]	Instrument	Tariff (value set) used	Comments
PF	994/ 11249	0.875 [0.002]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms (integrated analysis of GLOW and SPOTLIGHT).
PD	350/ 1243	0.820 [0.007]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms (integrated analysis of GLOW and SPOTLIGHT).

Abbreviations. PD post progression; PF pre-progression; N Number of patients; n number of observations; SE standard error

14.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Treatment-related grade 3+ AEs with occurring in ≥5% in any arm of the GLOW, SPOTLIGHT trials were included in the model. Patients incurred a one-time QALY loss associated with AEs by taking the product of the disutility, the percent of trial participants that experienced each AE, and the AE duration. Disutility values for AEs were independent of treatment and applied to all treatment options. Disutility inputs were derived from a published NICE health technology assessments (TA857)[33], and the published literature (Shah et al., 2022; Lloyd et al., 2006)[34, 35]

14.3.1 Disutility results from the literature applied

Table 37 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Disutility associated with grade 3+ TEAE with incidence ≥ 5% in any arm				
Neutropenia	-0.090	NA	NA	Shah et al. (2022).[34]
Neutrophil count decreased	-0.050	NA	NA	Shah et al. (2022) [34].
Vomiting	-0.103	NA	NA	NICE TA857*
Nausea	-0.103	NA	NA	NICE TA857*
Anaemia	-0.120	NA	NA	Shah et al. (2022) [34].
Decreased appetite	0.000	NA	NA	Shah et al. (2022)
Hypokalaemia	-0.070	NA	NA	Shah et al. (2022) [34]
Asthenia	-0.115	NA	NA	Lloyd et al (2006)[35] (fatigue)
Diarrhoea	-0.050	NA	NA	Shah et al. (2022) [34].
Duration of utility decrement associated with grade 3+ TEAE with incidence ≥ 5% in any arm				

Applied in Zolbetuximab + chemo and chemo arms				
Neutropenia	1,9 weeks	NA	NA	Shah et al. (2022).[34]
Neutrophil count decreased	2.4 weeks	NA	NA	Shah et al. (2022) [34].
Vomiting	1 week	NA	NA	NICE TA857*
Nausea	1 week	NA	NA	NICE TA857*
Anaemia	2.1 weeks	NA	NA	Shah et al. (2022) [34].
Decreased appetite	0	NA	NA	Shah et al. (2022)
Hypokalaemia	0.5 weeks	NA	NA	Shah et al. (2022) [34]
Asthenia	1 week	NA	NA	Lloyd et al (2006)[35] (fatigue)
Diarrhoea	1 week	NA	NA	Shah et al. (2022) [34].

* Company submission Table 38. Appraisal committee 1 papers pg 126, [33]

15. Resource use and associated costs

15.1 Medicines - intervention and comparator

Table 38 provides an overview of medicines applied in the health economic evaluation.

In the CUA analysis, CAPOX was chosen as the backbone chemotherapy in the calculation of costs. With a three-week cycle length for CAPOX, the model considered Q3W dosing cycle for zolbetuximab as well (800mg/m^2 followed by 800mg/m^2 Q3W). Nine series of oxaliplatin was assumed. [1]

The prices for oxaplatin and capecitabin were chosen from the strength and package with the lowest PPP per mg (medicinpriser.dk, price period 20240930). Drug wastage was only included for zolbetuximab. This means that the calculated target dose was rounded to the nearest 100mg vial before calculating the zolbetuximab cost. For chemotherapy, target dose was estimated from mean BSA, while for zolbetuximab the mean (integer) number of vials needed was based on the distribution of BSA observed in SPOTLIGHT. SPOTLIGHT was chosen as this study had the largest group of Caucasians. Note that for the vial calculation, the BSA distribution was stratified for race (white/ non-white). The proportion of inhabitants in Denmark with Asian heritage was used to reweight the estimated mean number of vials from the two strata [36]. For chemotherapy, the target dose was reduced by RDI%, while for zolbetuximab only the number of skipped infusions was considered. Cost of treatment was calculated based on patients on treatment at the start of each chemo-cycle.

Treatment duration was estimated from the GLOW and SPOTLIGHT separately (see summary in section 8.1.1.3 and further details in appendix D) as the pooled dataset did not include time to treatment discontinuation data. The extrapolated curves were then weighted based on the assumed proportion of patients with CAPOX as backbone chemotherapy and with FOLFOX as backbone chemotherapy.

In the CMA analysis, only costs of intervention and comparator were included. Pembrolizumab was chosen among the two available PD-(L)1 inhibitors. In the CMA drug wastage was included for both intervention and comparator by rounding the target dose up to nearest integer number of vials. A fixed duration of treatment of 8 months was assumed based on average treatment durations mentioned in the public assessments reports for each products where the mean (SD) treatment duration in months were reported as pembrolizumab + chemo 9.1 months (7.6); [32] nivolumab + XELOX 7.9 months (5.5); nivolumab + FOLFOX 8.5 months (6.5); [28] zolbetuximab + chemo 7.5 months (7.3). [18]

Table 38 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Zolbetuximab (iv)	800mg/m^2 +600 mg/m^2	99%*	Every 3 weeks	No
CAPOX (only included in the CUA model comparing zolbetuximab plus chemotherapy to chemotherapy alone)				
Oxaplatin (iv)	130mg/m^2	95%	Every 3 weeks for a total of 9 cycles	Yes
Capecitabin (po)	1000mg/m^2	83%	Once daily for 2 weeks per 3 week cycle	Yes
PD-(L)1 inhibitor (only included in the CMA model comparing zolbetuximab to PD-(L)1 inhibitors for combination with chemotherapy)				
Pembrolizumab	2 mg/kg	100%	Q3W	No
Nivolumab	4,5 mg/kg	100%	Q3W	No

* note that RDI for zolbetuximab in the CUA is estimated as infusions started. This means that the mean number of vials per infusion is only reduced by the number of skipped dosages observed in GLOW/SPOTLIGHT

15.2 Medicines– co-administration

The model considers anti-emetic prophylaxis as co-administered medication. Four levels of emetic risk were included: low, moderate low, moderate high and high. Chemotherapy alone or in combination with PD-(L)1 inhibitor was considered to be treated based on the moderate-low (level 2) regime. Combination of zolbetuximab to CAPOX/ or FOLFOX was assumed to require one additional step (from 2 to 3). This means that the additional cost antiemetic medicine for zolbetuximab plus chemotherapy compared to chemotherapy alone or compared to chemotherapy in combination with PD-(L)1 inhibitor consists of the cost of one package (125mg + 2×80 mg pack) of aprepitant.

Table 39 Co-administered anti-emetic medication

Regimen	Last added antiemetic in regimen				Total cost of regime
	Substance	Dose	Total dose	Cost	
1 5-HT3	Ondansetron p.o	20mg + 8 mg x 4	52	12.94	12.94
2 5-HT3+DEX	Dexamethason p.o.	12 mg + 8 mg x 4	44	46.75	59.69
3 5-HT3+DEX+NK1	Aprepitant	125 mg + 80 mg x 2	n.a	180.97	240.66
4 5-HT3+DEX+NK1+OLZ	Olanzapine	5 mg x 3	15	0.94	241.60

Dosing sourced from SMPC of the relevant medication. Oral adminstration was chosen for all medication, Ondansetron was selected as 5-HT3 receptor antagonist. Cost of medication estimated from Medicinpriser.dk at the lowest cost per mg in relevant strength (except for apripitant where the 3 day treatment package wiith lowest cost was chosen).

The costs associated with antiemetic were added to all patients in the CUA model (but with different assumptions on risk group). In the CMA, the cost of antiemetic treatment was only added in the zolbetuximab arm and only as the additional cost of aprepitant.

15.3 Administration costs

Administration costs were included in the CUA as one out-patient visit per treatment cycle irrespective of regimen. The DRG tariff (*06MA98 Planlagt besøg (DC169M) Kræft i mavesækken med metastaser*) was sourced from DRG 2024.In the CMA, the administration costs are set to zero as all three antibody therapies are administered during a chemo-therapy outpatient visit.

Table 40 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
I.V. infusion	Every 2 or every 3 weeks*	1561	06MA98	DRG 2024

* Zolbetuximab and PD-(L)1 inhibitor dosing frequency it determined by the dose frequency in the chemotherapy regimen. Zolbetuximab and nivolumab is administered Q2W with FOLFOX and pembrolizumab Q6W. All antibody treatments are administered Q3W with CAPOX.

15.4 Disease management costs

Table 41 presents the disease management cost by modelled health state in the CUA model. Resource utilization and unit costs were sourced from the DMC assessment of nivolumab in GEJ/GC. [1] Unit costs were updated to 2024 price levels.

Table 41 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
PF (pre-progression) health state				
CT-scan	Every 2 months	2,021	30PR07	DRG 2024

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Outpatients visit	Every month	1,561	06MA98	DRG 2024
Outpatient nurse visit	Every 2 weeks	245	NA	DMC unit cost catalogue. 30 min visit
Cost per patient year in state		**36,726**		**Calculated**
PD (post-progression) health state				
CT-scan	Twice yearly	2,021	30PR07	DRG 2024
Outpatients visit	Twice yearly	1,561	06MA98	DRG 2024
Cost per patient year in state		**7,164**		**Calculated**

15.5 Costs associated with management of adverse events

Table 42 provides an overview of the DRG tariffs applied to the included adverse events in the CUA model (Grade 3 or above; incidence in any arm 5% or above).

Costs are for patients with metastatic gastric cancer ((DC169M) *Kræft i mavesækken med metastaser*). Details of costing are presented below.

Table 42 Cost associated with management of adverse events

	DRG code	DRG tariff
Neutropenia	16MA98; (DD709) *Neutropeni UNS*	2,111
Neutrophil count decreased	16MA98; (DD709) *Neutropeni UNS*	2,111
Vomiting	06MA11; (DR119C) *Opkastning*	7,818
Nausea	06MA11; (DR119B) *Kvalme*	7,818
Anaemia	06MA98; (DD649) *Anæmi UNS*	2,111
Decreased appetite	10MA98 (DR630) *Appetitløshed*	1,847
Hypokalaemia	10MA98; (DE876) *Hypokaliæmi*	1,847
Asthenia	06MA98; (DF480) *Neurasteni*	1,561
Diarrhoea	06MA11; (DK529B) *Ikke-infektiøs diarré UNS*	7,818

15.6 Subsequent treatment costs

A simplified approach was chosen for the subsequent lines of treatment in the CUA model, because the choice of first-line treatment is not assumed to influence subsequent lines. As a consequence, patients – irrespective of model arm - experiencing progression will have a one-off event cost estimated based 10 weeks (2.3 months) of treatment with docetaxel 75 mg/m^2 Q3W. In the integrated analysis of GLOW and SPOTLIGHT (FAS population; final OS data-cut) [redacted]% of patients in the intervention arms and [redacted]% of patients in the control arms received subsequent anti-cancer treatment. The same proportions of patients in the model were assumed to receive subsequent treatment.

Table 43 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Duration
Docetaxel (i.v.)	75mg/m^2	100%	Every 3 weeks*	Yes	10 weeks**

* cost of an outpatient visits was added for each infusion as average infusion per week × duration

** treatment duration based on DMC preferred model for subsequent treatment in the assessmen of nivolumab in G/GEJC [1]

15.7 Patient costs

Assumptions related to patient time and transport cost in the CUA model are presented in Table 44. Time associated with hospital visits was sourced from Medicinrådets assessment of pembrolizumab in oesophagus cancer[43] and unit costs was sourced from Medicinrådets *Værdisætning af enhedsomkostniger v1.8.* [44] Additional patient time for zolbetuximab infusions were estimated at 3h based on observed average infusion time in the integrated safety set. In the CMA, only the additional cost of zolbetuximab infusion time was added 3h @ 188 = 564 DKK. No patient costs were added in the comparator arms. Transportation costs were not included as these are unaffected by choice of antibody therapy.

Table 44 Patient costs used in the CUA model

Activity	Time spent [minutes, hours, days]
IV administration	
Zolbetuximab + chemotherapy	5h @188 DKK + transport (140 DKK)
Chemotherapy	2h @188 DKK + transport (140 DKK)
CT-scan	1 h @188 DKK + transport (140 DKK)
Outpatient visit	1 h @188 DKK + transport (140 DKK)
Nurse visit	½ h @188 DKK + transport (140 DKK)

15.8 Other costs

Costs associated with CLDN18.2 test were added for each patient starting treatment with zolbetuximab. Prior to initiating zolbetuximab treatment, a CLDN18 test result is needed to confirm eligibility.

The VENTANA CLDN18 (43-14A) RxDx Assay is a semi-quantitative IHC assay using mouse monoclonal anti-claudin 18, clone 43-14A, intended for laboratory use in the assessment of CLDN18 protein in formalin-fixed, paraffin-embedded gastric adenocarcinoma including GEJ tissue specimens by IHC. The intended use of the VENTANA CLDN18 (43-14A) RxDx Assay is as an aid in identifying patients with gastric or GEJ adenocarcinoma who may be eligible for treatment with zolbetuximab.

The test cost is added to the zolbetuximab arm in the model as an average cost per eligible patient and calculated as the unit cost of a Ventana test kit divided by the prevalence of CLDN18.2 among patients with HER2-negative tumors. The percentage of HER2- patients who can be expected to have CLDN18.2+ cancer was sourced from GLOW/SPOTLIGHT. Among patients screened for inclusion, 38.4% were CLDN18.2 positive (based on the 75% cut-off which should be applied in clinical practice).

Table 45 CLDN18.2 test cost

	Value	Note
Cost of Ventana® CLDN18 array / per patient	[redacted]/ test kit	CLDN18 CDx assay (08285918001, pack of 50 test-kits). Roche email conversation.
Percent patients CLDN18+ of HER2- patients	38.4%	GLOW/SPOTLIGHT (see section 1.2)
Average cost per patient eligible for zolbetuximab	[redacted]	Calculated

The CLDN18.2 was applied in both the CUA and CMA, however, no cost of PD-(L)1 test was included in the cost-minimization analysis comparing zolbetuximab to PD-(L)1 inhibitor.

Based on the DMC preferred base case for the assessment of nivolumab in G/GEJC, costs for palliation and care associated with deaths were not included in the base case analysis.

16. Results. Comparison to chemotherapy

16.1 Base case overview

Table 46 Base case overview

Feature	Description
Comparator	Chemotherapy alone (CAPOX used for cost-calculation)
Type of model	Partitioned survival model (PSM)
Time horizon	40 years (life time)
Treatment line	1st line
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in integrated data from GLOW/SPOTLIGHT. Danish population weights were used to estimate health-state utility values
Costs included	Intervention medication costs Co-medication Drug administration (i.v. infusions) Health state cost Costs of adverse events Patient costs
Dosage of medicine	Based on body surface area (1.81 m^2) In CAPOX (both arms) 9 series of oxaplatin is assumed [1]

Feature	Description
Average time on treatment	Intervention: 7.8 months Comparator: 6.0 months
Parametric function for PFS	Intervention: log-logistic Comparator: log-logistic
Parametric function for OS	Intervention: log-logistic Comparator: gamma
Inclusion of waste	For zolbetuximab only
Average time in model health state Pre-progression (PF) Post-progression (PD) Overall	Undiscounted. Zolbetuximab plus chemotherapy compared to chemotherapy alone 1.7 years vs 1.0 years 0.7 years vs 0.4 years 2.4 years vs 1.5 years

16.1.1 Base case results

The results of the base case analysis are presented in Table 47. Zolbetuximab in combination with chemotherapy is associated with improved life-expectancy (0.72 LYG/patient) and improved quality adjusted life-years (0.62 QALY/patient) compared to chemotherapy alone. At list prices, the incremental societal cost is 519,320 DKK/patient. The incremental cost is primarily driven by treatment cost but also by the increased health care cost associated with longer life-expectancy.

Table 47 Base case results, discounted estimates

	Zolbetuximab plus chemotherapy	Chemotherapy alone	Difference
Treatment costs	[redacted]	[redacted]	[redacted]
PF treatment costs	[redacted]	[redacted]	[redacted]
PD treatment costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]
PF health state costs	[redacted]	[redacted]	[redacted]
PD health state costs	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]
Total direct cost	**568,595**	**61,754**	**506,841**
Patient cost	[redacted]	[redacted]	[redacted]
Total societal cost	**596,458**	**77,138**	**519,320**
Life-years PF state	[redacted]	[redacted]	[redacted]
Life-years PD state	[redacted]	[redacted]	[redacted]
Total life years	2.15	1.43	0.72
QALY PF state	[redacted]	[redacted]	[redacted]

	Zolbetuximab plus chemotherapy	Chemotherapy alone	Difference
QALY PD state	[redacted]	[redacted]	[redacted]
QALY Side-effects	[redacted]	[redacted]	[redacted]
Total QALYs	**1.85**	**1.23**	**0.62**
Incremental costs per life year gained		**718,117**	
Incremental cost per QALY gained (ICER)		**841,129**	

16.2 Sensitivity analyses

16.2.1 Deterministic sensitivity analyses

Results obtained from deterministic one-way sensitivity analyses are presented in Table 48 and Figure 19 (parameters with highest impact on ICER only). Zolbetuximab dosing (average integer number of vials need per infusion) assumptions were varied simultaneously for the 400mg, 600mg and 800mg dosing options. Lower and higher limits are the 95% confidence intervals estimated using a bootstrap analysis of SPOTLIGHT data (N:5000). Clinical extrapolation parameters and health state utilities were varied within 95% confidence intervals. For other parameters see description of variation in table below.

Note that variation of the parameters of the OS gamma function within the range of the confidence intervals will result in predicted median survival that are not credible description of the observed outcomes. Hence the ICER estimated at the confidence interval limits should be interpreted with caution, but a high sensitivity of the economic analysis to assumption on long-term survival can be concluded.

Overall, the results were mainly sensitive to parameters determining the long-term survival of patients in chemotherapy only (standard of care) arm in the model, followed by parameters of the zolbetuximab OS extrapolation and discount rate.

Table 48 One-way sensitivity analyses results

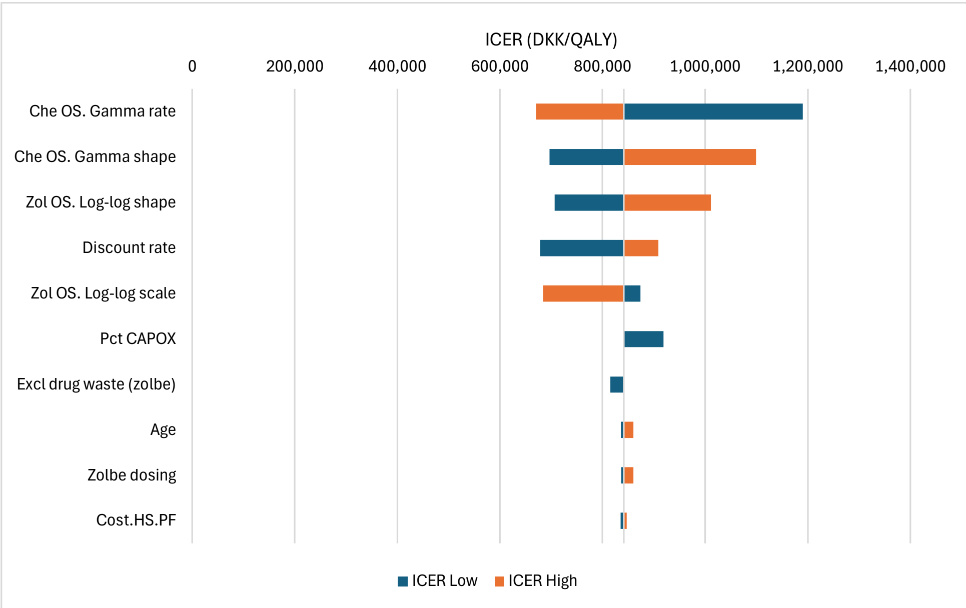
	Change	Rationale	Δ cost (DKK)	Δ QALY	ICER (DKK/QALY)
Base case			519,320	0.62	841,129
Age	55	55-65 years	519,415	0.62	835,924
	65		519,018	0.60	860,038
Cost of iv infusion	1248.8	±20%	518,252	0.62	839,398
	1873.2		520,389	0.62	842,859
Patient cost of infusion (zol)	864	±20%	516,818	0.62	837,075
	1296		521,823	0.62	845,182
Cost antiemetics (zol)	192.524	±20%	518,992	0.62	840,597

	Change	Rationale	Δ cost (DKK)	Δ QALY	ICER (DKK/QALY)
	288.786		519,649	0.62	841,660
Health state cost (PF)	29380.8	±20%	515,550	0.62	835,023
	44071.2		523,090	0.62	847,235
Health state cost (PD)	5731.2	±20%	519,020	0.62	840,642
	8596.8		519,621	0.62	841,616
CDLN18.2 Test cost	1641.42	±20%	518,910	0.62	840,464
	2462.13		519,731	0.62	841,793
Subsequent treatment cost (zol)	4919.13	±20%	518,136	0.62	839,210
	7378.70		520,505	0.62	843,047
Excl drug waste (zolbe)	Yes	BC No	503,475	0.62	815,464
Patient cost PF	9216	±20%	519,320	0.62	841,129
	13824		518,138	0.62	839,213
Patient cost PD	1049.6	±20%	520,503	0.62	843,044
	1574.4		519,265	0.62	841,040
Discount rate	0	0%-5%	519,376	0.62	841,218
	0.05		532,919	0.79	678,611
Percent treated with CAPOX	0.8	Low: 80% (BC 100%)	514,550	0.57	909,209
BSA	1.78	Bootstrap 95% CI	519,320	0.62	841,129
	1.84		519,320	0.62	841,129
Zolbetuximab dosing (vials per infusion)	14.7; 11.2; 7.6	Bootstrap 95% CI for 800, 600, 400 mg/m2, respectively	567,004	0.62	918,360
	15.2, 11.5; 7.8		519,320	0.62	841,129
PF utility weight	0.87108	95% CI	519,357	0.62	841,187
	0.87892		519,284	0.62	841,069
PD utility weight	0.80628	95% CI	516,273	0.62	836,193
	0.83372		530,799	0.62	859,720
Excl AE disutility	Yes	BC No	519,320	0.62	841,129
Excl Age-adjusted utility	Yes	BS: No	519,320	0.62	841,129
Zol OS. Log-log shape	1.552	95% CI	519,320	0.62	841,129
	1.838		519,320	0.62	841,129
Zol OS. Log-log scale	68.813	95% CI	519,320	0.62	843,865
	76.518		519,320	0.62	838,410

	Change	Rationale	Δ cost (DKK)	Δ QALY	ICER (DKK/QALY)
Che OS. Gamma shape	1.339	95% CI	519,320	0.61	845,047
	1.703		519,320	0.62	837,247
Che OS. Gamma rate	0.017	95% CI	519,320	0.62	841,129
	0.023		519,320	0.62	840,394
Zol PFS. Log-log shape	1.483	95% CI	519,320	0.62	841,129
	1.781		519,320	0.62	836,685
Zol PFS. Log-log scale	40.916	95% CI	520,609	0.74	706,365
	50.213		518,154	0.51	1,011,071
Che PFS. Log-log shape	1.658	95% CI	519,074	0.59	873,894
	1.966		520,835	0.76	683,652
Che PFS. Log-log scale	31.917	95% CI	521,136	0.75	696,346
	37.955		517,431	0.47	1,099,112

Abbreviations: AE adverse event; BSA Body surface area; Che Chemotherapy, CI Confidence Interval; DKK Danish Krone; Excl Exclude, Gamma Gamma survival function; HS health state; ICER Incremental cost-effectiveness ratio; Log-log Log-logarithmic Survival Function, OS Overall Survival, PD Progressed Disesae; PF Progression-Free; Zol Zolbetuximab.

Figure 19 Tornado diagram showing 10 parameters with highest impact on ICER (DKK/QALY)



Abbreviations: BSA Body surface area; Che Chemotherapy, DKK Danish Krone; Excl Exclude, Gamma Gamma survival function; HS health state; ICER Incremenal cost-effectiveness ratio; Log-log Log-logarithmic Survival Function, OS Overall Survial, PF Progression-Free; Zol Zolbetuximab.

16.2.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis was carried out using a stochastic model for all trial-based assumptions, ie., parametric survival curves for OS, PFS and TTD as well as age, HSUV, BSA and zolbetuximab dosing, see Appendix D for details.

Figure 20 presents the scatterplot from 1500 simulations.

Figure 20 Scatterplot for simulations (N:1500). Incremental cost by incremental QALY

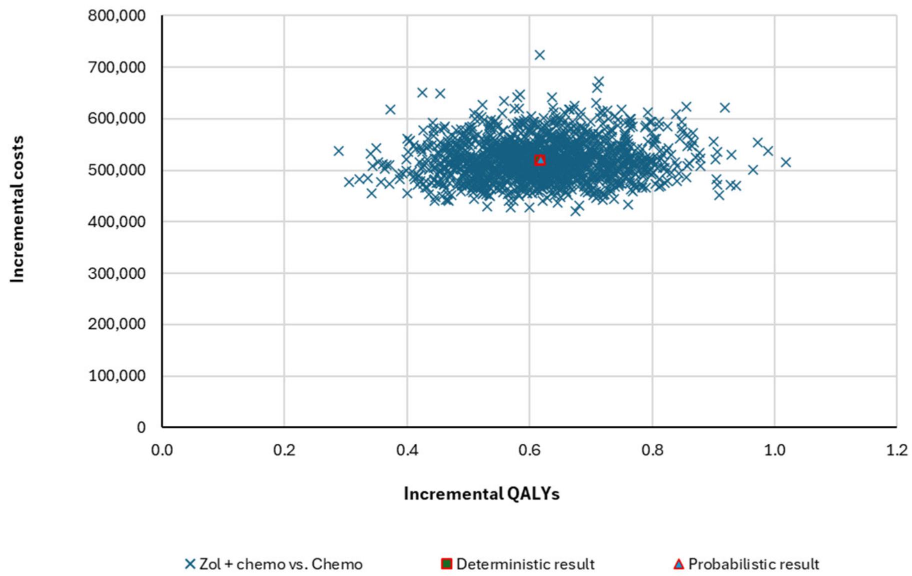


Table 49 show the average of simulations of incremental cost, LY and QALY and the resulting ICER (cost per QALY). Incremental cost, QALY and life-years gains are almost identical to the deterministic result and an ICER in the stochastic analysis close to the deterministic analysis. Figure 21 shows the convergence of the simulation ICER by increasing number of simulations. The ICER based on average simulated outcomes stabilized at around 400 simulations.

Table 49 Average outcomes (N: 1500 simulations)

Treatment	Costs (DKK)	LYG	QALYs
Chemo	71,148	1.434	1.230
Zolbetuximab + chemo	591,400	2.158	1.848
Incremental	71,148	1.434	1.230
ICER (cost per QALY)	841,105		

Figure 22 provides the CEAC curves from the simulation when all pharmaceuticals are priced at PPP level.

Figure 21 Convergence of average ICER by simulation

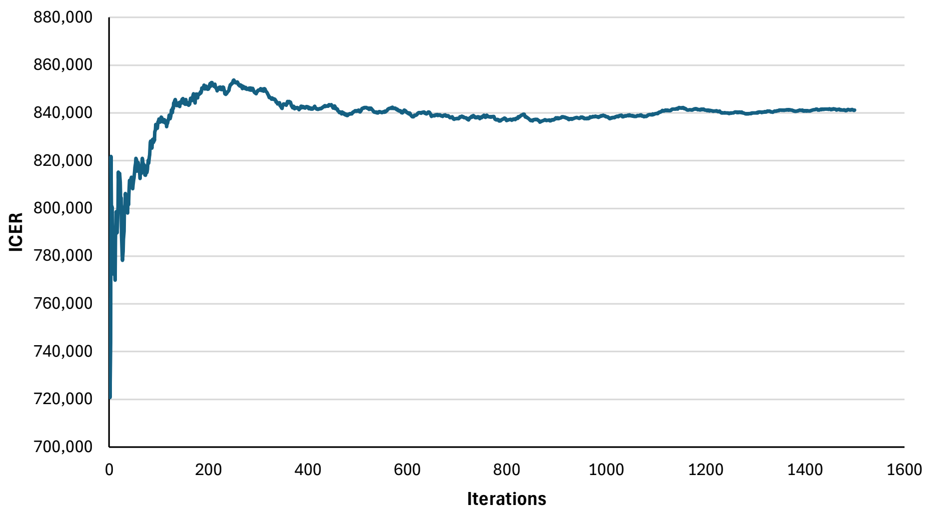
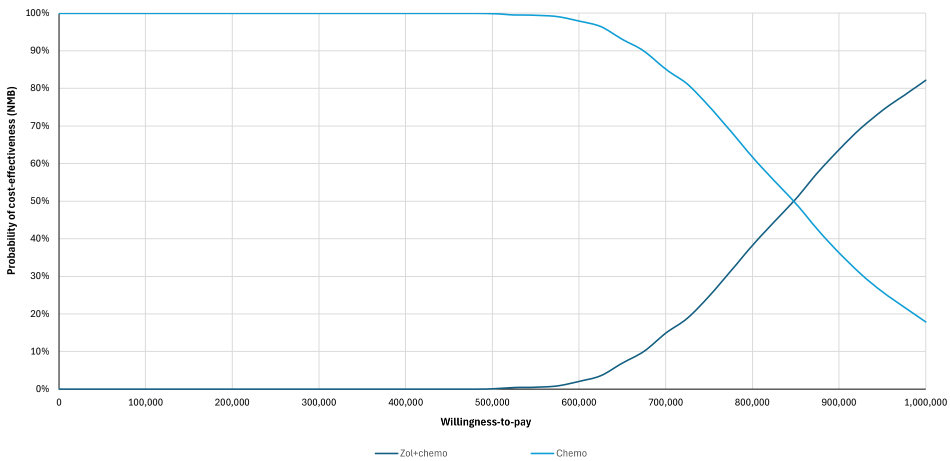


Figure 22 Cost-effectiveness acceptability curve. Zolbetuximab + chemotherapy compared to chemotherapy



17. Results. Comparison to PD-(L)1 inhibitors

17.1 Base case overview

Table 50 Base case overview

Feature	Description
Comparator	PD-(L)1 inhibitors in combination with chemotherapy
Type of model	Cost per patient
Time horizon	8 months
Treatment line	1st line.
Measurement and valuation of health effects	Not applicable
Costs included	Medicine cost (excluding cost of chemotherapy) Co-medication cost (zolbetuximab arm only) Cost of CDLN18.2 test (zolbetuximab arm only) Patient time cost of zolbetuximab infusion (zolbetuximab arm only)
Dosage of medicine	Zolbetuximab based on BSA Q3W PD-(L)1 inhibitor based on weight Q3W
Average time on treatment	Intervention:8 months Comparator: 8 months
Inclusion of waste	Yes
Parametric functions	Not applicable
Average time in model health state	Not applicable

17.1.1 Base case results

Table 51 presents the result of the base case analysis. At list prices, treatment with zolbetuximab (Q3W) is associated with cost-savings compared to treatment with pembrolizumab (Q3W) and increased costs compared to nivolumab.

Table 51 Base case results

	Zolbetuximab	Pembrolizumab	Difference	Nivolumab	Difference
Medicine costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDLN18.2 test cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	**453,156**	**474,619**	**-21,462**	**300,038**	**153,119**

17.2 Sensitivity analyses

17.2.1 Deterministic sensitivity analyses

Table 48 presents the scenario analyses including dose frequency, drug waste, and patient weight. The scenario analyses related to Q3W did not change the conclusion of the base case analysis comparing to pembrolizumab at list prices. When combined with chemotherapy administrated Q2W (zolbetuximab Q2W compared to pembrolizumab Q6W), zolbetuximab was more costly than pembrolizumab in all scenarios where pembrolizumab is dosed based on weigh. Compared to nivolumab at list prices, Zolbetuximab is associated with a higher cost, both when combined with chemotherapy with 3 and 2 weeks cycles.

Table 52 One-way sensitivity analyses results

Scenario	Base case value	Alternative Value	Note	Incremental cost vs Nivolumab	Pembrolizumab
Combined with chemotherapy administrated Q3W					
Base case				**-21,462**	**153,119**
BSA	1.81	1.78		-21,462	153,119
		1.84		-21,462	153,119
PD-(L)1 inhibitor dosing	By weight	Fixed		-21,462	115,614
Drug wastage	Include	Exclude		119,208	155,037
Duration of treatment (m)	8	7		-18,036	140,674
		9		-24,888	165,563
		12		-38,593	215,343
CDLN18.2 test cost	2,052	1,026	±50%	-22,488	152,093
		3,078		-20,436	154,144
Antiemetics cost	180.97	90.49	±50%	-22,458	152,123
		271.46		-20,467	154,114
Combined with chemotherapy administrated Q2W					
Base case				**103,990**	**192,276**
BSA	1.81	1.78		103,990	192,276
		1.84		103,990	192,276
PD-L(1) dosing	By weight	Fixed		-25,452	165,000
Drug wastage	Include	Exclude		93,592	167,456
Duration of treatment (m)	8	7		110,528	171,598
		9		162,172	212,954
		12		207,278	274,987
CDLN18.2 test cost	2,119	1,059	±50%	102,964	191,250
		3,178		105,016	193,302
Antiemetics cost	180.97	90.49	±50%	102,542	190,828
		271.46		105,437	193,724

17.2.2 Probabilistic sensitivity analyses

Not applicable

18. Budget impact analysis

As presented in section 3.2, it is expected that a total of 90 patients will be eligible for treatment with zolbetuximab yearly. If a positive recommendation is granted, it is expected that a total of [redacted] of those will be treated with zolbetuximab the year of launch, [redacted] will be treated with a PD-(L)1 inhibitor and [redacted] will be treated with chemotherapy. It is expected that the market share for zolbetuximab will increase over time with [redacted] patients treated with zolbetuximab year 5 after launch, [redacted] with a PD-(L)1 inhibitor and [redacted] patients with chemotherapy alone. If a positive recommendation for zolbetuximab is not granted, it is expected that [redacted] patients will be treated with zolbetuximab (Table 53). The budgetary consequences of introducing zolbetuximab in Denmark is estimated to be [redacted] million DKK the year of launch increasing to [redacted] million DKK year five (Table 54 and Table 55). The budget impact analyses are available in the two Excel models (cost-minimization and cost-utility analysis, respectively).

Number of patients (including assumptions of market share)

Table 53 Number of new patients expected to be treated over the next five-year period if the medicine is recommended or not recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Zolbetuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-(L)1 inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Zolbetuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-(L)1 inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 54 Expected budget impact of recommending the medicine. CDLN18.2 positivity and CPS ≥5. (million DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Situation with Zolbetuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Situation without Zolbetuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Due to rounding the budget impact may not always correspond to difference in rows above

Table 55 Expected budget impact of recommending the medicine. CDLN18.2 positivity and CPS <5. (million DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Situation with Zolbetuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Situation without Zolbetuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Due to rounding the budget impact may not always correspond to difference in rows above

19. List of experts

NA

20. References

1. Medicinrådet. Medicinrådets anbefaling vedrørende nivolumab i kombination med kemoterapi til 1. linjebehandling af fremskredent HER2-negativ adenokarcinom i mavesæk, mavemund eller spiserør og PD-L1 CPS ≥ 5.; 2022. Available from: https://medicinraadet-classic.azureedge.net/media/y5oatvan/medicinr%C3%A5dets-anbefaling-vedr-nivo-kemo-til-adenokarcinom-i-maves%C3%A6k-mavemund-eller-spiser%C3%B8r-vers-1-0-x.pdf.
2. Medicinrådet. Medicinrådets anbefaling vedr. pembrolizumab i kombination med kemoterapi til behandling af HER2-negativ adenokarcinom i mavesæk eller mavemund. Patienter med PD-L1CPS ≥ 1. 2024.
3. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2022;33(10):1005–20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/35914639.
4. Cavatorta O, Scida S, Miraglia C, Barchi A, Nouvenne A, Leandro G, et al. Epidemiology of gastric cancer and risk factors. Acta Biomed. 2018;89(8-S):82–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6502220/.
5. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. Seminars in radiation oncology. 2013;23(1):3–9.
6. Quante M, Wang TC, Bass AJ. Adenocarcinoma of the oesophagus: is it gastric cancer? Gut. 2023;72(6):1027–9.
7. Shankaran V, Xiao H, Bertwistle D, Zhang Y, You M, Abraham P, et al. A Comparison of Real-World Treatment Patterns and Clinical Outcomes in Patients Receiving First-Line Therapy for Unresectable Advanced Gastric or Gastroesophageal Junction Cancer Versus Esophageal Adenocarcinomas. Advances in therapy. 2021;38(1):707–20.
8. Dansk Esophago-Gastrisk Cancer Database. Årsrapport 2022. 2023.
9. NORDCAN. Online Statistics: Stomach cancer.; 2024. Available from: https://nordcan.iarc.fr/en/dataviz/trends?mode=cancer&group_populations=1&populations=208&multiple_cancers=1&cancers=70&years=2018_2023&key=total&sexes=0.
10. Shah MA, Shitara K, Ajani JA, Bang YJ, Enzinger P, Ilson D, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nature medicine. 2023;29(8):2133–41.
11. Shitara K, Lordick F, Bang Y-J, Enzinger P, Ilson D, Shah MA, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. The Lancet. 2023;401(10389):1655–68. Available from: https://doi.org/10.1016/S0140-6736(23)00620-7 [Last accessed 2023/10/30].
12. Waters R, Sewastjanow-Silva M, Yamashita K, Abdelhakeem A, Iwata KK, Moran D, et al. Retrospective Study of Claudin 18 Isoform 2 Prevalence and Prognostic Association in Gastric and Gastroesophageal Junction Adenocarcinoma. JCO Precis

Oncol. 2024;8:e2300543. Available from: https://www.ncbi.nlm.nih.gov/pubmed/38781542.
13. Shitara K, Xu R-H, Moran DM, Guerrero A, Li R, Pavese J, et al. Global prevalence of CLDN18.2 in patients with locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Biomarker analysis of two zolbetuximab phase 3 studies (SPOTLIGHT and GLOW). Journal of Clinical Oncology. 2023;41(16_suppl):4035–. Available from: https://doi.org/10.1200/JCO.2023.41.16_suppl.4035 [Last accessed 2023/11/02].
14. DMCG. Kliniske retningslinjer. Onkologisk behandling af ikke-kurabel cancer i esophagus og ventrikel. 2025. Available from: https://www.dmcg.dk/kliniske-retningslinjer/kliniske-retningslinjer-opdelt-paa-dmcg/esophagus--cardia--og-ventrikelcancer/onkologisk-behandling-af-non-kurabel-cancer-i-esophagus-gej-og-ventrikel/.
15. DECG. Kliniske retningslinjer, Onkologisk behandling af ikke-kurabel cancer i esophagus og ventrikel. Version 2.0. 2023.
16. ESMO. ESMO Gastric Cancer Living Guideline, v1.4 September 2024. 2024. Available from: https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline.
17. EMA. Vyloy EPAR. Product information 2024.
18. EMA. Vyloy. Public assessment report. EMA/378968/2024 2024.
19. Lægemiddelstyrelsen. Produktresumé. Capecitabin. 2024.
20. Herrstedt J, Clark-Snow R, Ruhlmann CH, Molassiotis A, Olver I, Rapoport BL, et al. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. ESMO open. 2024;9(2). Available from: https://doi.org/10.1016/j.esmoop.2023.102195.[Last accessed 2024/10/28].
21. EMA. Opdivo - EPAR. Summary of product characteristics2023.
22. NIH. ClinicalTrials.gov. NCT02872116. 2024. Available from: https://clinicaltrials.gov/study/NCT02872116?term=NCT02872116&rank=1.
23. NIH. ClinicalTrials.gov. NCT03675737 2024. Available from: https://clinicaltrials.gov/study/NCT03675737?term=NCT03675737&rank=1.
24. Nair S, Gupta P, Nair A. Systematic literature review update: clinical systematic review in advanced gastric cancer. Clarivate; 2024.
25. Lordick F, Van Cutsem E, Shitara K, Xu RH, Ajani JA, Shah MA, et al. Health-related quality of life in patients with CLDN18.2-positive, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma: results from the SPOTLIGHT and GLOW clinical trials. ESMO open. 2024;9(8):103663. Available from: https://www.ncbi.nlm.nih.gov/pubmed/39146670.
26. Shitara K, Shah MA, Lordick F, Van Cutsem E, Ilson DH, Klempner SJ, et al. Zolbetuximab in Gastric or Gastroesophageal Junction Adenocarcinoma. N Engl J Med. 2024;391(12):1159–62. Available from: https://www.ncbi.nlm.nih.gov/pubmed/39282934.
27. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27–40. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34102137 [Last accessed 2023/01/04].
28. EMA. Opdivo. CHMP Assessment report (Variation) EMEA/H/C/003985/II/0096. 2021 Sept 16.
29. Shitara K, Moehler M, Ajani JA, Shen L, Garrido M, Gallardo C, et al. Nivolumab plus chemotherapy vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: 4-year follow-up of the CheckMate 649 study. ASCO Gastrointestinal Cancers Syposium. San Francisco, CA: US; 2024.

30. Moehler M, Xiao H, Blum SI, Elimova E, Cella D, Shitara K, et al. Health-Related Quality of Life With Nivolumab Plus Chemotherapy Versus Chemotherapy in Patients With Advanced Gastric/Gastroesophageal Junction Cancer or Esophageal Adenocarcinoma From CheckMate 649. J Clin Oncol. 2023;41(35):5388–99.
31. Rha SY, Oh DY, Yanez P, Bai Y, Ryu MH, Lee J, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2023;24(11):1181–95.
32. EMA. Keytruda. CHMP Assessment report (variation). EMEA/H/C/003820/II/0135. 2023 Oct 12.
33. National Institute for Health and Care Excellence. Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma [ID1465] Committee Papers. 2022.
34. Shah BD, Smith NJ, Feng C, Jeyakumar S, Castaigne JG, Faghmous I, et al. Cost-Effectiveness of KTE-X19 for Adults with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia in the United States. Advances in therapy. 2022;39(8):3678–95. Available from: https://www.ncbi.nlm.nih.gov/pubmed/35727476.
35. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683–90. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16967055.
36. Danmarks Statistik. FOLK1C. Befolkningen den 1. i kvartalet efter herkomst, køn, område, tid, oprindelsesland og alder (2025K2). 2025. Available from: https://statistikbanken.dk/statbank5a/default.asp?w=1536 [Last accessed June, 2025].
37. Davidson M, Cafferkey C, Goode EF, Kouvelakis K, Hughes D, Reguera P, et al. Survival in Advanced Esophagogastric Adenocarcinoma Improves With Use of Multiple Lines of Therapy: Results From an Analysis of More Than 500 Patients. Clinical Colorectal Cancer. 2018;17(3):223–30. Available from: https://doi.org/10.1016/j.clcc.2018.05.014.[Last accessed 2024/01/19].
38. Merchant SJ, Kong W, Gyawali B, Hanna TP, Chung W, Nanji S, et al. First-Line Palliative Chemotherapy for Esophageal and Gastric Cancer: Practice Patterns and Outcomes in the General Population. JCO Oncol Pract. 2021;17(10):e1537–e50. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33449833.
39. Kubota Y, Kawazoe A, Mishima S, Nakamura Y, Kotani D, Kuboki Y, et al. Comprehensive clinical and molecular characterization of claudin 18.2 expression in advanced gastric or gastroesophageal junction cancer. ESMO open. 2023;8(1):100762.
40. Janjigian YY, Shitara K, Moehler MH, Garrido M, Gallardo C, Shen L, et al. Nivolumab (NIVO) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 3-year follow-up from CheckMate 649. Journal of Clinical Oncology. 2023;41(16_suppl):4025–. Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.16_suppl.4025.
41. Sahin U, Tureci O, Manikhas G, Lordick F, Rusyn A, Vynnychenko I, et al. FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. Annals of oncology : official journal of the European Society for Medical Oncology. 2021;32(5):609–19. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33610734.
42. Janjigian YY, Ajani JA, Moehler M, Shen L, Garrido M, Gallardo C, et al. First-Line Nivolumab Plus Chemotherapy for Advanced Gastric, Gastroesophageal Junction,

and Esophageal Adenocarcinoma: 3-Year Follow-Up of the Phase III CheckMate 649 Trial. J Clin Oncol. 2024;42(17):2012–20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/38382001.
43. Medicinrådet. Medicinrådets anbefaling vedrørende pembrolizumab i kombination med platin- og fluoropyrimidinbaseret kemoterapi til førstelinjebehandling af lokalt fremskredent inoperabelt eller metastatisk karcinom i spiserøret eller HER2-negativ adenokarcinom i den gastro-esofageale overgang, Siewert I, hos voksne med PD-L1 CPS ≥ 10. Version 1.0. 2022.
44. Medicinrådet. Værdisætning af enhedsomkostninger. Version 1.8. 2024.
45. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50(6):683–91.
46. Pellino A, Brignola S, Riello E, Niero M, Murgioni S, Guido M, et al. Association of CLDN18 Protein Expression with Clinicopathological Features and Prognosis in Advanced Gastric and Gastroesophageal Junction Adenocarcinomas. Journal of personalized medicine. 2021;11(11).
47. Jaffer A. Ajani FL, Yung-Jue Bang, Peter Enzinger, David Ilson, Manish A. Shah, Eric Van Cutsem, Rui-Hua Xu,, Giuseppe Aprile JX, Roberto Pazo-Cid, Yoon-Koo Kang, Jianning Yang, Diarmuid Moran,, Pranob Bhattacharya MM, Ahsan Arozullah, Jung Wook Park, Kohei Shitara. Updated efficacy and safety results from phase 3 SPOTLIGHT study evaluating zolbetuximab + mFOLFOX6 as first-line (1L) treatment for patients with claudin-18 isoform 2-positive (CLDN18.2+), HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma. European Society for Medical Oncology. Madrid: Spain; 2023.
48. Janjigian YY, Shitara K, Moehler MH, Garrido M, Gallardo C, Shen L, et al. Nivolumab (NIVO) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 3-year follow-up from CheckMate 649. American Society of Clinical Oncology; 2023.
49. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/oesophageal adenocarcinoma (CheckMate 649): a multicentre, randomised, open-label, phase 3 trial. Lancet (London, England). 2021;398(10294):27.
50. Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L value set: a hybrid model using cTTO and DCE data. Applied Health Economics and Health Policy. 2021;19:579–91.
51. Ajani JA, Lordick F, Bang Y-J, Enzinger P, Ilson D, Shah MA, et al. Updated efficacy and safety results from phase 3 SPOTLIGHT study evaluating zolbetuximab + mFOLFOX6 as first-line (1L) treatment for patients with claudin-18 isoform 2-positive (CLDN18.2+), HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma. ESMO2023.
52. Lordick F, Shitara K, Ajani JA, Bang Y, Enzinger P, Ilson D, et al. 134MO Updated efficacy and safety results from phase III GLOW study evaluating zolbetuximab + CAPOX as first-line (1L) treatment for patients with claudin-18 isoform 2-positive (CLDN18.2+), HER2-, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma. . Annals of Oncology. 2023;34(4_Supplement).
53. Lordick F, Van Cutsem E, Shitara K, Xu RH, Ajani JA, Shah MA, et al. 1530P Health-related quality of life (hrqol) in patients with claudin-18 isoform 2-positive (CLDN18.2+) locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mg/GEJ) adenocarcinoma: Results from SPOTLIGHT and

GLOW. Annals of Oncology. 2023;34:S860–S1. Available from: https://doi.org/10.1016/j.annonc.2023.09.1442.[Last accessed 2024/01/19].
54. Elimova E, Wyrwicz L, Blum SI, Xiao H, Li M, Kondo K, et al. Health-related quality of life (HRQOL) in patients (pts) with advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC) or esophageal adenocarcinoma (EAC): Results of nivolumab plus chemotherapy (NIVO+chemo) versus chemo from CheckMate 649. J Clin Oncol 39, 2021 (suppl 28; abstr 167). 2021.
55. Moehler M, Garrido M, Salman P, Shen L, Wyrwicz L, Yamaguchi K, et al. Nivolumab (NIVO) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): Expanded efficacy, safety, and subgroup analyses from CheckMate 649. . Annals of Oncology. 2020;31 (Suppl 2):214–5.
56. Mohler M, Blum SI, Xiao H, Davenport E, Wang J, Hunter S, et al. Health-related quality of life (HRQOL) in patients (pts) with advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC) or esophageal adenocarcinoma (EAC): Interim results of nivolumab plus chemotherapy (N+C) versus (C) from CheckMate 649. Oncology Research and Treatment. 2021;44 (SUPPL 2):214–5.
57. Janjigian YY, Shitara K, Moehler M, Garrido M, Gallardo C, Shen L, et al. Nivolumab (NIVO) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 3-year follow-up from CheckMate 649. Journal of Clinical Oncology. 2023;41(4_Suppl).
58. Janjigian YY, Ajani JA, Moehler M, Garrido M, Shen L, Yamaguchi K, et al. LBA7 - Nivolumab (NIVO) plus chemotherapy (Chemo) or ipilimumab (IPI) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): CheckMate 649 study. Annals of oncology : official journal of the European Society for Medical Oncology. 2021;2021(32 (suppl_5)).
59. Shitara K, Ajani JA, Moehler M, Garrido M, Gallardo C, Shen L, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. Nature. 2022;603(7903):942–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/35322232.
60. Shitara K, Moehler M, Garrido M, Gallardo C, Shen L, Yamaguchi K. Nivolumab (NIVO) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): Expanded efficacy, safety, and subgroup analyses from CheckMate 649. Journal of Clinical Oncology. 2022;40(4_Suppl).
61. Lowery M, Wyrwicz L, Oh DY, Shiu KK, Yanez Weber P, Bai Y, et al. 1516P Health-related quality of life (hrqol) analysis from KEYNOTE-859: First-line (1L) pembrolizumab (pembro) + chemotherapy (chemo) for advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. Annals of Oncology. 2023;34:S854–S5. Available from: https://doi.org/10.1016/j.annonc.2023.09.1429.[Last accessed 2024/11/07].
62. Wainberg ZA, Shiu KK, Rivera F, Medley LC, Aghmesheh M, Dunne RF, et al. First-line pembrolizumab (pembro) plus chemotherapy (chemo) for advanced gastroesophageal junction cancer (GEJC) and esophageal adenocarcinoma (EAC): Analysis of KEYNOTE-590 and KEYNOTE-859 by tumor type. Journal of Clinical Oncology. 2024;42(3_Suppl).

Appendix A. Main characteristics of studies included

Table 56 Main characteristic of studies included (SPOTLIGHT)

Trial name: SPOTLIGHT		**NCT number: NCT03504397**
Objective	Establish the relative efficacy and safety of zolbetuximab given in addition to chemotherapy vs chemotherapy alone	
Publications – title, author, journal, year	Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. Lancet 2023;401:1655-68.[11] Shitara K, Shah MA, Lordick F et al. Zolbetuximab in Gastric or Gastroesophageal Junction Adenocarcinoma. N Engl J Med.. 2024 Sep 26;391(12):1159-1162. doi: 10.1056/NEJMc2409512. Epub 2024 Sep [26]	
Study type and design	SPOTLIGHT was a Phase 3, multicentre, double-blind, randomised controlled trial (RCT) designed to evaluate the efficacy and safety of zolbetuximab + folinic acid in combination with fluorouracil and oxaliplatin (mFOLFOX6) versus placebo + mFOLFOX6 as first-line treatment in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GE0J adenocarcinoma Enrolled patients were randomly assigned (1:1) to zolbetuximab plus mFOLFOX6 or placebo plus mFOLFOX6 by masked site staff via interactive response technology by block randomisation (block sizes of two) and stratified according to region (Asia vs non-Asia), number of organs with metastases (0–2 vs ≥3), and previous gastrectomy (yes vs no). The randomisation list and study drug masking were maintained by the interactive response technology system Stratification factors were region, number of organs with metastatic sites, and prior gastrectomy.	
Sample size (n)	Zolbetuximab (800 mg/m² loading dose followed by 600 mg/m² every 3 weeks) plus mFOLFOX6 (every 2 weeks) (n=283) Placebo plus mFOLFOX6 (every 2 weeks) (n=282)	
Main inclusion criteria	• Age ≥18 years with: ○ Histologically confirmed diagnosis of G/GEJ adenocarcinoma, radically confirmed and evaluable (measurable and/or non-measurable disease according to RECIST v1.1. per local assessment) locally advanced unresectable or metastatic disease ○ CLDN18.2 in ≥75% of tumour cells as determined by central IHC testing HER2-negative tumour	

Trial name: SPOTLIGHT	NCT number: NCT03504397
Main exclusion criteria	• Prior systemic chemotherapy for locally advanced unresectable or metastatic G/GEJ adenocarcinoma (patients may have received either neo-adjuvant or adjuvant chemotherapy, immunotherapy, or other systemic anticancer therapies as long as it was completed ≥6 months before randomization) • Radiotherapy for locally advanced unresectable or metastatic G/GEJ adenocarcinoma ≤14 days prior to randomization and has not recovered from any related toxicity • Systemic immunosuppressive therapy • Prior severe allergic reaction or intolerance to known ingredients of zolbetuximab or other monoclonal antibodies, including humanised or chimeric antibodies • Prior severe allergic reaction or intolerance to any component of mFOLFOX6 • Known dihydropyrimidine dehydrogenase deficiency • An active autoimmune disease that has required systemic treated ≤3 months prior to randomization • Significant CV disease
Intervention	Zolbetuximab (800 mg/m² loading dose followed by 600 mg/m² every 3 weeks) plus mFOLFOX6 (every 2 weeks) (n=283)
Comparator(s)	Placebo plus mFOLFOX6 (every 2 weeks) (n=282)
Follow-up time	Median follow-up time was 33.28 months in the zolbetuximab+ FOLFOX arm and 31.38 months in the placebo + FOLFOX arm.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Progression Free Survival (PFS). PFS is defined as the time from the date of randomization until the date of radiological progressive disease (per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 by Independent Review Committee (IRC)) or death from any cause, whichever is earliest. Overall Survival (OS). OS is defined as the time from the date of randomization until the date of death from any cause. Objective Response Rate (ORR). ORR is defined as the proportion of participants who have a best overall response of Complete Response (CR) or Partial Response (PR) as assessed by Independent Review Committee (IRC) per RECIST 1.1. Duration Of Response (DOR). DOR, defined as the time from the date of the first response (CR/PR) until the date of progressive disease as assessed by IRC per RECIST 1.1 or date of death from any cause, whichever is earliest. Median follow-up time was 33.28 months in the zolbetuximab+ FOLFOX arm and 31.38 months in the placebo + FOLFOX arm. Safety and tolerability assessed by adverse events (AEs)

Trial name: SPOTLIGHT	NCT number: NCT03504397

	Health Related Quality of Life (HRQoL) measured by the European Organization for Research and Treatment of Cancer (EORTC-QLQ-C30) questionnaire, the QLQ-OG25 questionnaire, the Global Pain (GP) questionnaire and the EuroQOL Five Dimensions Questionnaire 5L (EQ-5D-5L) questionnaire
	
	Time to confirmed deterioration (TTCD) calculated using the physical function (PF), OG25-Pain and Global Health Status (GHS)/QoL scores as measured by EORTC QLQ-C30 and QLQ-OG25. TTCD is defined as time to first confirmed deterioration (time from randomization to first clinically meaningful deterioration that is confirmed at the next scheduled visit).
	
	Endpoints included in this application:
	• PFS per RECIST v1.1 by ICR
	• OS
	• Clinical response: ORR and DOR
	• Patient reported outcomes:
	  • Change from baseline in patient reported outcome assessment measured by the EQ-5D-5L
	  • Mean scores in patient reported outcome assessment measured by the EQ-5D-5L

Method of analysis	All efficacy analyses were intention-to-treat analyses. The Kaplan-Meier method was used to estimate the distribution of progression-free survival, overall survival, and duration of response, and a stratified log-rank test was used to assess between-group differences. A Cox proportional hazard model, stratified according to region (Asia *vs* non-Asia), number of organs with metastases (0–2 *vs* ≥3), and previous gastrectomy (yes *vs* no), was used to estimate hazard ratios (HRs) and corresponding 95% CIs. The Cochran-Mantel-Haenszel test was used to assess between-group differences in objective response rate.
Subgroup analyses	Prespecified subgroup analysis were carried out for PFS and OS: age, sex, geographical region, number of metastatic sites, prior gastrectomy, tumour type, country, and race at baseline
Other relevant information	NA

Table 57. Main characteristic of studies included (GLOW)

Trial name: GLOW	NCT number: NCT03653507
Objective	Establish the relative efficacy and safety of zolbetuximab given in addition to chemotherapy vs chemotherapy alone
Publications – title, author, journal, year	Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med 2023;29:2133-41.[10] Shitara K, Shah MA, Lordick F et al. Zolbetuximab in Gastric or Gastroesophageal Junction Adenocarcinoma. N Engl J Med.. 2024 Sep 26;391(12):1159-1162. doi: 10.1056/NEJMc2409512. Epub 2024 Sep [26]
Study type and design	GLOW is a Phase 3, multicentre, double-blind RCT designed to evaluate the efficacy and safety of zolbetuximab + CAPOX versus placebo + CAPOX as first-line treatment in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma Patients were randomly assigned 1:1 to receive intravenous infusion of zolbetuximab 800 mg/m2 (cycle 1, day 1) followed by 600 mg/m2 (day 1 of subsequent cycles) plus CAPOX (oral capecitabine, 1,000 mg/m2, twice daily on days 1–14 of each cycle; intravenous infusion of oxaliplatin, 130 mg/m2, day 1 of each cycle) for eight 21-day cycles versus placebo plus CAPOX. Randomization was performed by blinded site staff using interactive response technology by block randomization with block sizes of two and was stratified according to region (Asia versus non-Asia), number of organs with metastases (0–2 versus ≥3) and prior gastrectomy (yes versus no). The randomization list and study drug blinding were maintained by the interactive response technology system. The sponsor, investigators, clinical staff and patients remained blinded to treatment throughout the study.
Sample size (n)	Zolbetuximab (800 mg/m² loading dose followed by 600 mg/m² every 3 weeks) plus CAPOX (every 3 weeks (n=254) Placebo plus CAPOX (every 3 weeks) (n=253)
Main inclusion criteria	Inclusion criteria: ● Age ≥18 years with: ○ Histologically confirmed diagnosis of G/GEJ adenocarcinoma, radically confirmed and evaluable (measurable and/or non-measurable disease according to RECIST v1.1. per local assessment) locally advanced unresectable or metastatic disease ○ CLDN18.2 in ≥75% of tumour cells as determined by central IHC testing ○ HER2-negative tumour

Trial name: GLOW	NCT number: NCT03653507
Main exclusion criteria	• Prior systemic chemotherapy for locally advanced unresectable or metastatic G/GEJ adenocarcinoma (patients may have received either neo-adjuvant or adjuvant chemotherapy, immunotherapy, or other systemic anticancer therapies as long as it was completed ≥6 months before randomization) • Radiotherapy for locally advanced unresectable or metastatic G/GEJ adenocarcinoma ≤14 days prior to randomization and has not recovered from any related toxicity • Systemic immunosuppressive therapy • Prior severe allergic reaction or intolerance to known ingredients of zolbetuximab or other monoclonal antibodies, including humanised or chimeric antibodies • Prior severe allergic reaction or intolerance to any component of CAPOX • Known dihydropyrimidine dehydrogenase deficiency • An active autoimmune disease that has required systemic treated ≤3 months prior to randomization • Significant CV disease
Intervention	Zolbetuximab (800 mg/m² loading dose followed by 600 mg/m² every 3 weeks) plus CAPOX (oral capecitabine, 1,000 mg/m2, twice daily on days 1–14 of each cycle; intravenous infusion of oxaliplatin, 130 mg/m2, day 1 of each cycle) for eight 21-day cycle) (n=254)
Comparator(s)	Placebo plus CAPOX (oral capecitabine, 1,000 mg/m2, twice daily on days 1–14 of each cycle; intravenous infusion of oxaliplatin, 130 mg/m2, day 1 of each cycle) for eight 21-day cycle) (n=253)
Follow-up time	At the final data cut the median duration of follow-up (months) 31.70 months in the zolbetuximab + CAPOX arm and 32.95 months in the placebo+ CAPOX arm
Is the study used in the health economic model?	Yes

Trial name: GLOW	NCT number: NCT03653507

Primary, secondary and exploratory endpoints	Progression free survival (PFS). PFS is defined as the time from the date of randomization until the date of radiological progressive disease (per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 by Independent Review Committee (IRC)) or death from any cause, whichever is earliest.
	
	Overall Survival (OS). OS is defined as the time from the date of randomization until the date of death from any cause.
	
	Time to confirmed deterioration (TTCD) in participant-reported physical functioning and Global Health Status/Quality of Life (GHS/QoL). TTCD is measured by EORTC QLQ-C30 and QLQ-OG25 plus STO22 Belching subscale and defined as time to first confirmed deterioration; that is, time from randomization to first clinically meaningful deterioration that is confirmed at the next scheduled visit.
	
	Objective Response Rate (ORR). ORR is defined as the proportion of participants who have a best overall response of Complete Response (CR) or Partial Response (PR) as assessed by Independent Review Committee (IRC) per RECIST 1.1.
	
	Duration Of Response (DOR). DOR, defined as the time from the date of the first response (CR/PR) until the date of progressive disease as assessed by IRC per RECIST 1.1 or date of death from any cause, whichever is earliest.
	
	Safety and tolerability assessed by adverse events (AEs)
	
	Health Related Quality of Life (HRQoL) measured by the European Organization for Research and Treatment of Cancer (EORTC-QLQ-C30) questionnaire, the QLQ-OG25 questionnaire, the Global Pain (GP) questionnaire and the EuroQOL Five Dimensions Questionnaire 5L (EQ-5D-5L) questionnaire
	
	Endpoints included in this application:
	
	• PFS per RECIST v1.1 by ICR
	• OS
	• Clinical response: ORR and DOR
	• Patient reported outcomes:
	  ◦ Change from baseline in patient reported outcome assessment measured by the EQ-5D-5L
	  ◦ Mean scores in patient reported outcome assessment measured by the EQ-5D-5L

Method of analysis	All efficacy analyses were intention-to-treat analyses. The Kaplan–Meier method was used to estimate the median and distribution of PFS, OS and DOR; stratified log-rank tests were used to assess between-group differences, and the stratified Cox proportional hazard model was used to calculate HRs and associated 95% CIs. The Cochran–

Trial name: GLOW	NCT number: NCT03653507
	Mantel–Haenszel test was used to assess between-group differences in ORR.
Subgroup analyses	Prespecified subgroup analysis were carried out for PFS and OS: age, sex, geographical region, number of metastatic sites, prior gastrectomy, tumour type, country, and race at baseline
Other relevant information	NA

Table 58 Main characteristic of studies included (CheckMate-649)

Trial name: CheckMate-649 [27, 40]	NCT number: NCT02872116
Objective	To compare the efficacy and safety of nivolumab given in addition to chemotherapy vs chemotherapy alone in patients with locally advanced or metastatic non-HER2 positive gastric, esophageal or gastro-esophageal junction adenocarcinoma.
Publications – title, author, journal, year	Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27-40.[27] Janjigian YY, Shitara K, Moehler MH, Garrido M, Gallardo C, Shen L, et al. Nivolumab (NIVO) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 3-year follow-up from CheckMate 649. Journal of Clinical Oncology. 2023;41(16_suppl):4025[40] Shitara K, Moehler M, Ajani JA, Shen L, Garrido M, Gallardo C, et al. Nivolumab plus chemotherapy vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: 4-year follow-up of the CheckMate 649 study. ASCO Gastrointestinal Cancers Symposium. San Francisco, CA: US; 2024.[29]
Study type and design	Phase 3, multi-centre, randomised, open-label, active-controlled study. Patients were randomised to receive nivolumab plus chemotherapy or chemotherapy alone. Randomization was stratified by tumour cell PD-L1 (≥1% vs. <1%), region (Asia vs. US/Canada vs. rest of world), ECOG performance status (0 vs. 1), and chemotherapy (XELOX vs. FOLFOX). Treatment for all arms was continued until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Trial name: CheckMate-649 [27, 40]	NCT number: NCT02872116
	Treatment with nivolumab monotherapy following nivolumab plus ipilimumab, was given for up to 24 months in the absence of disease progression or unacceptable toxicity.
Sample size (n)	1,581 patients randomised to receive nivolumab plus XELOX/FOLFOX (n=789) and XELOX/FOLFOX (n=792) of which 955 (60%) were PD-L1 positive with a CPS ≥ 5 (nivo + XELOX/FOLFOX; n=473; XELOX/FOLFOX; n=482)
Main inclusion criteria	Eligible patients were men or women, >18 years old, with previously untreated, unresectable, non-HER-2-positive GC, EC, or GEJC, and histologically confirmed predominant adenocarcinoma, regardless of PD-L1 expression Additional inclusion criteria were as follows: • No prior systemic treatment, including HER2 inhibitors, as primary therapy for advanced or metastatic disease • Prior adjuvant treatment (chemotherapy and/or radiotherapy) must have been completed at least 6 months prior to randomization • Presence of at least one measurable lesion or evaluable disease by CT or MRI per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria • Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 • An evaluable tumour cell PD-L1 expression classification (≥1% or <1%, or indeterminate) by the central lab
Main exclusion criteria	•Known HER2-positive status • Presence of tumour cells in the brain or spinal cord that have not been treated • Active known or suspected autoimmune disease • Any serious or uncontrolled medical disorder or active infection • Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) • Any positive test result for hepatitis B or C indicating acute or chronic infection
Intervention	Nivo + CAPOX/FOLFOX (n = 789); (CPS≥5 subgroup: n=473)
Comparator(s)	CAPOX/FOLFOX (n = 792); (CPS≥5 subgroup; n=482)
Follow-up time	Not reported (minimum follow up 48.1 months). At the latest data cut, efficacy inputs were based on data with minimum follow-up time of 4 years, reported in Shitara 2024[29]
Is the study used in the health economic model?	Yes (cost minimization)
Primary, secondary and exploratory endpoints	Dual primary endpoint: OS in PD-L1 positive (CPS ≥5) patients based on the PD-L1 immunohistochemistry (IHC) 28-8 pharmDX and PFS (per BICR) in PD-L1 positive (CPS ≥5) patients Secondary endpoints: OS in PD-L1 positive (CPS ≥1) patients and in all randomised patients (hierarchically tested) OS in PD-L1 positive (CPS ≥10) patients PFS (per BICR) in PD-L1 positive (CPS ≥1, ≥10) patients or

Trial name: **CheckMate-649** [27, 40]	NCT number: NCT02872116
	all randomised patients ORR (per BICR) in PD-L1 positive (CPS ≥1, ≥5, ≥10) patients or all randomised patients Safety and tolerability Exploratory: DRR by BICR and by investigator DOR by BICR and by investigator TTSD using GaCS of FACT-Ga PFS and ORR by investigator in subjects with different PD-L1 CPS cutoffs PFS2 or TSST PFS and ORR by BICR and by investigator and OS in subjects with different PD-L1 CPS cutoffs Incidence of death, AEs, SAEs, IMAEs and select AEs OS, PFS, and ORR in subjects with different MSI status Nivolumab ADA and characterization of Nab EQ-5D-3L descriptive system and VAS FACT-Ga including GaCS and FACT-G7
Method of analysis	The proportional hazards assumption was tested using a Cox model with treatment and treatment by time interaction at prespecified significance level of 0·1. For time-to-event endpoints, the median was estimated using the Kaplan-Meier method, and the corresponding two-sided 95% confidence intervals (CIs) were calculated using the log-log transformation method. A post-hoc exploratory analysis was performed to assess a potential treatment effect by baseline characteristics on OS using Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction as terms
Subgroup analyses	For OS and PFS prespecified subgroup analyses were conducted by age, sex, race, region, ECOG status, tumour location, prior surgery, organs with metastasis, liver metastasis, signed ring cell carcinoma, lauren classification, tumour cell PD-(L)1 expression and chemotherapy regimen
Other relevant information	NA

Table 59 Main characteristic of studies included (KEYNOTE-859)

Trial name: **KEYNOTE-859**	NCT number: NCT03675737
Objective	To compare the efficacy and safety of pembrolizumab plus chemotherapy with placebo plus chemotherapy in patients with locally advanced or metastatic HER2-negative gastric or gastro-esophageal junction adenocarcinoma.
Publications – title, author, journal, year	Rha SY, Oh DY, Yanez P, Bai Y, Ryu MH, Lee J, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2023;24(11):1181-95.**[31]**
Study type and design	Multicentre, double-blind, placebo-controlled, randomised, phase 3 trial

Trial name: KEYNOTE-859		NCT number: NCT03675737
Sample size (n)	Pembro + CAPOX/FOLFOX (n = 790) CAPOX/FOLFOX (n = 789)	
Main inclusion criteria	• locally advanced unresectable or metastatic G/GEJ adenocarcinoma with known PD-(L)1 expression status • HER2 negative cancer • Measurable disease • ECOG 0-1 within 3 days prior to the start of study intervention • Adequate organ function within 10 days prior to the start of study treatment	
Main exclusion criteria	• Has squamous cell or undifferentiated gastric cancer • Has had previous therapy for locally advanced, unresectable or metastatic gastric/GEJ cancer. Participants may have received prior neoadjuvant and/or adjuvant therapy as long as it was completed ≥6 months prior to randomization • Has received prior therapy with an anti-programmed cell death (PD)-1, anti-PD-(L)1 or anti-programmed cell death ligand 2 (PD-L2) agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), OX- 40, CD137) • Has received prior systemic anticancer therapy including investigational agents within 4 weeks prior to randomization or has not recovered from all adverse events (AEs) due to any previous therapies to ≤Grade 1 or baseline • Has received prior radiotherapy within 2 weeks prior to study start or has not recovered from all previous radiation-related toxicities, required corticosteroids, and have not had radiation pneumonitis. • Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study treatment • Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment • Has a known additional malignancy that is progressing or has required active treatment within the past 5 years with the exception of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy • Has known active CNS metastases and/or carcinomatous meningitis • Has an active autoimmune disease that has required systemic treatment in past 2 years • Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis • Has an active infection requiring systemic therapy • Has a known history of HIV infection • Has a known history of Hepatitis B or known active Hepatitis C virus • Has a known history of active tuberculosis • Has hypokalemia, hypomagnesemia, hypocalcemia	

Trial name: KEYNOTE-859	NCT number: NCT03675737
	• Has had an allogenic tissue/solid organ transplant
Intervention	Pembro + CAPOX/FOLFOX (n = 790); CPS≥5 subgroup: n=379
Comparator(s)	CAPOX/FOLFOX (n = 789); CPS≥5 subgroup: n=388
Follow-up time	Median duration of follow up 13 months. Interim analysis: Oct 3, 2022 [31]. Final analysis not published
Is the study used in the health economic model?	Yes (cost minimization)
Primary, secondary and exploratory endpoints	Primary: Overall Survival (OS) in All Participants, OS In Participants With PD-L1 Combined Positive Score (CPS) ≥1, OS In Participants With PD-L1 Combined Positive Score (CPS) ≥10. OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the analysis were censored at the date of the last follow-up. OS was estimated using the product-limit (Kaplan-Meier) method for censored data. Progression Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Assessed by Blinded Independent Central Review (BICR) in All Participants, PFS in Participants With PD-L1 Combined Positive Score (CPS) ≥1, PFS in Participants With PD-L1 Combined Positive Score (CPS) ≥10 Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Assessed by Blinded Independent Central Review (BICR) in All Participants, ORR in Participants With PD-L1 Combined Positive Score (CPS) ≥1, ORR in Participants With PD-L1 Combined Positive Score (CPS) ≥10 Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Assessed by Blinded Independent Central Review (BICR) in All Participants, DOR in Participants With PD-L1 Combined Positive Score (CPS) ≥1, DOR in Participants With PD-L1 Combined Positive Score (CPS) ≥10 [Time Frame: Up to 49.5 months] Number of Participants Who Experienced an Adverse Event (AE) Number of Participants Who Discontinued Study Treatment Due To an Adverse Event (AE)
Method of analysis	Overall survival, progression-free survival, and duration of response were estimated using the non-parametric Kaplan-Meier method. Between-group differences in overall survival and progression-free survival were assessed using a stratified log-rank test. The HRs and associated 95% CIs for overall survival and progression-free survival were assessed using a stratified Cox proportional hazards model with

Trial name: KEYNOTE-859	NCT number: NCT03675737
	the Efron method of handling ties. The proportional hazards assumption was evaluated using the Cox regression model with treatment and treatment by time interaction
Subgroup analyses	For OS, PFS and DOR prespecified subgroup analyses by age, sex, race, stratification factors, microsatellite instability status, ECOG status, disease status, primary location, histological subtype, liver Metastases, previous gastrectomy or oesophagectomy, tumour burden and number of metastases
Other relevant information	NA

Appendix B. Efficacy results per study

Results per study

Table 60 Results per study (SPOTLIGHT/GLOW) (integrated analysis) (final data cut SPOTLIGHT: 8 September 2023; final GLOW data-cut: dated 12 January 2024). [26]

Results of SPOTLIGHT/GLOW (integrated analysis)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS assessed by IRC (median duration, months)	Zolbe + chemo	537	9.17 (8.44–10.41)	0.99	NA	NA	HR: 0.712	0.610- 0.831	<0.0001	The Kaplan-Meier method was used to estimate the distribution of progression-free survival, overall survival, and duration of response, and a stratified log-rank test was used to assess between-group differences. A Cox proportional hazard model, stratified according to region, number of organs with metastases, and previous gastrectomy, was used to estimate hazard ratios (HRs) and corresponding 95% CIs.	Shitara et al 2024[26]
	Placebo + chemo	535	8.18 (7.59-8.38)								Shitara et al 2024[26]
OS (median duration, months)	Zolbe + chemo	537	16.39 (14.98-17.87)	2.69	NA	NA	HR: 0.774	0.672-0.892	0.0002		Shitara et al 2024[26]
	Placebo + chemo	535	13.70 (12.32-15.28)								Shitara et al 2024[26]
Duration of response (DOR)	Zolbe + chemo	537	8.1 (6.4-9.0)	1.6	NA	NA	NA	NA	NA		Shitara et al 2024[26]

Results of SPOTLIGHT/GLOW (integrated analysis)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
(median duration, months)	Chemo	535	6.5 (6.2-7.7)								Shitara et al 2024[26]
Objective response rate (ORR) (%)	Zolbe + chemo	537	45.4 (41.2-49.8)	1.8	NA	NA	NA	NA	NA	The Cochran-Mantel-Haenszel test was used to assess between-group differences in objective response rate.	Shitara et al 2024[26]
	Chemo	535	43.6 (39.3-47.9)								Shitara et al 2024[26]

Table 61. Results per study (SPOTLIGHT) (final data cut SPOTLIGHT: 8 September 2023) [26]

Results of SPOTLIGHT											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS assessed	Zolbe + chemo	283	11.0 (9.7-12.5)	2.1	NA	NA	HR: 0.73	(0.59-0.91)	NA	The Kaplan-Meier method was used to estimate the	Shitara et al 2024[26]

Results of SPOTLIGHT											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
by IRC (median duration, months)	Placebo + chemo	282	8.9 (8.2-10.4)							distribution of progression-free survival, overall survival, and duration of response, and a stratified log-rank test was used to assess between-group differences. A Cox proportional hazard model, stratified according to region, number of organs with metastases, and previous gastrectomy, was used to estimate hazard ratios (HRs) and corresponding 95% CIs.	Shitara et al 2024[26]
OS (median duration, months)	Zolbe + chemo	283	18.2 (16.1-20.6)	2.6	NA	NA	HR: 0.78	(0.64-0.95)	NA		Shitara et al 2024[26]
	Placebo + chemo	282	15.6 (13.7-16.9)								Shitara et al 2024[26]
Duration of response (DOR) (median duration, months)	Zolbe + chemo	283	9.0 (7.5–10.4)	0.9	NA	NA	NA	NA	NA		Shitara et al 2024[26]
	Chemo	282	8.1 (6.5–11.4)								Shitara et al 2024[26]
Objective response	Zolbe + chemo	283	48.1 (42.1–54.1)	0.6	NA	NA	NA	NA	NA	The Cochran-Mantel-Haenszel test was used to assess	Shitara et al 2024[26]

Results of SPOTLIGHT											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
rate (ORR) (%)	Chemo	282	47.5 (41.6–53.5)							between-group differences in objective response rate.	Shitara et al 2024[26]

Table 62. Results per study (GLOW) (final GLOW data-cut: dated 12 January 2024). [26]

Results of GLOW											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS assessed by IRC (median duration, months)	Zolbe + chemo	254	8.2 (7.3-8.8)	1.4	NA	NA	HR: 0.69	(0.55-0.86)	NA	The Kaplan-Meier method was used to estimate the distribution of progression-free survival, overall survival, and duration of response, and a stratified log-rank test was used to assess between-group differences. A Cox proportional hazard model, stratified	Shitara et al 2024[26]
	Placebo + chemo	253	6.8 (6.1-8.1								Shitara et al 2024[26]
OS (median	Zolbe + chemo	254	14.3 (12.1-16.4)	2.1	NA	NA	HR: 0.76	(0.62-0.94)	NA		Shitara et al 2024[26]

Results of GLOW											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
duration, months)	Placebo + chemo	253	12.2 (10.3-13.7)							according to region, number of organs with metastases, and previous gastrectomy, was used to estimate hazard ratios (HRs) and corresponding 95% CIs.	Shitara et al 2024[26]
Duration of response (DOR) (median duration, months)	Zolbe + chemo	254	6.3 (5.4-8.3)	0.2	NA	NA	NA	NA	NA		Shitara et al 2024[26]
	Chemo	253	6.1 (4.4-6.3)								Shitara et al 2024[26]
Objective response rate (ORR) (%)	Zolbe + chemo	254	42.5 (36.4-48.9)	3.4	NA	NA	NA	NA	NA	The Cochran-Mantel-Haenszel test was used to assess between-group differences in objective response rate.	Shitara et al 2024[26]
	Chemo	253	39.1 (33.1-45.4)								Shitara et al 2024[26]

Table 63. Results per study (CheckMate 649, CPS≥5) [29] (48 months (4year) follow up)[29]

Results of CheckMate 649											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS assessed by IRC (median duration, months)	Nivolumab + chemo	473	8.3 (7.0-9.3)	2.2	NA	NA	HR= 0.71	0.61-0.82	p<0.0001	The survival rates are based on the Kaplan–Meier estimator. The estimate of the hazard ratio between treatment groups was calculated using a stratified Cox proportional hazards model, with treatment as the sole covariate. Ties were handled using the exact method. Confidence intervals (CIs) adjusted for the corresponding significance level for the hazard ratio were provided	Shitara 2024[29]
	chemo	482	6.1 (5.5-6.9)								Shitara 2024[29]
OS (median duration, months)	Nivolumab + chemo	473	14.4 (13.1-16.2)	3.3	NA NA	NA NA	HR=0.70	0.61-0.82	p<0.0001		Shitara 2024[29]
	chemo	482	11.1 (10.1-12.1)								Shitara 2024[29]
Objective response rate (ORR) (%)	Nivolumab + chemo	473	50 (55-65)	5	NA	NA	NA	NA	NA		Shitara et al 2024[29]
	Chemo	482	45 (40-50)								Shitara et al 2024[29]

Results of CheckMate 649											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Duration of response (DOR) (median duration, months)	Nivolumab + chemo	473	9.6 (8.2-12.4)	2.6	NA	NA	NA	NA	NA		Shitara et al 2024[29]
	Chemo	482	7 (5.6-8)								Shitara et al 2024[29]

Table 64. Results per study (KEYNOTE 859) (CPS≥5) (interim analysis, data cut October 3 2022) [1, 32]

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS assessed by IRC (median duration, months)	Pembro + chemo	379	7.1 (6.1-8.3)	21.5	NA	NA	HR 0.69	0.58-0.8	p<0.0001	Overall survival, progression-free survival, and duration of response were estimated using the non-parametric Kaplan-Meier method. Between-group differences in overall survival and progression-free survival	Medicinrådet 2024 /EPAR[1, 32]
	Chemo	388	5.6 (5.4-5.9)								Medicinrådet 2024 /EPAR [1, 32]

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (median duration, months)	Pembro + chemo	379	14.0 (12.1-15.4)	2.5	NA	NA	HR 0.70	0.60-0.82	p<0.0001	were assessed using a stratified log-rank test. The HRs and associated 95% CIs for overall survival and progressionfree survival were assessed using a stratified Cox proportional hazards model with the Efron method of handling ties.	Medicinrådet 2024 /EPAR [1, 32]
	Chemo	388	11.5 (10.3;12.5)								Medicinrådet 2024 /EPAR Medicinrådet, [1, 32]

Appendix C. Comparative analysis of efficacy

C.1 Clinical evidence synthesis

C.1.1 Background

No direct evidence is available comparing zolbetuximab to the main standard of care in clinical practice. PD-(L)1 inhibitors in combination with chemotherapy have been shown to be cost-effective compared to chemotherapy alone and therefore seen as the main standard of care.

Pembrolizumab have been approved for patients with CPS≥1 and nivolumab is approved for patients with CPS≥5. Both PD-(L)1 inhibitors and zolbetuximab are documented efficacious and tolerable treatment options in HER2-negative metastatic G/GEJC patients. PD-(L)1 inhibitors are documented in a subgroup of patients with CPS≥1/CPS≥5 and zolbetuximab is documented in a subgroup of patients with CLDN18.2 positive tumours.

C.1.2 Objective

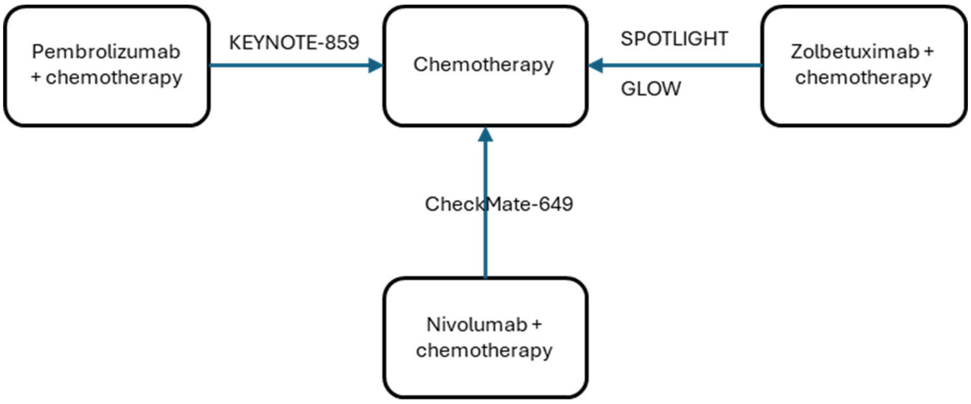
The purpose of the indirect treatment comparison was to establish the relative efficacy of zolbetuximab in combination with chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma compared to pembrolizumab in combination with chemotherapy and nivolumab in combination with chemotherapy, respectively.

C.2 Methods

The SLR (described in section Appendix H) identified 4 clinical trials. [24] Figure 23: presents the overall network of evidence, which contains all four studies in the evidence base. All studies compared two treatment regimens: one of zolbetuximab, nivolumab or pembrolizumab in addition to chemotherapy, compared to chemotherapy alone (placebo given in addition to chemotherapy).

Under the assumptions that the new regimens' relative efficacy is similar irrespective of the chemotherapy backbone and irrespective of the chemotherapy comparator, the relative efficacy can be established using chemotherapy as a common comparator arm.

Figure 23: Overall network diagram



Note: The chemotherapy node in the network represents CAPOX (Q3W), FOLFOX or mFOLFOX6 (Q2W), FP (Q3W), or XELOX (Q3W).

Abbreviations: CAPOX capecitabine and oxaliplatin; FP 5-fluorouracil + cisplatin; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; mFOLFOX6 modified FOLFOX; XELOX capecitabine plus oxaliplatin

Randomization in both KEYNOTE-859 and CheckMate-649 was stratified for PD-(L)1 expression. In KEYNOTE-859 the primary endpoint was assessed in the intention-to-treat (ITT) population, and the populations with CPS≥ 1, and CPS ≥10. In CheckMate 649 the predefined primary analysis was in patients with CPS≥ 5. Since the recommended use of pembolizumab in Denmark is restricted to a subgroup of the approved indications, data from the CPS≥5 was used for both pembrolizumab and nivolumab.

C.2.1 Outcomes

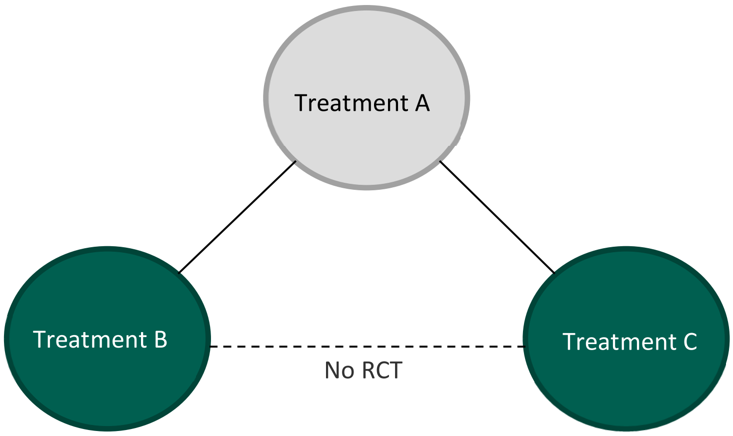
OS and PFS was measured in all trials. In the indirect treatment comparison, hazard ratios were used a measure of treatment effects from the individual trials.

C.2.2 Statistical method

Clinical efficacy (OS and PFS) was compared using separate Bucher analysis (zolbetuximab compared to pembrolizumab and zolbetuximab compared to nivolumab, respectively). Medicinrådet have previously concluded that the two PD-(L)1 inhibitors are clinically equivalent for patients with CPS ≥ 5. [1], however, the indirect comparisons were performed without any a'priori assumptions on relative effects between the PD-(L)1 comparators.

The Bucher adjusted indirect comparison method is one approach that can be applied when there is an absence of direct evidence about relative performance between treatments and there is a common comparator [45]. Suppose that there are two treatments B and C that are compared against a common comparator, treatment A, via two distinct sets of randomised trials. The Bucher method can be used to derive an indirect estimate of the relative effect of B versus C on the basis of the direct estimates of the relative effects of B versus A and C versus A (Figure 24).

Figure 24. Example treatment network



Let HR_{AB}, HR_{AC} and HR_{BC} represent the true relative effects of B versus A, C versus A and C versus B, respectively. Similarly, $\log \widehat{HR}_{AB}$ and $\log \widehat{HR}_{AC}$ represent the direct estimates of $\log HR_{AB}$ and $\log HR_{AC}$ respectively and $\text{SE}(\log \widehat{HR}_{AB})$ and $\text{SE}(\log \widehat{HR}_{AC})$ be the estimated log-hazard ratios and standard errors.

The indirect estimate of $\log OR_{BC}$ and its corresponding standard error can be obtained using the Bucher method by,

$$\log(\widehat{HR}_{BC}) = \log(\widehat{HR}_{AC}) - \log(\widehat{HR}_{AB})$$

$$\text{SE}\big(\log(\widehat{HR}_{BC})\big) = \sqrt{\text{SE}\big(\log(\widehat{HR}_{AB})\big)^2 + \text{SE}\big(\log(\widehat{HR}_{AC})\big)^2}\,.$$

Thus, this information can be combined and exponentiated to form a 95% confidence interval (CI) estimate of HR_{BC}.

In the various analyses, the estimated log-hazard ratios and standard errors were either obtain from a single study (comparators) or estimates from the pooled dataset (zolbetuximab). Standard errors were in all cases estimated from 95% confidence intervals for HR as the difference in logarithms of confidence interval limits divided by 2×1.96.

Absolute effects were estimate as percentage points difference in 12-months rate of PFS and OS and difference in median PFS and median OS. The differences were calculated under the assumption of proportional hazards and assuming constant hazards:

Difference in 12 month survival: $e^{\ln(ACR)*HR-ACR}$, where ACR is the assumed comparator survival rate

Difference in median survival: AmR/HR – AmR, where AmR is the assumed assumed median survival.

ACR was set to the 12-month survival rates in the nivolumab arm of the CheckMate study and AmR was set to the mid-point of median survival in the pembrolizumab arm of KEYNOTE-859 and the nivolumab arm of CheckMate-649 .

All calculation were performed in *Microsoft Excel.*

C.2.3 Assumptions

Similarity

The four trials included in the network are summarised in Table 65 to Table 68. The studies were of similar design and quality. The studies were double-blinded placebo-controlled trials except CheckMate-649 which was a randomized open-label design but with OS and PFS (assessed by independent outcomes review committee) this is unlikely to influence the relative efficacy.

Baseline characteristics from the clinical trials for zolbetuximab, pembrolizumab and nivolumab in patients with advanced/metastatic G/GEJ adenocarcinoma are presented in Table 66.

The median age is comparable across trials (59-62 years) and the share of male patients included is approx. 62-71% across the clinical trials. The clinical trials, however, included a varying proportion of white patients; in the clinical trials of zolbetuximab approximately half of all included patients were white, whereas the single included clinical study of nivolumab included 75% of patients being white.

Distribution of ECOG score was comparable across trials and tumour location was fairly comparable across trials. All patients were HER2 negative in the clinical trials.

A fundamental difference is that the zolbetuximab trials only included patients with claudin 18.2 expression while the PD-(L)1 inhibitor trials did not collect CLDN18.2 status. The questions are 1) is the efficacy of zolbetuximab dependent on PD-(L)1 status and is efficacy of PD-(L)1 inhibition dependent on CDLN18.2 status and 2) are expected outcomes with backbone chemotherapy (as common comparator) sufficiently similar.

There is no known biological mechanism by which PD-(L)1 CPS could affect zolbetuximab's mechanism of action. Furthermore, it is documented that the treatment effect of zolbetuximab is independent of combined positive score (CPS). Thus, the treatment effect of zolbetuximab is favourable both in patients eligible for a PD-(L)1 inhibitor and in patients not eligible for treatment with a PD-(L)1 inhibitor. Subgroup analysis of efficacy data from the SPOTLIGHT and GLOW trials was performed to investigate the effect of PD-(L)1 expression thresholds (CPS <1 vs CPS ≥1; CPS <5 vs CPS ≥5; and overall) on PFS and OS, and the relationship between baseline characteristics and PD-(L)1 expression distribution.

In addition, it has been demonstrated that CLDN18.2 expression have no impact on treatment outcomes with chemotherapy or PD-(L)1 inhibitors [39]. Among patients treated with PD-(L)1 inhibitors (n=164), the objective response rates (ORRs) were 14.3% and 19.0% (P = 0.810), and the duration of treatment (DCRs) were 31.7% and 48.0% (P = 0.301) in the CLDN18.2-positive (moderate-to-strong expression in ≥75%) and CLDN18.2-negative groups, respectively. The median PFS with PD-(L)1 inhibitor was 1.8 and 1.9 months in the CLDN-positive and CLDN-negative groups, respectively [HR 1.07 [95% CI 0.75;1.52]; p = 0.725] [39]. Hence, treatment with a PD-(L)1 inhibitor appears to be independent of CLDN18.2 status.

All studies compared one intervention in combination with chemotherapy with chemotherapy alone. For the Bucher analyses equivalence of the chemo-backbone in the clinical evidence base was assumed:

a. CAPOX

b. FOLFOX

c. Fluorouracil + cisplatin (CF)

The assumption is supported by the fact that all of the included chemotherapy regimens were platinum-based. In CheckMate-649 and KEYNOTE-859, the choice of chemotherapy was determined by the investigator before randomization; as such, the characteristics of patients receiving each chemotherapy backbone are expected to be balanced across treatment arm and within-trial OS HRs of subgroups by specific chemotherapy in CheckMate-649 and KEYNOTE-859 were broadly similar. Furthermore, HRs for SPOTLIGHT and GLOW (for zolbetuximab + chemotherapy versus chemotherapy) were very similar, despite different chemotherapy backbone (i.e. CAPOX in GLOW and FOLFOX in SPOTLIGHT).

In a recent US retrospective research study that used tissue samples from a total of 304 patients with G/GEJ adenocarcinoma, along with clinical data extracted from patient medical records, it was demonstrated that the overall prevalence of CLDN18.2-positive tumours (with ≥75% cutoff) was 47.2% in HER2- patients. Among CLDN18.2 positive patients more than two thirds had a CPS≥1. The study furthermore demonstrated that there was no association between overall survival and CLDN18.2 positivity [12]. This is supported by another study evaluating the association of CLDN18 protein expression with clinicopathological features and prognosis in a series of 350 advanced G/GEJ adenocarcinomas where it was documented that CLDN18 expression was not correlated with OS in G/GEJ cancer [46], a finding that was also confirmed in another study in a Japanese population [39].

In summary,

- Backbone chemo therapies are comparable across the included pivotal trials
- Efficacy of the backbone, platinum-based chemotherapy appears independent of both PD-(L)1 status and CDLN18.2 status in HER2- locally advanced or metastatic G/GEJ cancer [32]
- Efficacy of PD-(L)1 inhibitors depend on tumour PD-(L)1 expression as measured by CPS.[34, 35] but not of CDLN18.2 status [32]
- On the other hand, efficacy of zolbetuximab appear independent of PD-(L)1 status.

Based on this it was concluded that the chemo-therapy backbone was sufficiently similar to allow indirect comparison via chemotherapy as the common comparator and, furthermore, that relative efficacy estimates from the two zolbetuximab trials (comparing to mFOLFOX6 and CAPOX, respectively) could be sourced from the integrated analysis (pooled dataset).

Furthermore, it was concluded that it is acceptable to compare relative treatment effect from the trials despite the selection of patients was based on different biomarkers in the two zolbetuximab studies and the PD-(L)1 inhibitor studies, because a large overlap of patients can be expected and because the potency of the two mechanisms of action (CDLN18.2 and PD-(L)1 inhibition, respectively) seem independent of each other (CDLN18.2 status is not an effect modifier for PD-(L)1 inhibition and *vice versa*).

Table 65: Comparative summary of studies considered for indirect treatment comparison

	SPOTLIGHT	GLOW	CheckMate-649	KEYNOTE-859
Study design	Phase 3, double-blind RCT	Phase 3, double-blind RCT	Phase 3, randomised, open-label	Phase 3, randomised, double-blind
Population	CLDN18.2-positive (≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative locally advanced unresectable/metastatic G/GEJ adenocarcinoma	CLDN18.2-positive (≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative locally advanced unresectable/metastatic G/GEJ adenocarcinoma	Previously untreated, unresectable advanced or metastatic HER2-negative, G/GEJ, or oesophageal adenocarcinoma, regardless of PD-(L)1 expression	Previously untreated histologically or cytologically confirmed locally advanced or metastatic HER2-negative G/GEJ adenocarcinoma
Intervention	Zolbetuximab + mFOLFOX6 (n = 283)	Zolbetuximab + CAPOX (n = 254)	Nivolumab + CAPOX/FOLFOX (n = 789)	Pembrolizumab + CAPOX/CF (n = 790)

Comparator	mFOLFOX6 (n = 282)	CAPOX (n = 253)	CAPOX/FOLFOX (n = 792)	CAPOX/CF (n = 789)
Primary endpoint	PFS	PFS	PFS and OS (patients with CPS≥5)	OS (all pt, patients with CPS≥1 and pt with CPS≥10)
Median follow-up duration	31.38–33.28 months*	31.70–32.95 months*	Not reported (minimum follow up 48.1 months)	13 months

Abbreviations: CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18.2; CF, fluorouracil + cisplatin; CPS, combined positive score; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJ, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; OS, overall survival; PD-(L)1, programmed death-ligand 1; PFS, progression-free survival; RCT, randomised controlled trial.
Note: * Median follow-up for OS differed between treatment arms; therefore a range has been included.
Source: Shitara et al. 2024 [26] Shitara et al. 2024[29]; Rha, 2023[31]

Table 66: Baseline characteristics for studies considered for indirect treatment comparison

	SPOTLIGHT		GLOW		CheckMate 649		KEYNOTE-859	
	Zolbetuximab + mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbetuximab + CAPOX (n = 254)	CAPOX (n = 253)	Nivolumab + CAPOX/ FOLFOX (n = 789)	CAPOX/ FOLFOX (n = 792)	Pembrolizumab + CF/CAPOX (n = 790)	CF/CAPOX (n = 789)
Age (years), median	62	60	61	59	62	61	61	62
Male gender, %	62	62	63	62	68	71	67	69
Race, %								
White	49	48	37	36	70	68	54	55
Asian	34	34	62	62	24	24	34	34
ECOG, %								
0	44	41	43	43	41	42	36	38
1	54	58	57	56	59	57	64	62
2	< 1	0	0	0	< 1	< 1	NR	NR
Tumour location, %								
Oesophagus	0	0	0	0	13	14	NR	NR
GEJ	23	26	14	17	17	16	19	23
GC	77	74	86	83	70	70	81	76
HER2 status, %								
Positive	0	0	0	0	0	0	0	0
Negative	100	100	100	100	NR	NR	100	100
Unknown	0	0	0	0	~40	~40	0	0

Abbreviations: CAPOX, capecitabine and oxaliplatin; CF, fluorouracil + cisplatin; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJ, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; SmPC, summary of product characteristics.

Source: Nivolumab EPAR [28]; Pembrolizumab EPAR. [32]; Shitara et al. 2024 *[26]* Shitara et al. 2024*[29]*; Rha, 2023[31]

Table 67: Summary of outcomes used for clinical studies considered for indirect treatment comparison

	GLOW/ SPOTLIGHT	CheckMate 649	KEYNOTE-859
Median OS	Zolbetuximab + SoC: 16.4 (15.0;17.9) SoC: 13.7 (13.3; 15.3)	Nivolumab + CAPOX/FOLFOX PD-(L)1 CPS ≥ 5: 14.4 months CAPOX/FOLFOX PD-(L)1 CPS ≥ 5: 11.1 months	Pembrolizumab + CAPOX/CF PD-(L)1 CPS ≥ 5: 14.0 (12.1; 15.4) CAPOX/CF PD-(L)1 CPS ≥ 5: 11.5 (10.2; 12.5)

12-month OS rate	Zolbetuximab + SoC: 62% SoC: 56%	Nivolumab + CAPOX/FOLFOX PD-(L)1 CPS ≥ 5: 56% CAPOX/FOLFOX PD-(L)1 CPS ≥ 5: 47%	Pembrolizumab + CAPOX/CF PD-(L)1 CPS ≥ 5: NR CAPOX/CF PD-(L)1 CPS ≥ 5: NR
Median PFS	Zolbetuximab + SoC: 9.2 (8.4;10.4) SoC: 8.2 (7.6; 8.4)	Nivolumab + CAPOX/FOLFOX PD-(L)1 CPS ≥ 5: 8.3 months CAPOX/FOLFOX PD-(L)1 CPS ≥ 5: 6.1 months	Pembrolizumab + CAPOX/CF PD-(L)1 CPS ≥ 1: 6.9 months CAPOX/CF PD-(L)1 CPS ≥ 1: 5.6 months Pembrolizumab + CAPOX/CF PD-(L)1 CPS ≥ 5: 7.1 (6.1; 8.3) CAPOX/CF PD-(L)1 CPS ≥ 5: 5.6 (5.4; 5.9)
12-month PFS rate	Zolbetuximab + SoC: 43% SoC: 30%	Nivolumab + CAPOX/FOLFOX PD-(L)1 CPS ≥ 5: 34% CAPOX/FOLFOX PD-(L)1 CPS ≥ 5: 22%	Pembrolizumab + CAPOX/CF PD-(L)1 CPS ≥ 5: NR CAPOX/CF PD-(L)1 CPS ≥ 5: NR

Abbreviations: CAPOX capecitabine and oxaliplatin; CF fluorouracil + cisplatin; CLDN18.2 claudin 18.2; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ITT intention-to-treat; mFOLFOX6 modified folinic acid in combination with fluorouracil and oxaliplatin; OS overall survival; PD-(L)1 programmed death-ligand 1; PFS progression-free survival.
Source: Pembrolizumab EPAR. [32]; Shitara et al. 2024 [26] Shitara et al. 2024[29]; Janjigian et al.2023[47]; Janjigian et al. 2023[40]; Medicinrådet (2024)[2]

Table 68: Comparative summary of quality assessment of included studies (NICE seven-criteria checklist)

Study acronym	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this approp-riate and were appropriate methods used to account for missing data?
GLOW	Yes Randomization was performed by blinded site staff using interactive response technology by block randomization with block sizes of two and was stratified according to region (Asia versus non-Asia), number of organs with metastases (0–2 versus ≥3) and prior gastrectomy (yes versus no).	Yes. The randomization list and study drug blinding were maintained by the interactive response technology system. The sponsor, investigators, clinical staff and patients remained blinded to treatment throughout the study.	Yes. There was no significant difference in the baseline characteristics reported between the two treatment arms	Yes. Double-blind (Participant, Investigator)	No. No imbalance with respect to drop-outs between groups	No. Author has measured same number of outcomes as reported	Yes. The efficacy included all the patients. Safety included mITT population
SPOTLIGHT	Yes. Masked site staff via interactive response technology by block	Unclear. No information	Yes. There was no significant difference in the baseline characteristics	Yes. Double-blind (Participant, Investigator)	Yes. Reported in figure 1 trial profile	No. Author has measured same number of outcomes as reported	Yes. The efficacy included all the patients. Safety included mITT population

	randomisation (block sizes of two)		reported between the two treatment arms				
CheckMate-649	Yes. Interactive web response system	Yes. Allocation concealment was adequate	Yes. There was no significant difference in the baseline characteristics reported between the two treatment arms	No. Open-label	No. No imbalance with respect to drop-outs between groups	Unclear. Protocol not available to assess this	No. The efficacy included all the patients. Safety analyses did not include ITT population
KEYNOTE-859	Yes. Using central interactive voice-response system (Almac Clinical Technologies, Souderton, PA, USA)	Yes. Treatment allocation/randomization occurred centrally; the treatment/randomization number identifies the participant for all procedures occurring after treatment allocation	Yes. Baseline characteristics was provided	Yes. Double-blinded	No. Figure 1, Lost to follow up data reported in Consort diagram.	No. All outcome s reported as per methodology	Yes. Efficacy endpoints were analysed in the ITT population

C.2.4 Analyses performed

The following analyses were performed for OS and PFS. As described in Table 69, the base case analysis compares results from the pooled dataset from GLOW and SPOTLIGHT to the subgroups from KEYNOTE-859 and CheckMate-649 that represents the recommended use in Denmark.

Table 69. Summary of relative effects by outcomes used for clinical studies considered for indirect treatment comparison

	Comparison to pembrolizumab	Comparison to Nivolumab
Base case	Pooled dataset GLOW+SPOTLIGHT vs KEYNOTE859 (CPS≥5)	Pooled dataset GLOW+SPOTLIGHT vs CheckMate-649 (CPS≥5)
Sensitivity analysis by CPS subgroup in PD-(L)1 studies	Pooled dataset GLOW+SPOTLIGHT vs KEYNOTE859 (5 ≤ CPS < 10) Pooled dataset GLOW+SPOTLIGHT vs KEYNOTE-859 (CPS ≥ 10)	Pooled dataset GLOW+SPOTLIGHT vs CheckMate-649 (5 ≤ CPS < 10) Pooled dataset GLOW+SPOTLIGHT vs CheckMate-649 (CPS ≥ 10)

Absolute differences were only performed in the base case analyses.

In light of the fact that CPS is a known effect modifier for the treatment effect of PD-(L)1 inhibitors, sensitivity analyses were performed based on CPS score at baseline for the PD-(L)1 inhibitor trials. In all analysis, results from the integrated analysis of ITT populations in GLOW and SPOTLIGHT was used, as zolbetuximab mechanism of action is not dependent on PD-(L)1 expression and both zolbetuximab and backbone chemotherapy is not related to CPS. All analyses were done for OS and PFS and separately for the comparisons to pembrolizumab and nivolumab (dependent on data availability – see Table 70).

Table 70. Summary of relative effects by outcomes used for clinical studies considered for indirect treatment comparison

	Zolbetuximab + chemo vs chemo		Pembrolizumab + chemo vs chemo	Nivolumab + chemo vs chemo
	SPOTLIGHT	GLOW	KEYNOTE-859	CheckMate 649
Overall survival (HR [95% CI])				
By study	0.78 [0.64; 0.95][a]	0.76 [0.62; 0.94][a]	HR [95%CI by CPS group) ≥1: 0.74 [0.65; 0.84][b]	HR [95%CI by CPS group)
Pooled	0.77 [0.67; 0.89][a]		≥5: 0.70 (0.60; 0.82)[c] 5-10: 0.94 (0.71; 1.25)[c] ≥ 10: 0.65 [0.53; 0.79]c	≥5: 0.70 [0.61; 0.81][d] 5-10: 0.92 [0.66; 1.28][d] ≥ 10: 0.66 [0.57; 0.77]
Progression free survival (HR [95% CI])				
By study	0.73	0.69	HR [95%CI by CPS group)	HR [95%CI by CPS group)

	Zolbetuximab + chemo vs chemo		Pembrolizumab + chemo vs chemo	Nivolumab + chemo vs chemo
	SPOTLIGHT	GLOW	KEYNOTE-859	CheckMate 649
	[0.59, 0.91][a]	[0.55, 0.86][a]	≥1: 0.72 [0.63; 0.82][b]	
Pooled	0.71 [0.61; 0.83][a]		≥5: 0.69 (0.58; 0.81)[c] 5-10: 0.93 (0.69; 1.25)[c] ≥ 10: 0.62 [0.51; 0.76][c]	≥5: 0.71 [0.61; 0.82][d] 5-10: Not reported ≥ 10: Not reported

Key: CLDN18.2, claudin 18.2; CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-(L)1, programmed death-ligand 1.
Notes: HR reported with 95% CI for each intervention (in combination) vs chemotherapy alone. HR < 1 indicates lower event rate for each treatment versus chemotherapy.

a) All analyses used the ITT population of the final SPOTLIGHT datacut (dated 8 September 2023), final GLOW datacut (dated 12 January 2024). Shitara et al. (2024) [26]
b) KEYNOTE-859 efficacy inputs were based on data cutoff date of October 3, 2022, reported in Rha 2023*[31]*
c) Medicinrådet (2024)[2]
d) CheckMate 649 efficacy inputs were based on data with minimum follow-up time of 4 years, reported in Shitara 2024.[29]

C.3 Results

Table 71 presents the results from the base case analyses of indirect treatment effect comparing zolbetuximab + chemotherapy to pembrolizumab + chemotherapy and zolbetuximab + chemotherapy to nivolumab + chemotherapy.

The analyses show that there are no statistically significant differences in OS or PFS of zolbetuximab and PD-(L)1 inhibitors (95% confidence intervals cross 1). Compared to pembrolizumab (patients with CPS≥5), HR for OS was [redacted] and for PFS [redacted]. Compared to nivolumab (patients with CPS≥5), HRs were 1.11 [redacted] and [redacted] for OS and PFS, respectively.

Table 71. Results of Bucher indirect comparison (HR with 95%CI) (CPS≥5)

	Zolbetuximab + chemo compared to pembrolizumab + chemo[a]	Zolbetuximab + chemo compared to nivolumab + chemo[b]
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: CI confidence interval; HR hazard ratio; OS Overall survival; PFS progression free survival
a) Analysis based on patients in KEYNOTE-859 with CPS≥ 5
b) Analysis based on patients in CheckMate-649 with CPS ≥ 5

Table 72 presents the results from sensitivity analyses with respect to CPS subgroups for the PD-(L)1 inhibitors. The analyses show that numerically the HRs of zolbetuximab are lower when compared to PD-(L)1 inhibitors in populations with less PD-(L)1 expression, and higher in populations with higher PD-(L)1 expression. All confidence intervals cross 1 suggesting that the estimated differences in treatment effect are not statistically significant.

Table 72. Sensitivity analysis. Results of Bucher indirect comparison by CPS score

	Zolbetuximab + chemo compared to pembrolizumab + chemo[a]	Zolbetuximab + chemo compared to nivolumab + chemo[a]
Overall survival (HR [95% CI])		
Base case	[redacted]	[redacted]
5 ≤ CPS <10	[redacted]	[redacted]
≥ 10	[redacted]	[redacted]
Progression free survival (HR [95% CI])		
Base case	[redacted]	[redacted]
5≤ CPS <10	[redacted]	[redacted]
≥ 10	[redacted]	[redacted]

Implied absolute differences for the base case analyses are reported in Table 73 and Table 74.

C.4 Discussion

The evidence synthesis indirectly compared the efficacy profiles of treatments for locally advanced unresectable or metastatic HER2-negative G/GEJ cancer using published results from the pivotal RCTs.

The sparsity of the evidence network limits the possibility to making inferences. The estimated indirect treatment effects are based on the overall treatment effect compared to chemotherapy alone. The analysis cannot fully account for differences in patient characteristics (e.g., using meta-regression) as there is not enough data to estimate the meta-regression coefficients. Furthermore, with a star-shaped network, consistency of results cannot be checked.

CheckMate 649[48, 49] and KEYNOTE-859[31] applied blended chemotherapy (on investigator discretion). The overall results with blended chemotherapy were used as the measure of treatment effect compared to chemotherapy alone. From the zolbetuximab clinical programme, the two pivotal studies had different backbone chemotherapies. For the indirect treatment comparison, the integrated efficacy analysis of the two trials was used. This approach is only a limitation to the method if relative treatment effects of the intervention and /or comparators are influenced by choice of chemotherapy.

A further limitation lies in the synthesis include treatments with different mechanisms of action. Zolbetuximab is a monoclonal antibody directed against the tight junction molecule claudin 18.2 (CLDN18.2). In contrast, PD-(L)1 inhibitors such as nivolumab and pembrolizumab are monoclonal antibodies that bind to the programmed death-1 (PD-1) receptor and block its interaction with PD-L1 and PD-L2. The licenses of the PD-(L)1 inhibitors and indeed efficacy depend on tumour PD-(L)1 expression based on CPS. Patients in the zolbetuximab trial was included based on CDLN18.2 expression while the CDLN18.2 status of patients in the PD-(L)1 inhibitor pivotal trials are unknown. The lack of clinical evidence of PD-(L)1 inhibitors in CDLN18.2 positive and lack of data to study the impact of CDLN18.2 status on treatment efficacy of PD-(L)1 inhibitors is a limitation to the indirect treatment comparison. However, there is no known biological mechanism by which PD-(L)1 CPS could affect zolbetuximab's mechanism of action or CLDN18.2 status could affect PD-(L)1 inhibitors mechanism of action. Furthermore, survival of patients on chemotherapy have been shown to be independent of both CDLN18.2 status and CPS levels.

Despite the limited clinical evidence network and limitations to the indirect treatment comparison, the presented evidence supports that zolbetuximab + chemotherapy is as efficacious as PD-(L)1 inhibitors + chemotherapy in prolonging the overall survival and progression-free survival. Numerically the HR for OS and PFS of zolbetuximab plus chemotherapy (compared to PD-(L)1 inhibitor plus chemotherapy) is lower (higher treatment effect) for patients with lower PD-(L)1 expression but 95% confidence intervals contained 1 in all analyses.

This implies that patients with locally advanced unresectable or metastatic HER2-negative G/GEJ cancer, whose tumours are CLDN 18.2 positive, can be expected to have OS and PFS outcomes, when treated with zolbetuximab plus chemotherapy, at the same levels as patients treated with PD-(L)1 inhibitors plus chemotherapy.

Table 73 Comparative analysis of studies comparing zolbetuximab combined with chemotherapy to nivolumab combined with chemotherapy for patients with CDLN18.2 positivity and PD-(L)1 expression (CPS≥5)

Outcome	Studies included in the analysis	Absolute difference in effect: Difference	Absolute difference in effect: CI	Absolute difference in effect: P value	Relative difference in effect: Difference	Relative difference in effect: CI	Relative difference in effect: P value	Method used for quantitative synthesis	Result used in the health economic analysis?
Median survival (months)	GLOW SPOTLIGHT CheckMate-649	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	HR estimated using Bucher analysis of studies (integrated analysis for zolbetuximab) comparing to chemotherapy. Difference and 95% CI for absolute effect based on ACM mid-point of median OS for nivolumab and pembrolizumab: [redacted] months	No
1-year survival (%-point difference)	GLOW SPOTLIGHT CheckMate-649	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	HR estimated using Bucher analysis of studies (integrated analysis for zolbetuximab) comparing to chemotherapy. Difference and 95% CI for absolute effect based on ACR equal to nivolumab 12-month survival rate: [redacted]	No

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
Median PFS (months)	GLOW SPOTLIGHT CheckMate-649	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	HR estimated using Bucher analysis of studies (integrated analysis for zolbetuximab) comparing to chemotherapy. Difference and 95% CI for absolute effect based on ACM mid-point of median OS for nivolumab and pembrolizumab: [redacted] months	No
12 months PFS (%-points difference)	GLOW SPOTLIGHT CheckMate-649	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	HR estimated using Bucher analysis of studies (integrated analysis for zolbetuximab) comparing to chemotherapy. Difference and 95% CI for absolute effect based on ACR equal to nivolumab 12-month PFS rate: [redacted]	No

Table 74 Comparative analysis of studies comparing zolbetuximab combined with chemotherapy to pembrolizumab combined with chemotherapy for patients with CDLN18.2 positivity and PD-(L)1 expression (CPS≥5)

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Median survival (months)	GLOW SPOTLIGHT KEYNOTE-859	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	HR estimated using Bucher analysis of studies (integrated analysis for zolbetuximab) comparing to chemotherapy. Difference and 95% CI for absolute effect based on ACM mid-point of median OS for nivolumab and pembrolizumab: [redacted]	No
1-year survival (%-point difference)	GLOW SPOTLIGHT KEYNOTE-859	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	HR estimated using Bucher analysis of studies (integrated analysis for zolbetuximab) comparing to chemotherapy. Difference and 95% CI for absolute effect based on ACR equal to nivolumab 12-month survival rate: [redacted]	No

Outcome	Studies included in the analysis	Absolute difference in effect: Difference	CI	P value	Relative difference in effect: Difference	CI	P value	Method used for quantitative synthesis	Result used in the health economic analysis?
Median PFS (months)	GLOW SPOTLIGHT KEYNOTE-859	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	HR estimated using Bucher analysis of studies (integrated analysis for zolbetuximab) comparing to chemotherapy. Difference and 95% CI for absolute effect based on ACM mid-point of median OS for nivolumab and pembrolizumab: [redacted]	No
12 months PFS (%-points difference)	GLOW SPOTLIGHT KEYNOTE-859	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	HR estimated using Bucher analysis of studies (integrated analysis for zolbetuximab) comparing to chemotherapy. Difference and 95% CI for absolute effect based on ACR equal to nivolumab 12-month PFS rate: [redacted]	No

Appendix D. Extrapolation

D.1 Extrapolation of OS

D.1.1 Data input

Integrated efficacy datasets from GLOW and SPOTLIGHT

D.1.2 Model

Parametric survival functions estimated from time to death of any cause in the data source. Separate functions were estimate for zolbetuximab plus chemotherapy and chemotherapy alone. Hence, no a'priori assumptions of proportional hazard were applied.

The following distributions for failure-time were estimated: Exponential, Weibull, Log-Logistic, Lognormal, Gompertz, Gamma, Generalized Gamma. Model estimates with 95% confidence intervals are available in section D.5.1.

D.1.3 Proportional hazards

Not applicable. no a'priori assumptions of proportional hazard were applied when estimating parametric survival function.

D.1.4 Evaluation of statistical fit (AIC and BIC)

Parametric function	AIC	BIC
Zolbetuxmiab plus chemotherapy		
Exponential	4245.2	4249.5
Weibull	4222.9	4231.5
Log-logistic	**4210.5**	**4219.1**
Lognormal	4225.0	4233.6
Gompertz	4241.2	4249.8
Gamma	4217.5	4226.1
Generalized Gamma	4214.7	4227.6
Chemotherapy alone		
Exponential	4571.1	4575.4
Weibull	4536.0	4544.6
Log-logistic	4534.8	4543.4
Lognormal	4578.9	4587.4
Gompertz	4558.7	4567.3

Gamma	**4532.4**	**4540.9**
Generalized Gamma	4534.1	4546.9

D.1.5 Evaluation of visual fit

Figure 25 provides an overview of the estimated models compared to KM-curves for each arm separately. The curves for zolbetuximab gives very similar fit within the period with observed data, whereas the different functional form differs slightly more both in the initial weeks of treatment and towards the end of the observation period. Given that KM curves are relatively mature, the model with best statical fit was chosen for the base case analysis. The chosen functions are compared to KM-curves in Figure 26. The log-logistic model for zolbetuximab plus chemo gives a close fit to the KM curve over the observation period. The gamma function for chemo-alone tends to overshoot the survival mid-range and undershoot towards the end of the KM curve.

Figure 25 Estimated OS models compared to KM. Upper panel zolbetuximab plus chemo. Lower panel chemo alone

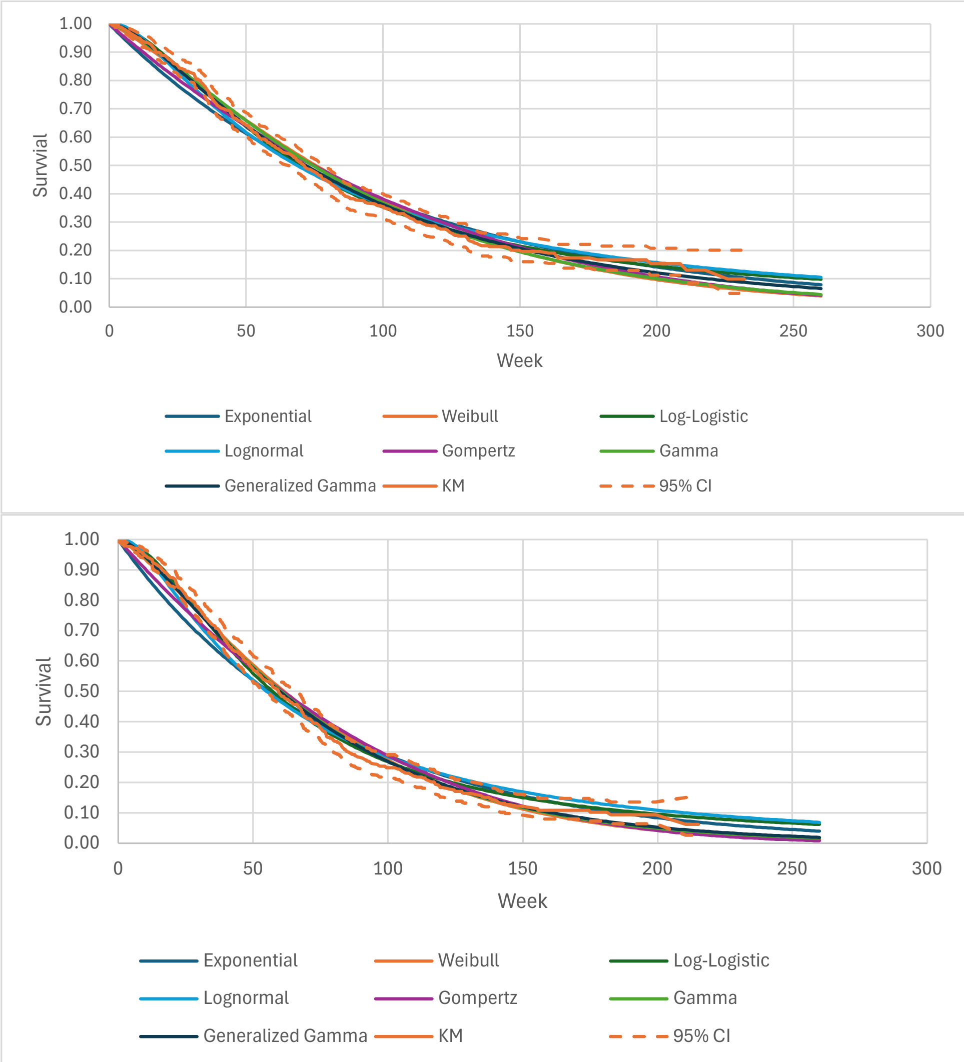
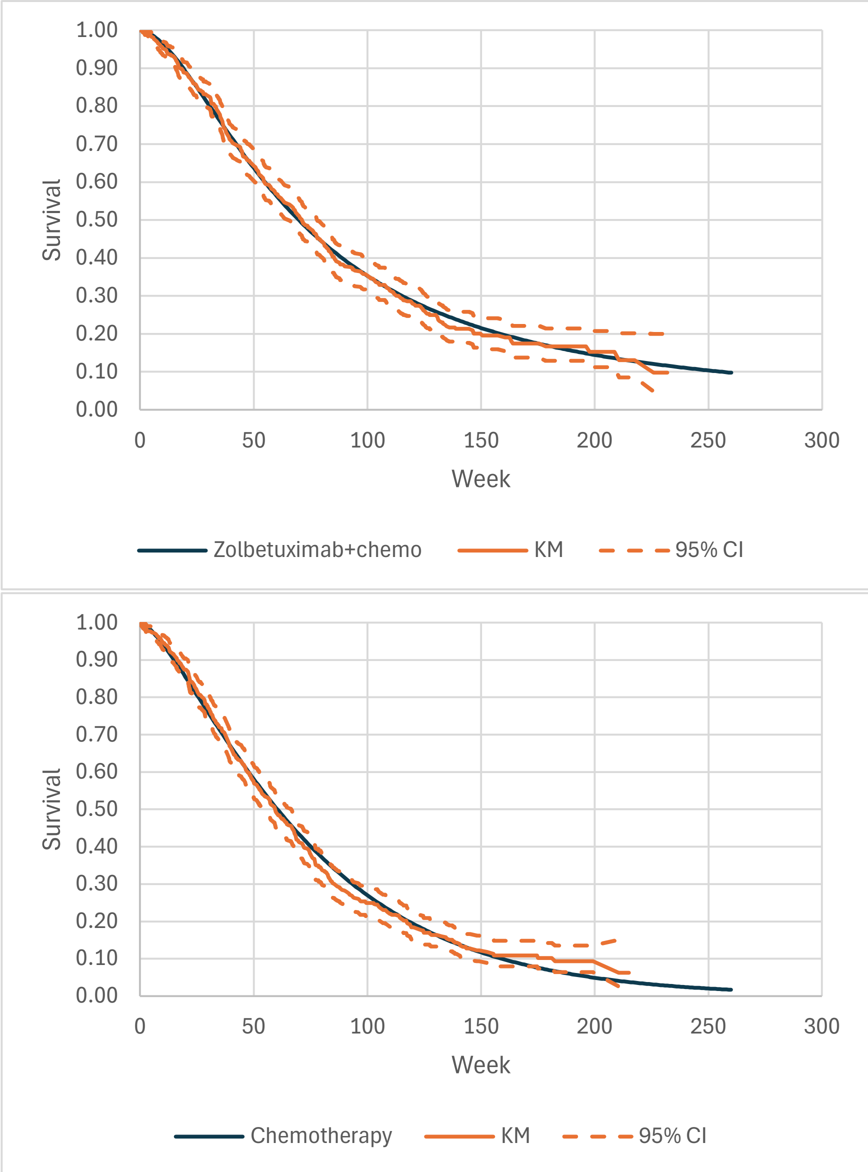


Figure 26 Predicted OS compared to KM by arm and week (function with best statistical it)



D.1.6 Evaluation of hazard functions

Instant hazards are shown below for the selected OS models compared to general mortality at model age. Hazards are shown for the long-term prediction but truncated when the predicted survival is below 10^{-8}. The selected functions (based on best statistical fit on the BIC and AIC criteria) show different patterns of hazard in the long-term. The log-logistic function chosen for the zolbetuximab plus chemo arm displays a decreasing hazard over time while the gamma function chosen for chemo alone shows a rapid increase before plateauing. However, the choices of the functions are consistent with observed hazards (Figure 28) where the pattern of instant hazards of the chosen functions are consistent with the observed (8-week rolling average) hazard observed in the clinical trial. Section D.5.2 presents the comparison of all estimated OS models to observed hazards.

Figure 27 Hazards by arm for selected models compared to general population hazard

[redacted]

Figure 28 Estimated OS hazard compared to KM. Upper panel zolbetuximab plus chemo. Lower panel chemo alone

Zolbetuximab plus chemotherapy

[redacted]

Chemotherapy

[redacted]

D.1.7 Validation and discussion of extrapolated curves

In order to validate the selected parametric OS function against expected outcomes in standard of care are, Astellas has commissioned a report on OS data from the Swedish national registry "*Nationella registret för esofagus- och magcancer*" (NREV) containing information on prognosis and baseline characteristics for patients with locally advanced, unresectable or metastatic HER2-negative adenocarcinoma of the stomach or GEJ who have received first-line palliative care. To only include contemporary patients, selection was made among patients who received first-line palliative care between May 1, 2017 and June 30, 2022. Standard of care (chemotherapy) in Sweden in the time window for selection of patients is the same as in Denmark.

Table 75 presents baseline characteristics for four different patient groups: gastric adenocarcinoma (A), GEJ adenocarcinoma (B), gastric and GEJ adenocarcinoma (C), and all adenocarcinomas (D). In Group C, the most relevant comparison group, the average age was [redacted] years and [redacted] of the patients had a functional status between 2-4. Although the patients in Group C are thus slightly older and have a poorer functional status than in SPOTLIGHT and GLOW they were all considered suitable for oncological treatment.

Table 75. Baseline Characteristics in Patients Locally Advanced Unresectable or Metastatic HER2negative Gastric Adenocarcinoma or GEJ Receiving a First-line Palliative Care Between May 1, 2017 and June 30, 2022

[redacted]

Note: Group A = gastric cancer, Group B = GEJ (ICD-10 C16.0 + C15.5), Group C = A + B, Group D = all adenocarcinomas. Patients in all groups are HER2 negative or unknown.

Figure 29 shows that the median survival was [redacted] months for the patients who were included in group C. The probability of survival after 2 years was [redacted] and after 5 years [redacted]. Although the patients included in Figure 29 are not fully comparable to the patients in SPOTLIGHT and GLOW, it is clear from the figure that there are hardly any long-term survivors with current oncological treatment in Sweden. This is in line with published data from earlier cohorts [39][38]

Figure 29. Survival in Patients With Locally Advanced Unresectable or Metastatic HER2 Negative Gastric Adenocarcinoma or GEJ Who Received a First-line Palliative Care Between May 1, 2017 and June 30, 2022

[redacted]

Note: Patients correspond to "Group C" in Table 75 taken from NREV

Table 76 provide an overview of the prediction in the chemotherapy arm of the model to the Swedish registry data set. Based on the expected 5-year survival in patients treated with chemotherapy in clinical practice, the gamma function seems to be the most reasonable extrapolation of overall survival in the comparison arm – and also reflecting the function with best statistical fit to the GLOW/SPOTLIGHT observed OS data.

Table 76 Comparison of OS using all models

	Median	36 months	48 months	60 months
Placebo plus chemotherapy				
SPOTLIGHT/GLOW[26]	**13.7**	**11%**	**9%**	**NA**
Exponential	12.9	14%	8%	4%
Weibull	14.2	10%	4%	1%
Log-Logistic	13.2	14%	9%	6%
Lognormal	12.7	16%	10%	7%
Gompertz	14.1	11%	3%	1%
Gamma	**13.9**	**11%**	**4%**	**2%**
Generalized Gamma	13.8	11%	5%	2%
NREV registry (cohort C)	[redacted]	[redacted]	[redacted]	[redacted]
Zolbetuximab plus chemotherapy				
SPOTLIGHT/GLOW*	**16.1**	**20%**	**15%**	**NA**
Exponential	16.4	22%	13%	8%
Weibull	17.4	18%	9%	4%
Log-Logistic	**16.1**	**20%**	**14%**	**10%**
Lognormal	15.8	22%	15%	11%
Gompertz	17.2	20%	10%	4%
Gamma	17.2	18%	9%	4%
Generalized Gamma	16.6	19%	11%	7%
Difference in base case OS curves	2.2	10%	9%	8%

* Approximative reading from graph

D.1.8 Adjustment of background mortality

In the very long-term prediction of OS in the zolbetuximab plus chemotherapy arm, the predicted hazard will be lower than the general population hazard. The OS applied in the model was therefore adjusted so that the applied OS hazard could be lower than the general population hazard. The adjustment is mainly theoretical as the number of patients surviving long enough for the adjustment to come into effect is very small (<1%).

D.1.9 Adjustment for treatment switching/cross-over

No adjustment for treatment switching was applied

D.1.10 Waning effect

No waning effect was modelled.

D.1.11 Cure-point

No a'priori assumption on cure-point was made. The OS model with the best statistical fit indicated that the OS hazard is decreasing over time and, hence, indicates a plateauing of the survival over time.

D.2 Extrapolation of PFS

D.2.1 Data input

For zolbetuximab + CAPOX/FOLFOX and CAPOX/FOLFOX, PFS efficacy data were based on pooled individual patient-level data from the GLOW (Final data cut) and SPOTLIGHT (Final data cut) trials.

D.2.2 Model

Parametric survival functions estimated from time to death of any cause in the data source. Separate functions were estimate for zolbetuximab plus chemotherapy and chemotherapy alone. Hence, no a'priori assumptions of proportional hazard were applied.

The following distributions for failure-time were estimated: Exponential, Weibull, Log-Logistic, Lognormal, Gompertz, Gamma, Generalized Gamma. Model estimates with 95% confidence intervals are available in section D.5.1.

D.2.3 Proportional hazards

Not applicable. No a'priori assumptions of proportional hazard were applied when estimating parametric survival function.

D.2.4 Evaluation of statistical fit (AIC and BIC)

The goodness-of-fit (AIC and BIC) associated with the different parametric functions are summarized in Table 77 and

Table 78**.** For both zolbetuximab + chemotherapy and chemotherapy alone, the log-logistic distribution was selected as the best fitting curve for PFS based on statistical measures of best fit.

Table 77. Statistical goodness of fit for PFS - zolbetuximab + chemotherapy

Parametric function	AIC	BIC
Exponential	3302.4	3306.7
Weibull	3298.6	3307.2
Log-logistic	**3247.8**	**3256.4**
Lognormal	3249.6	3258.1
Gompertz	3300.2	3308.8
Gamma	3290.6	3299.2
Generalized Gamma	3250.7	3263.6

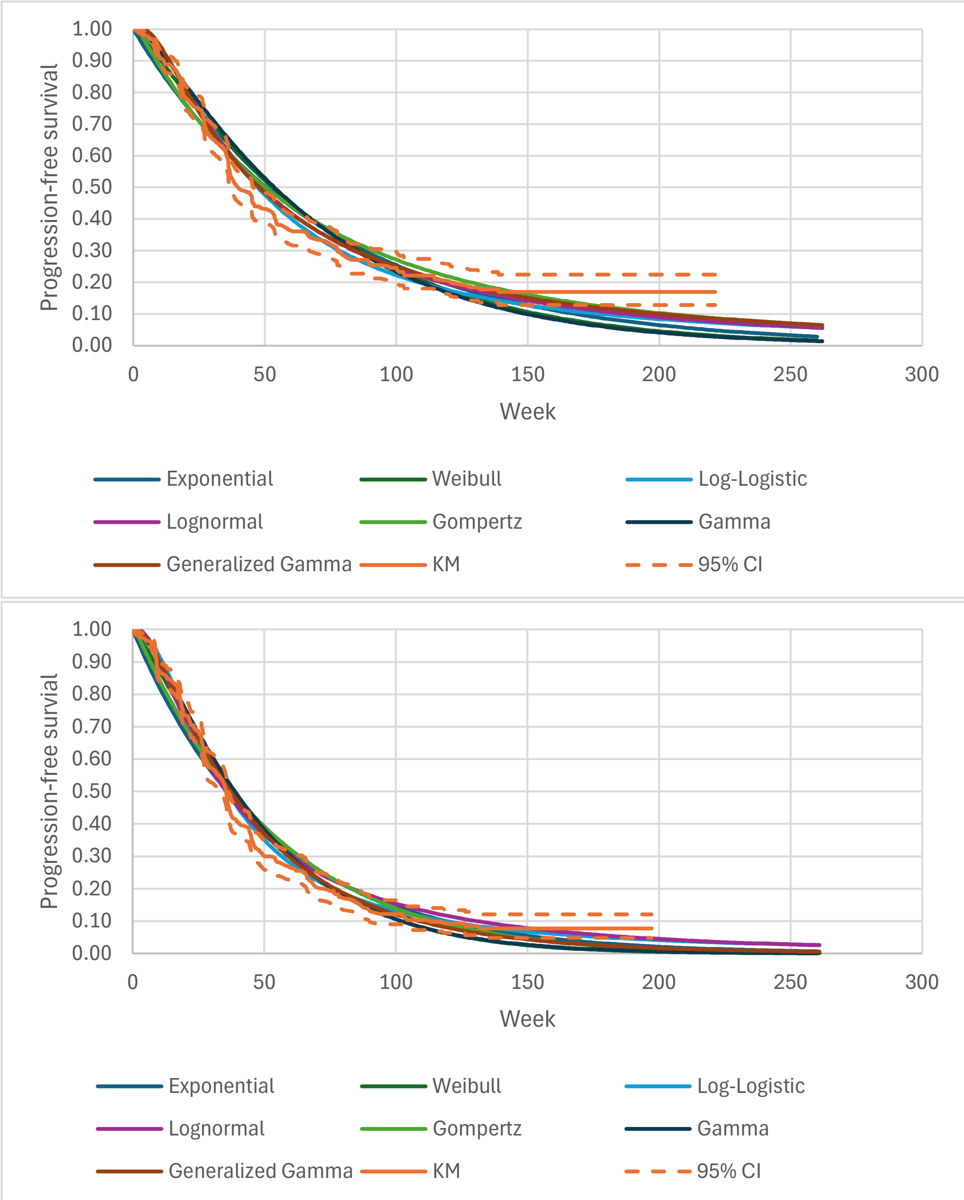
Table 78. Statistical goodness of fit for PFS – chemotherapy alone

Parametric function	AIC	BIC
Exponential	3651.9	3656.2
Weibull	3630.5	3639.0
Log-logistic	**3598.6**	**3607.2**
Lognormal	3631.5	3640.1
Gompertz	3653.0	3661.6
Gamma	3620.7	3629.3
Generalized Gamma	3613.7	3626.6

D.2.5 Evaluation of visual fit

For both arms the estimated models are very similar with a tendency to overestimate the PFS mid-term and underestimate PFS long-term. The mid-term survival for the log-logistic distribution is within the upper 95% confidence interval of the KM for both arms and the underestimate at the tail is within the confidence interval for the chemo arm (but below the lower 95% confidence interval for the zolbetuximab plus chemo arm).

Figure 30 Estimated PFS models compared to KM. Upper panel zolbetuximab plus chemo. Lower panel chemo alone



D.2.6 Evaluation of hazard functions

The hazard functions for both selected PFS models show a sharp increase in the short term and a steady decrease over time. These give a good representation of the smoothed hazards for both arms (Figure 31). Section D.5.2 presents the comparison of all estimated PFS models to observed hazards. From visual inspection, Log-logistic, log-normal and generalized gamma are the only functions that captures the mid-term as well as right-end observed hazards (holds for both zolbetuximab plus chemotherapy and placebo plus chemotherapy).

Figure 31 Comparison of hazards in the chosen PFS models

[redacted]

Figure 32 Estimated PFS hazard compared to KM. Upper panel zolbetuximab plus chemo. Lower panel chemo alone

[redacted]

Observed hazard was estimated as the 8 week rolling average weekly change in cumulative hazards (-ln(KM(t)).

D.2.7 Validation and discussion of extrapolated curves

The chosen models give good predictions of the trial data with a tendency to underestimate the observed rates at year 3. Although the log-logistic curves are associated with a decreasing hazard there is a relatively large drop in PFS from 3 to 4 years, which means that the lower hazards in the longer-term extrapolation affect very few patients in the model.

Table 79 Comparison of PFS rates from the selected model and observed rates

	6 months	1 year	2 years	3 years	4 years
Zolbetuximab+ chemotherapy					
Observed PFS (KM data)[26]	na	43%	22%	17%	na
Estimated PFS	71.2%	44.4%	20.6%	11.8%	7.8%
Chemotherapy alone					
Observed PFS (KM data)[26]	na	30%	11%	8%	na
Estimated PFS	62.9%	32.6%	12.2%	6.2%	3.8%

Models (sorted by BIC)	Median	36 months	48 months	60 month
Observed (zolbetuximab plus chemo)	**10.5**	**17%**	**Na**	**Na**
Log-Logistic	10.5	12%	8%	6%
Lognormal	10.7	13%	8%	6%
Generalized Gamma	10.6	14%	9%	6%
Gamma	11.9	9%	3%	1%
Exponential	11.7	12%	6%	3%
Weibull	12.0	9%	4%	2%
Gompertz	11.1	15%	9%	6%
Observed (Chemo)	**8.0**	**8%**	**Na**	**Na**
Log-Logistic	8.0	6%	4%	2%
Generalized Gamma	8.3	4%	1%	1%
Gamma	8.7	2%	1%	0%
Weibull	8.8	2%	0%	0%
Lognormal	8.0	7%	4%	2%
Exponential	8.3	5%	2%	1%
Gompertz	8.5	4%	1%	0%

D.2.8 Adjustment of background mortality

Not applied. By construction of the traces, the PFS cannot exceed the overall survival. Overall survival is adjusted for background mortality as described above.

D.2.9 Adjustment for treatment switching/cross-over

No adjustment for next line of therapy was performed

D.2.10 Waning effect

The KM curves for both arms indicate that some level of plateau is reached in the trial data for both arms, hence adjustment of efficacy data does not seem warranted.

D.2.11 Cure-point

Choice of the log-logistic models means that the hazard will be decreasing over time. The log-logistic model had best statistical goodness-of-fit for both arms due to the tendency for PFS to plateau (albeit at a low level of survival of 17% in the zolbetuximab plus chemo arm and 8% in the chemo alone arm). Based on this, no cure-point was not modelled explicitly, and the extrapolation of trial data was used for the full model horizon.

D.3 Extrapolation of time to treatment discontinuation

D.3.1 Data input

Parametric survival curves were estimate using data from GLOW and SPOTLIGHT on time to treatment discontinuation (TTD). Data were analysed separately for GLOW and SPOTLIGHT and separately for zolbetuximab and placebo (chemo alone).

The KM-data for TTD in all arms at the final OS data-cuts are mature with observed treatment persistence rate at the right-most point on the KM curve between 1% and 6%.

D.3.2 Model

The following distributions for failure-time were estimated: Exponential, Weibull, Log-Logistic, Lognormal, Gompertz, Gamma, Generalized Gamma. Separate functions were estimated for the intervention and comparators arms, ie., no assumption on proportionality of hazards were made. Model estimates with 95% confidence intervals are available in section D.5.1.

D.3.3 Proportional hazards

No a'priori assumptions on proportional hazards were made.

D.3.4 Evaluation of statistical fit (AIC and BIC)

For all TTD data sets except placebo arm in SPOTLIGHT, the gamma function had best statistical fit (AIC and BIC) with Weibull or generalized gamma as second best statistical fit. For the placebo arm in SPOTLIGHT, log-normal had best statistical fit with gamma as second best.

Table 80. Statistical goodness of fit for TTD models by study and arm

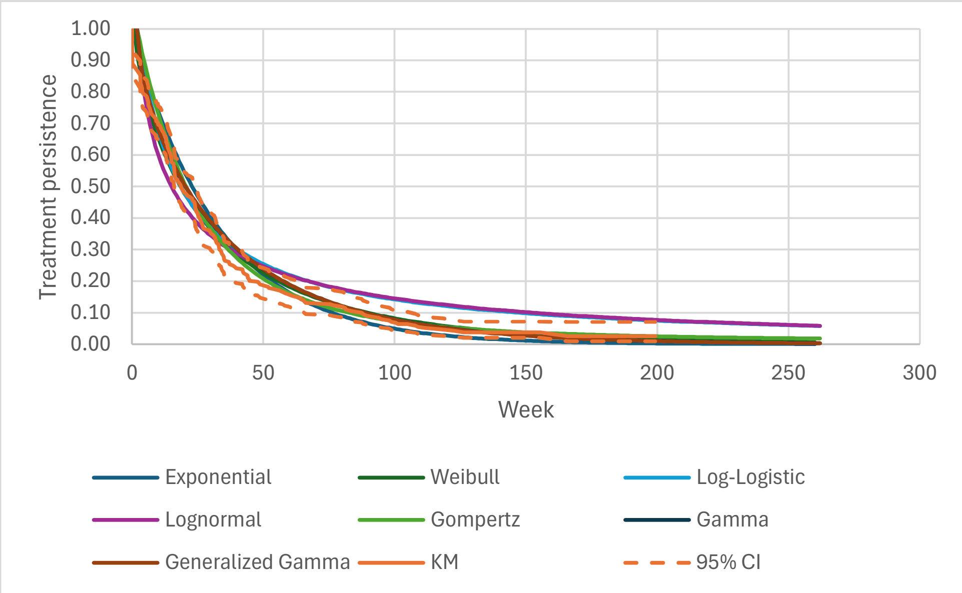
	GLOW		SPOTLIGHT	
Function	AIC	BIC	AIC	BIC
Zolbetuximab plus chemotherapy				
Exponential	2197.7	2201.3	2469.8	2473.4
Weibull	2161.8	2168.9	2442.7	2450.0
Log-Logistic	2202.2	2209.3	2477.6	2484.9
Lognormal	2226.1	2233.1	2513.6	2520.9
Gompertz	2179.9	2187.0	2455.5	2462.8
Gamma	**2158.8**	**2165.8**	**2439.3**	**2446.6**
Generalized Gamma	2160.8	2171.4	2441.1	2452.0
Placebo plus chemotherapy				

	GLOW		SPOTLIGHT	
Function	AIC	BIC	AIC	BIC
Exponential	2103.8	2107.3	2443.5	2447.2
Weibull	2096.8	2103.9	2440.4	2447.7
Log-Logistic	2155.2	2162.2	2479.6	2486.8
Lognormal	2118.0	2125.0	**2428.7**	**2436.0**
Gompertz	2104.4	2111.5	2445.1	2452.3
Gamma	**2096.6**	**2103.6**	2437.5	2444.8
Generalized Gamma	2098.5	2109.0	2437.6	2448.5

D.3.5 Evaluation of visual fit

Figure 33 compare each of the estimated models to KM data (TTD) from GLOW. For both zolbetuximab and placebo, log-normal and log-logistics seem to predict persistence levels at the right-hand tail of the KM-curve poorly and predicts time on treatment above the 95%CI for the observed time on treatment. The exponential survival function gives the lowest prediction and the right of the KM curve (at the level of the lower 95% confidence interval).

Figure 33 Estimated failure-time models and KM curves (with 95% CI). TTD in GLOW. Upper panel. Zolbetuximab plus chemo. Lower panel: placebo plus chemotherapy



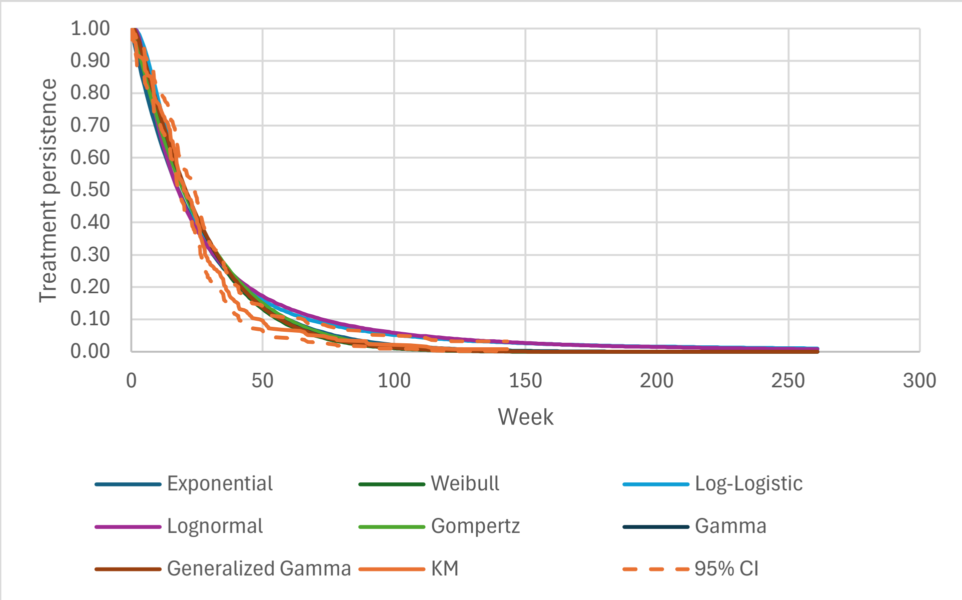
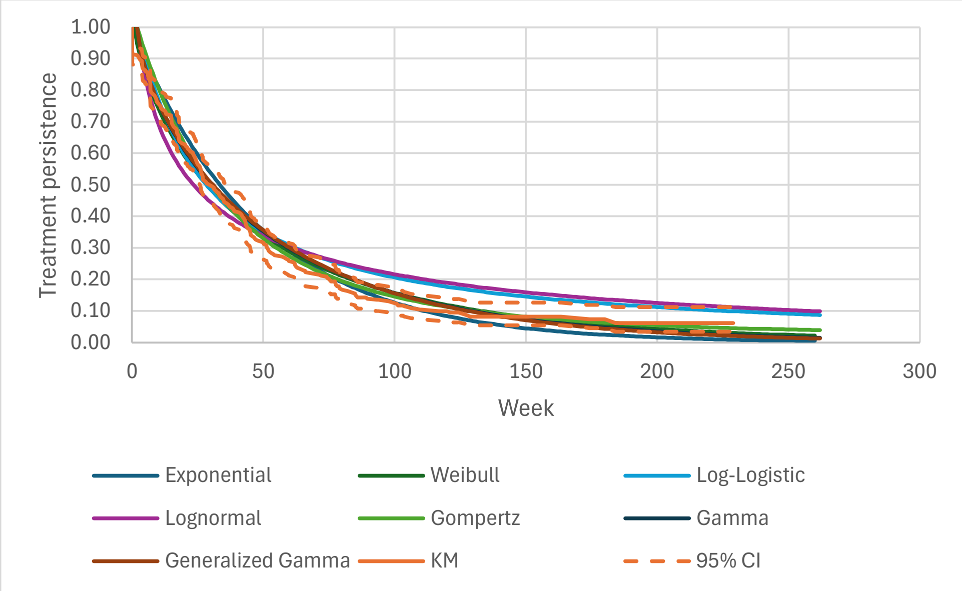
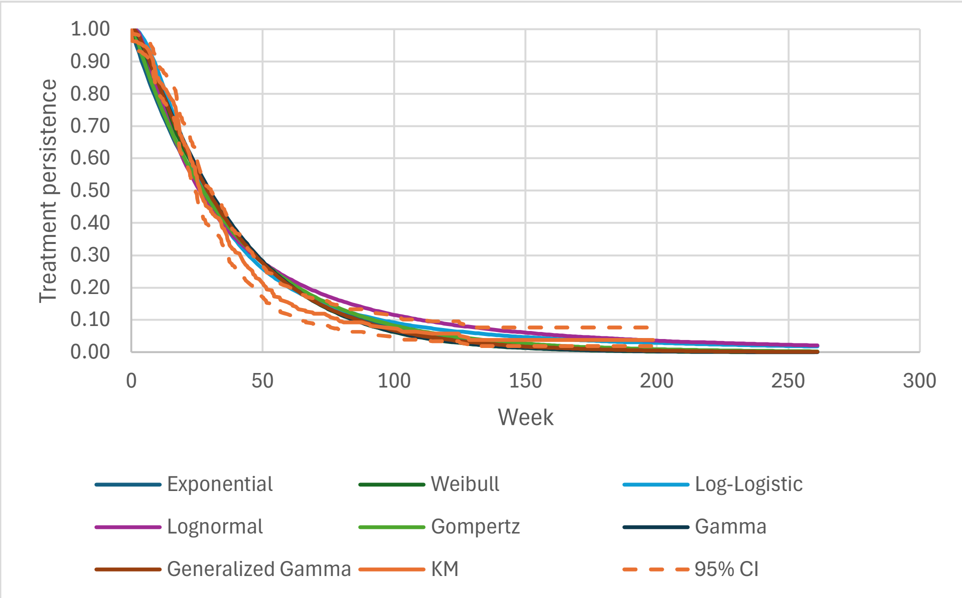


Figure 40 compare each of the estimated models to KM data (TTD) from GLOW. For zolbetuximab, log-normal and log-logistics seem to predict persistence levels at the right-hand tail of the KM-curve poorly and predicts time on treatment above the 95%CI for the observed time on treatment. The exponential survival function gives the lowest prediction and the right of the KM curve (at the level of the lower 95% confidence interval). For placebo, there are no major differences between the estimated curves. All curves have the same tendency to overpredict treatment persistence at one year (at the upper 95% CI of the KM curve). Log-normal and log-logistic function predict the KM-curve at the right hand tail the closest with other function tending towards the lower 95%-CI of the KM-curve.

Figure 34 Estimated failure-time models and KM curves (with 95% CI). TTD in SPOTLIGHT. Upper panel. Zolbetuximab plus chemo. Lower panel: placebo plus chemotherapy





D.3.6 Evaluation of hazard functions

Section D.5.2 presents the comparison of all estimated TTD models to observed hazards. Visual inspection of the hazards for zolbetuximab arms in both studies confirms that the gamma function is best at capturing the observed hazards from a high initial rate but quickly dropping to a fairly constant level. For the placebo arms, although the smoothed hazards functions have quite similar shapes, the SPOTLIGHT data extends further in time. This drives the statistical fit towards selecting gamma in the GLOW data set (sharp initial increase in hazard followed by a rapid transition to a stable, slightly increasing level) but giving better statistical fit for the log-normal function in the SPOTLIGHT study (sharp initial increase followed by a declining hazard).

D.3.7 Validation and discussion of extrapolated curves

Based on the fact that the TTD data is mature and therefore the extrapolation only covers very few patients and the fact that functional form gives similar predictions (apart from log-normal and log-logistic in the zolbetuximab arms), it was decided to use the functions determined by best statistical fit.

D.3.8 Adjustment of background mortality

Not applicable.

D.3.9 Adjustment for treatment switching/cross-over

Not applicable.

D.3.10 Waning effect

Not applicable.

D.3.11 Cure-point

Not applicable.

extrapolation.

D.4 Sub-group results

D.4.1 Data input

The extrapolations above in sections D.1 and D.2 were estimated using the overall FAS population in the integrated data-set. In order to confirm the claim that efficacy of zolbetuximab is not related to PD-(L)1 expression, a sensitivity analysis was conducted where the subgroup of patients with CPS <5 at baseline. Please note that the GLOW/ SPOTLIGHT clinical trials were not stratified for CPS. Furthermore, CPS at baseline were collected retroactively from patients with biopsy tissue available.

The subgroup analysis was performed by estimating alternative parametric survival functions for OS and PFS. Figure 35 shows the comparison of KM-curves applied in the subgroup analysis compared to the total population. Both in terms of level and shape the differences between the KM-curves (subgroup compared to overall population) are neglectable.

Figure 35 Comparation of KM for overall population and subgroup with known CPS<5

OS	PFS
[redacted]	

D.4.2 Summary

Table 81 Summary of assumptions associated with CPS < 5 subgroup

Method/approach	Description/assumption	
Data input	OS and PFS from GLOW/ SPOTLIGHT (FAS population with known CPS <5)	
Model	Exponential, Weibull, Log-Logistic, Lognormal, Gompertz, Gamma, Generalized Gamma	
Assumption of proportional hazards between intervention and comparator	No a'priori assumptions on proportionality were made	
	OS	**PFS**
Function with best AIC fit	Zol+chemo: Log-Logistic Chemo: Gamma	Zol+chemo: Log-Logistic Chemo: Log-logistic
Function with best BIC fit	Zol+chemo: Log-Logistic Chemo: Gamma	Zol+chemo: Log-Logistic Chemo: Log-logistic
Function with best visual fit	Zol+chemo: Log-Logistic Chemo: Gamma	Zol+chemo: Log-Logistic Chemo: Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Zol+chemo: Log-Logistic Chemo: Gamma	Zol+chemo: Log-Logistic Chemo: Log-logistic
Validation of selected extrapolated curves (external evidence)	Not attempted	Not attempted
Function with the best fit according to external evidence	Not attempted	Not attempted
Selected parametric function in base case analysis	Zol+CAPOX: Log-Logistic Capox: Gamma	Zol+FOLFOX: Log-Logistic FOLFOX: Log-Logistic
Adjustment of background mortality with data from Statistics Denmark	TTD can – by construction of traces – not exceed PFS or OS which is adjusted for general population morality	
Adjustment for treatment switching/cross-over	No	

Method/approach	Description/assumption
Assumptions of waning effect	No.
Assumptions of cure point	No a'priori assumptions of cure-point were made.

D.4.3 Parametric functions

Table 82. Statistical goodness of fit for subgroup models by outcome and arm. Integrated data-set (patients with known CPS<5)

	Zolbetuximab plus chemotherapy		Placebo plus chemotherapy	
Function	AIC	BIC	AIC	BIC
OS				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
PFS				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Figure 36 Estimated failure-time models and KM curves (with 95% CI) for OS/PFS in CPS<5 subgroup. Upper panels: Zolbetuximab plus chemo. Lower panels: placebo plus chemotherapy

[redacted]

D.4.4 Model selection

In terms of statistical goodness of fit (Table 82), the models for the parametric survival function are ranked similar to the models for the full population. Only exception is the PFS function for chemotherapy where the log-normal model moved up in rank in terms of goodness of fit (from 5 in the overall population to 2 in BIC and 3 in AIC). Log-logistic remained the model with best goodness of fit.

The predicted median failure time and estimated survival at 3,4, and 5 years are very similar to the models for the overall population. On this basis, it is reasonable to use the same survival functions in the sensitivity analysis as in the overall population.

Function	Median	36 months	48 months	60 months
OS. Zolbetuximab + Chemo				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
PFS. Zolbetuximab + Chemo				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
OS. Chemo				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
PFS. Chemo				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]

Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]

D.5 Additional material

D.5.1 Parameter estimates (all models)

OS		Zolbetuximab plus chemo		Placebo plus chemo	
Model	Parameter	Est	95% CI	Est	95% CI
Exponential	rate	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	Q	[redacted]	[redacted]	[redacted]	[redacted]

PFS		Zol plus chemo		PBO plus chemo	
Model	Parameter	Est	95% CI	Est	95% CI
Exponential	rate	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	shape	[redacted]	[redacted]	[redacted]	[redacted]

PFS		Zol plus chemo		PBO plus chemo	
Model	Parameter	Est	95% CI	Est	95% CI
	scale	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	Q	[redacted]	[redacted]	[redacted]	[redacted]

TTD		Zol plus chemo		PBO plus chemo	
Model	Parameter	Est	95% CI	Est	95% CI
GLOW					
Exponential	rate	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	Q	[redacted]	[redacted]	[redacted]	[redacted]
SPOTLIGHT		[redacted]	[redacted]	[redacted]	[redacted]
Exponential	rate	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]

TTD		Zol plus chemo		PBO plus chemo	
Model	Parameter	Est	95% CI	Est	95% CI
Gompertz	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	Q	[redacted]	[redacted]	[redacted]	[redacted]

Sensitifity analyses		Zol plus chemo		PBO plus chemo	
Model	Parameter	OS	PFS	OS	PFS
Exponential	rate	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	Q	[redacted]	[redacted]	[redacted]	[redacted]

D.5.2 Predicted and observed hazards. All outcomes and distributions

Instant hazards are shown for all outcomes and estimated function on the following pages. For the OS models the graphs also display the general population mortality rate at the model age. Observed hazards were estimated as the 8-week rolling average of weekly change in cumulative hazard (estimated as -ln(S(t), where S(t) is the nearest observed KM rate at week *t* for the outcome and study arm in question).

Figure 37 Comparison of predicted and observed hazards rates for OS. Zolbetuximab plus chemotherapy left panel. Placebo plus chemotherapy right panel.

[redacted]

Figure 38 Comparison of predicted and observed hazards rates for PFS. Zolbetuximab plus chemotherapy left panel. Placebo plus chemotherapy right panel.

[redacted]

Figure 39 Comparison of predicted and observed hazards rates for TTD in GLOW. Zolbetuximab plus chemotherapy left panel. Placebo plus chemotherapy right panel.

[redacted]

Figure 40 Comparison of predicted and observed hazards rates for TTD in SPOTLIGHT. Zolbetuximab plus chemotherapy left panel. Placebo plus chemotherapy right panel.

[redacted]

Figure 41 Comparison of predicted and observed hazards rates for OS (CPS<5). Zolbetuximab plus chemotherapy left panel. Placebo plus chemotherapy right panel.

[redacted]

Figure 42 Comparison of predicted and observed hazards rates for PFS (CPS<5). Zolbetuximab plus chemotherapy left panel. Placebo plus chemotherapy right panel.

[redacted]

Appendix E. Serious adverse events

For the clinical studies of zolbetuximab, and pembrolizumab, serious adverse events occurring in ≥1% of participants in any treatment group are reported below. For nivolumab, serious adverse events occurring in ≥2% of participants in any treatment group are reported. All data is sourced from the respective the EPAR assessment reports.

Zolbetuximab vs chemotherapy (integrated safety analysis SPOTLIGHT/GLOW)

Table 83. Serious TEAE occuring ≥1% of participants in any treatment group (Integrated safety analysis) (safety analysis set)[18]

MedDRA v25.0 System Organ Class Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Serious TEAE	**245 (46.0)**	**245 (46.5)**
Blood and Lymphatic System Disorders	**29 (5.4)**	**24 (4.6)**
Anaemia	10 (1.9)	10 (1.9)
Neutropenia	10 (1.9)	5 (0.9)
Febrile neutropenia	8 (1.5)	4 (0.8)
Thrombocytopenia	4 (0.8)	2 (0.4)
Gastrointestinal Disorders	**109 (20.5)**	**92 (17.5)**
Vomiting	38 (7.1)	24 (4.6)
Nausea	30 (5.6)	17 (3.2)
Diarrhoea	15 (2.8)	14 (2.7)
Intestinal obstruction	10 (1.9)	4 (0.8)
Upper gastrointestinal haemorrhage	10 (1.9)	4 (0.8)
Abdominal pain	8 (1.5)	15 (2.8)
General Disorders and Administration Site Conditions	**42 (7.9)**	**35 (6.6)**
Pyrexia	12 (2.3)	8 (1.5)
Asthenia	7 (1.3)	4 (0.8)
Fatigue	7 (1.3)	6 (1.1)
Hepatobiliary Disorders	**17 (3.2)**	**20 (3.8)**
Hepatic function abnormal	3 (0.6)	3 (0.6)
Cholecystitis	2 (0.4)	5 (0.9)
Infections and Infestations	**54 (10.1)**	**44 (8.3)**
Pneumonia	12 (2.3)	13 (2.5)
Sepsis	6 (1.1)	3 (0.6)
COVID-19	3 (0.6)	5 (0.9)
Investigations	**19 (3.6)**	**19 (3.6)**
Platelet count decreased	8 (1.5)	6 (1.1)
Neutrophil count decreased	2 (0.4)	5 (0.9)
Metabolism and Nutrition Disorders	**31 (5.8)**	**24 (4.6)**

MedDRA v25.0 System Organ Class Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Decreased appetite	11 (2.1)	5 (0.9)
Hypokalaemia	11 (2.1)	8 (1.5)
Musculoskeletal and Connective Tissue Disorders	**3 (0.6)**	**6 (1.1)**
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**24 (4.5)**	**34 (6.5)**
Malignant neoplasm progression	19 (3.6)	25 (4.7)
Nervous System Disorders	**17 (3.2)**	**16 (3.0)**
Renal and Urinary Disorders	**13 (2.4)**	**14 (2.7)**
Acute kidney injury	4 (0.8)	3 (0.6)
Respiratory, Thoracic and Mediastinal Disorders	**23 (4.3)**	**37 (7.0)**
Pulmonary embolism	8 (1.5)	12 (2.3)
Respiratory failure	4 (0.8)	2 (0.4)
Dyspnoea	3 (0.6)	10 (1.9)
Pleural effusion	3 (0.6)	10 (1.9)
Vascular Disorders	**15 (2.8)**	**6 (1.1)**
Hypotension	5 (0.9)	1 (0.2)
Deep vein thrombosis	4 (0.8)	1 (0.2)

Pembrolizumab vs chemo (KEYNOTE 859)

Table 84 Serious adverse events with a frequency of at least 1% (pembrolizumab (03OCT2022) (KEYNOTE 859)[32]

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	785		787	
with one or more adverse events	355	(45.2)	316	(40.2)
with no adverse events	430	(54.8)	471	(59.8)
Diarrhoea	31	(3.9)	25	(3.2)
Pneumonia	30	(3.8)	14	(1.8)
Vomiting	19	(2.4)	23	(2.9)
Colitis	16	(2.0)	4	(0.5)
Pulmonary embolism	15	(1.9)	6	(0.8)
Nausea	14	(1.8)	11	(1.4)
Abdominal pain	12	(1.5)	9	(1.1)
Acute kidney injury	12	(1.5)	11	(1.4)
Pyrexia	12	(1.5)	9	(1.1)
Death	11	(1.4)	4	(0.5)
Decreased appetite	9	(1.1)	10	(1.3)
Gastrointestinal haemorrhage	9	(1.1)	8	(1.0)
Upper gastrointestinal haemorrhage	9	(1.1)	8	(1.0)
Anaemia	8	(1.0)	8	(1.0)
Dysphagia	8	(1.0)	15	(1.9)
Hypokalaemia	8	(1.0)	6	(0.8)
Intestinal obstruction	8	(1.0)	6	(0.8)
Pleural effusion	8	(1.0)	2	(0.3)
Pneumonitis	8	(1.0)	2	(0.3)
Sepsis	7	(0.9)	7	(0.9)
Ascites	5	(0.6)	9	(1.1)
Febrile neutropenia	3	(0.4)	7	(0.9)
Obstruction gastric	3	(0.4)	9	(1.1)
Thrombocytopenia	3	(0.4)	1	(0.1)
Urinary tract infection	3	(0.4)	2	(0.3)
Dyspnoea	1	(0.1)	2	(0.3)
Neutropenia	1	(0.1)	1	(0.1)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Nivolumab vs chemo (CheckMate-649)

Table 85 Serious adverse events reported in ≥ 2% of All Treated Subjects (nivolumab) (June 2020) (CheckMate study)[28]

System Organ Class (%)	Nivo+Chemo N = 782			Chemo N = 767		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	423 (54.1)	281 (35.9)	81 (10.4)	335 (43.7)	229 (29.9)	63 (8.2)
Gastrointestinal disorders	133 (17.0)	103 (13.2)	3 (0.4)	123 (16.0)	100 (13.0)	0
Vomiting	25 (3.2)	17 (2.2)	0	24 (3.1)	19 (2.5)	0
Diarrhoea	19 (2.4)	14 (1.8)	0	12 (1.6)	9 (1.2)	0
Dysphagia	10 (1.3)	9 (1.2)	0	16 (2.1)	15 (2.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	123 (15.7)	55 (7.0)	60 (7.7)	100 (13.0)	39 (5.1)	51 (6.6)
Malignant neoplasm progression	109 (13.9)	45 (5.8)	60 (7.7)	90 (11.7)	33 (4.3)	51 (6.6)
Infections and infestations	72 (9.2)	53 (6.8)	4 (0.5)	33 (4.3)	28 (3.7)	0
Pneumonia	22 (2.8)	16 (2.0)	2 (0.3)	10 (1.3)	9 (1.2)	0
Blood and lymphatic system disorders	52 (6.6)	42 (5.4)	2 (0.3)	24 (3.1)	22 (2.9)	0
Anaemia	24 (3.1)	18 (2.3)	0	9 (1.2)	8 (1.0)	0
Febrile neutropenia	18 (2.3)	16 (2.0)	1 (0.1)	7 (0.9)	7 (0.9)	0
Respiratory, thoracic and mediastinal disorders	45 (5.8)	27 (3.5)	3 (0.4)	29 (3.8)	19 (2.5)	2 (0.3)
Pneumonitis	17 (2.2)	11 (1.4)	0	1 (0.1)	0	0
General disorders and administration site conditions	40 (5.1)	19 (2.4)	2 (0.3)	30 (3.9)	15 (2.0)	2 (0.3)
Pyrexia	20 (2.6)	5 (0.6)	0	10 (1.3)	3 (0.4)	0

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Appendix F. Health-related quality of life

PRO assessments were completed by patients using an electronic tablet device; if completion by patients was not possible, assessments were administered to patients by site personnel using an electronic tablet device. Assessments were completed at screening, every 3 weeks while on treatment before any antiemetic or study drug treatment and before discussion of patient disease status, at treatment discontinuation, and 30 days and 90 days after treatment discontinuation.[25]

The combined ITT population consisted of 1072 patients: 537 patients in the zolbetuximab plus chemotherapy arms (SPOTLIGHT, 283; GLOW, 254) and 535 patients in the placebo plus chemotherapy arms (SPOTLIGHT, 282; GLOW, 253). Demographic and baseline characteristics were well balanced between treatment arms in both SPOTLIGHT and GLOW. Baseline characteristics are presented in Table 7 in the main document, and is also presented in the publication of HRQoL by Lordick and colleagues (2024). [25]

F.1 EQ-5D - VAS

Patterns of missing data and completion for SPOTLIGHT and GLOW are presented in Table 86 (SPOTLIGHT) and Table 87 (GLOW). Note that completion rates are not available for the EQ-5D VAS answers, specifically. The number of missing responses in the tables therefore refer to the number of subjects who did not complete the full EQ-5D questionnaire. In SPOTLIGHT and GLOW, compliance rates were mostly >70% for visits with ≥10% patients in either treatment arm completing the EQ-5D-5L assessments.[25]

Table 86 Pattern of missing data and completion for EQ-5D at primary data-cut (SPOTLIGHT)

	SPOTLIGHT (EQ-5D) Compliance rate		
	FAS (N = 565)		
Analysis Visit	Missing*	Expected	Compliance†
Baseline	[redacted]	[redacted]	[redacted]
C1 D22	[redacted]	[redacted]	[redacted]
C2 D1	[redacted]	[redacted]	[redacted]
C2 D22	[redacted]	[redacted]	[redacted]
C3 D1	[redacted]	[redacted]	[redacted]
C3 D22	[redacted]	[redacted]	[redacted]
C4 D1	[redacted]	[redacted]	[redacted]
C4 D22	[redacted]	[redacted]	[redacted]

	SPOTLIGHT (EQ-5D) Compliance rate		
	FAS (N = 565)		
Analysis Visit	Missing*	Expected	Compliance†
C5 D1	[redacted]	[redacted]	[redacted]
C5 D22	[redacted]	[redacted]	[redacted]
C6 D1	[redacted]	[redacted]	[redacted]
C6 D22	[redacted]	[redacted]	[redacted]
C7 D1	[redacted]	[redacted]	[redacted]
C7 D22	[redacted]	[redacted]	[redacted]
C8 D1	[redacted]	[redacted]	[redacted]
C8 D22	[redacted]	[redacted]	[redacted]
C9 D1	[redacted]	[redacted]	[redacted]
C9 D22	[redacted]	[redacted]	[redacted]
C10 D1	[redacted]	[redacted]	[redacted]
C10 D22	[redacted]	[redacted]	[redacted]
C11 D1	[redacted]	[redacted]	[redacted]
C11 D22	[redacted]	[redacted]	[redacted]
C12 D1	[redacted]	[redacted]	[redacted]
C12 D22	[redacted]	[redacted]	[redacted]
C13 D1	[redacted]	[redacted]	[redacted]
C13 D22	[redacted]	[redacted]	[redacted]
C14 D1	[redacted]	[redacted]	[redacted]
C14 D22	[redacted]	[redacted]	[redacted]
C15 D1	[redacted]	[redacted]	[redacted]
C15 D22	[redacted]	[redacted]	[redacted]
C16 D1	[redacted]	[redacted]	[redacted]
C16 D22	[redacted]	[redacted]	[redacted]
C17 D1	[redacted]	[redacted]	[redacted]
C17 D22	[redacted]	[redacted]	[redacted]
C18 D1	[redacted]	[redacted]	[redacted]
C18 D22	[redacted]	[redacted]	[redacted]
C19 D1	[redacted]	[redacted]	[redacted]
C19 D22	[redacted]	[redacted]	[redacted]
C20 D1	[redacted]	[redacted]	[redacted]

	SPOTLIGHT (EQ-5D) Compliance rate		
	FAS (N = 565)		
Analysis Visit	Missing*	Expected	Compliance†
C20 D22	[redacted]	[redacted]	[redacted]
C21 D1	[redacted]	[redacted]	[redacted]
C21 D22	[redacted]	[redacted]	[redacted]
C22 D1	[redacted]	[redacted]	[redacted]
C22 D22	[redacted]	[redacted]	[redacted]
C23 D1	[redacted]	[redacted]	[redacted]
C23 D22	[redacted]	[redacted]	[redacted]
C24 D1	[redacted]	[redacted]	[redacted]
C24 D22	[redacted]	[redacted]	[redacted]
C25 D1	[redacted]	[redacted]	[redacted]
C25 D22	[redacted]	[redacted]	[redacted]
C26 D1	[redacted]	[redacted]	[redacted]
C26 D22	[redacted]	[redacted]	[redacted]
C27 D1	[redacted]	[redacted]	[redacted]
C27 D22	[redacted]	[redacted]	[redacted]
C28 D1	[redacted]	[redacted]	[redacted]
C28 D22	[redacted]	[redacted]	[redacted]
C29 D1	[redacted]	[redacted]	[redacted]
C29 D22	[redacted]	[redacted]	[redacted]
C30 D1	[redacted]	[redacted]	[redacted]
C30 D22	[redacted]	[redacted]	[redacted]
C31 D1	[redacted]	[redacted]	[redacted]
C32 D1	[redacted]	[redacted]	[redacted]
30 SFU	[redacted]	[redacted]	[redacted]
90 FU	[redacted]	[redacted]	[redacted]

Abbreviation: 30 SFU: 30-days safety follow-up; 90 FU; 90-days follow-up; C Cycle; D Day
"† N (FAS) minus number of subjects with in complete EQ-5D data divided by N (FAS)
* Compliance (or adjusted completion) rate is calculated as the number of subjects with non-missing EQ-5D questionaire divided by the number of subjects with PRO assessments expected by visit.

Table 87 Pattern of missing data and completion for EQ-5D at primary data-cut (GLOW)

	GLOW (EQ-5D) Compliance rate FAS (N = 507)		
Analysis Visit	Missing*	Expected	Compliance†
Baseline	[redacted]	[redacted]	[redacted]
C2 D1	[redacted]	[redacted]	[redacted]
C3 D1	[redacted]	[redacted]	[redacted]
C4 D1	[redacted]	[redacted]	[redacted]
C5 D1	[redacted]	[redacted]	[redacted]
C6 D1	[redacted]	[redacted]	[redacted]
C7 D1	[redacted]	[redacted]	[redacted]
C8 D1	[redacted]	[redacted]	[redacted]
C9 D1	[redacted]	[redacted]	[redacted]
C10 D1	[redacted]	[redacted]	[redacted]
C11 D1	[redacted]	[redacted]	[redacted]
C12 D1	[redacted]	[redacted]	[redacted]
C13 D1	[redacted]	[redacted]	[redacted]
C14 D1	[redacted]	[redacted]	[redacted]
C15 D1	[redacted]	[redacted]	[redacted]
C16 D1	[redacted]	[redacted]	[redacted]
C17 D1	[redacted]	[redacted]	[redacted]
C18 D1	[redacted]	[redacted]	[redacted]
C19 D1	[redacted]	[redacted]	[redacted]
C20 D1	[redacted]	[redacted]	[redacted]
C21 D1	[redacted]	[redacted]	[redacted]
C22 D1	[redacted]	[redacted]	[redacted]
C23 D1	[redacted]	[redacted]	[redacted]
C24 D1	[redacted]	[redacted]	[redacted]
C25 D1	[redacted]	[redacted]	[redacted]
C26 D1	[redacted]	[redacted]	[redacted]
C27 D1	[redacted]	[redacted]	[redacted]
C28 D1	[redacted]	[redacted]	[redacted]
C29 D1	[redacted]	[redacted]	[redacted]
C30 D1	[redacted]	[redacted]	[redacted]
C31 D1	[redacted]	[redacted]	[redacted]
C32 D1	[redacted]	[redacted]	[redacted]

	GLOW (EQ-5D) Compliance rate FAS (N = 507)		
Analysis Visit	Missing*	Expected	Compliance†
C33 D1	[redacted]	[redacted]	[redacted]
C34 D1	[redacted]	[redacted]	[redacted]
C35 D1	[redacted]	[redacted]	[redacted]
C36 D1	[redacted]	[redacted]	[redacted]
C37 D1	[redacted]	[redacted]	[redacted]
C38 D1	[redacted]	[redacted]	[redacted]
C39 D1	[redacted]	[redacted]	[redacted]
C40 D1	[redacted]	[redacted]	[redacted]
30 SFU	[redacted]	[redacted]	[redacted]
90 FU	[redacted]	[redacted]	[redacted]

Abbreviation: 30 SFU: 30-days safety follow-up; 90 FU; 90-days follow-up; C Cycle; D Day
"† N (FAS) minus number of subjects with in complete EQ-5D data divided by N (FAS)
* Compliance (or adjusted completion) rate is calculated as the number of subjects with non-missing EQ-5D questionaire divided by the number of subjects with PRO assessments expected by visit.

The planned assessment of EQ-5D VAS in the two studies are described in the main application document. Table 88 (SPOTLIGHT) and Table 89 (GLOW) present the summary of measures by visit and study arm as well as the difference (Mean and 95% CI).

Table 88 HRQoL EQ-5D VAS summary statistics (SPOTLIGHT, FAS primary-data-cut)

	Zolbetuximab + mFOLFOX6 N = 283		Placebo + mFOLFOX6 N = 282		Zolbetuximab vs Placebo
Analysis Visit	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Zolbetuximab + mFOLFOX6 N = 283		Placebo + mFOLFOX6 N = 282		Zolbetuximab vs Placebo
Analysis Visit	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)
Cycle 7 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 days safety follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90 days follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SPOTLIGHT FAS. Primary data-cut (09 Sep 2022)

Table 89 HRQoL EQ-5D summary statistics (GLOW, FAS primary-data-cut)

	Zolbetuximab + CAPOX		Placebo + CAPOX		Zolbetuximab vs
	N = 254		N = 253		placebo
Analysis Visit	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 22 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 23 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 24 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 26 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 27 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 days safety follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90 days follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

GLOW (FAS) Primary data-cut (07October2022)

F.2 Statistical analyses for estimating HSUV

Three methods were used to describe utilities by health states: the descriptive analysis, the generalized estimating equation (GEE) model, and the mixed effects model. The estimation was conducted for the integrated data from SPOTLIGHT and GLOW trials using the preference-weight set for Denmark based on Jensen et al. 2021.[50]

F.2.1 Descriptive analysis

Descriptive statistics on the health utilities measured by the EQ-5D-5L during the trial period were summarized for all randomized subjects by health states, irrespective of the treatment they received. Such data were used to inform health-state specific utility inputs for the CEA model and subsequently estimate the quality-adjusted life years.

- **Pre-progression health state** is defined as the period for subjects treated with the study drug who have not experienced disease progression, or death due to any cause. Pre-progression utility was estimated among EQ-5D assessments occurred during the pre-progression health state.
- **Post-progression health state** is defined as the period for subjects who have experienced disease progression and are still alive. Post-progression utility was estimated based on EQ-5D data collected after the disease progression date up to death.

For subjects who were censored for PFS, EQ-5D-5L assessments occurred after the censor date were not included in the analysis. No imputation was performed for missing evaluations and thus a subject who did not have an evaluation on a scheduled visit would be excluded from the analysis for that visit.

F.2.2 Generalized estimating equation model

Generalized estimating equation (GEE) is a marginal or population-average model that provides the population-averaged estimates of the parameters. The model is semi-parametric model that does not require distribution assumption of the outcome. For the GEE model, utilities from all included patients were used. The dependent variable was EQ-5D-5L utilities, and the independent variable was the health state (pre- vs. post-progression) with pre-progression as the reference group. An exchangeable working correlation structure was specified assuming the values collected from the same patient at different time points were expected to be correlated. A robust variance estimator was used to account for correlation within patients' repeated assessments.

F.2.3 Mixed effects model

Mixed effects model is a subject specific model, where both population-averaged estimates and subject specific random effects are of interests. The model is a likelihood-based parametric model, and a Gaussian distribution has been assumed for the outcome. For the mixed effects model, utilities from all included patients were used. The dependent variable was EQ-5D-5L utilities, and the independent variable was the health state (pre- vs. post-progression) with pre-progression as the reference group. Both random intercepts and slopes were considered in the analysis. The patient effects were included as random effects to account for unobserved, patient's specific characteristics and multiple observations per patient. The population-averaged estimates are the average of individual subject results.

F.2.4 Data for HSUV estimation

In the pooled data from the GLOW and SPOTLIGHT trials, the numbers of patients were 994 and 350, respectively and the numbers of observations were 11249 and 1243, respectively (Table 90).

Table 90. Number of patients and observations with non-missing EQ-5D data

Pre-progression		Post-progression	
Number of patients	Number of observations	Number of patients	Number of observations
994	11249	350	1243

Note: No imputation was performed for missing evaluations and thus a subject who did not have an evaluation on a scheduled visit would be excluded from the analysis for that visit.

Pattern of completion is presented per visit Table 91 below and by visit and health state in Table 92 (used in the model). Note that

- Tables are based on the integrated data from GLOW and SPOTLIGHT EQ-5D responses (final OS data-cut).
- Assessment schedules during the treatment period were different between the GLOW and SPOTLIGHT trials. Assessments were scheduled on Day 1 of each cycle in GLOW (21 days per cycle) but were scheduled on Day 1 and Day 22 of each cycle in SPOTLIGHT (42 days per cycle). Scheduled visits in GLOW and SPOTLIGHT were harmonized from cycles into weeks.
- Screening and unscheduled visits are not included in this table. Only post-randomization visits were considered in the utility analysis, which led to the exclusion of most screening visits. Unscheduled visits, by definition, are also excluded, as they occur on an as-needed basis rather than at predetermined times.

Table 91 Pattern of missing data and completion for EQ-5D-5L (SPOTLIGHT and GLOW; final OS data-cut) by visit

Analysis visit*	Missing of HRQoL population	Expected to complete (% of population)	Completion (% of expected)
Baseline	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]
Week 10	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Week 19	[redacted]	[redacted]	[redacted]

Week 22	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]
Week 31	[redacted]	[redacted]	[redacted]
Week 34	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]
Week 43	[redacted]	[redacted]	[redacted]
Week 46	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]
Week 55	[redacted]	[redacted]	[redacted]
Week 58	[redacted]	[redacted]	[redacted]
Week 61	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]
Week 67	[redacted]	[redacted]	[redacted]
Week 70	[redacted]	[redacted]	[redacted]
Week 73	[redacted]	[redacted]	[redacted]
Week 76	[redacted]	[redacted]	[redacted]
Week 79	[redacted]	[redacted]	[redacted]
Week 82	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]
Week 91	[redacted]	[redacted]	[redacted]
Week 94	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]
Week 100	[redacted]	[redacted]	[redacted]
Week 103	[redacted]	[redacted]	[redacted]
Week 106	[redacted]	[redacted]	[redacted]
Week 109	[redacted]	[redacted]	[redacted]
Week 112	[redacted]	[redacted]	[redacted]
Week 115	[redacted]	[redacted]	[redacted]
Week 118	[redacted]	[redacted]	[redacted]
Week 121	[redacted]	[redacted]	[redacted]
Week 124	[redacted]	[redacted]	[redacted]
Week 127	[redacted]	[redacted]	[redacted]

Week 130	[redacted]	[redacted]	[redacted]
Week 133	[redacted]	[redacted]	[redacted]
Week 136	[redacted]	[redacted]	[redacted]
Week 139	[redacted]	[redacted]	[redacted]
Week 142	[redacted]	[redacted]	[redacted]
Week 145	[redacted]	[redacted]	[redacted]
Week 148	[redacted]	[redacted]	[redacted]
Week 151	[redacted]	[redacted]	[redacted]
Week 154	[redacted]	[redacted]	[redacted]
Week 157	[redacted]	[redacted]	[redacted]
Week 160	[redacted]	[redacted]	[redacted]
Week 163	[redacted]	[redacted]	[redacted]
Week 166	[redacted]	[redacted]	[redacted]
Week 169	[redacted]	[redacted]	[redacted]
Week 172	[redacted]	[redacted]	[redacted]
Week 175	[redacted]	[redacted]	[redacted]
Week 178	[redacted]	[redacted]	[redacted]
Week 181	[redacted]	[redacted]	[redacted]
Week 184	[redacted]	[redacted]	[redacted]
Week 187	[redacted]	[redacted]	[redacted]
Week 190	[redacted]	[redacted]	[redacted]
Week 193	[redacted]	[redacted]	[redacted]
Week 196	[redacted]	[redacted]	[redacted]
Week 199	[redacted]	[redacted]	[redacted]
Week 202	[redacted]	[redacted]	[redacted]
Week 205	[redacted]	[redacted]	[redacted]
Week 208	[redacted]	[redacted]	[redacted]
Week 211	[redacted]	[redacted]	[redacted]
Week 214	[redacted]	[redacted]	[redacted]
Week 217	[redacted]	[redacted]	[redacted]
Week 220	[redacted]	[redacted]	[redacted]
Week 223	[redacted]	[redacted]	[redacted]
SDD Visit	[redacted]	[redacted]	[redacted]
30 D SFU	[redacted]	[redacted]	[redacted]
90 D FU	[redacted]	[redacted]	[redacted]

Abbreviations 30 D SFU 30-days safety follow-up; 90 D FU 90-days follow-up; SDD Study Drug Discontinuation Visit

* Week in table refers in day one of each cycle in GLOW and day one or day 22 of each cycle in SPOTLIGHT. Mean only calculated for visits with 5 or more complete questionaires

Table 92 Completion rates for EQ-5D-5L (SPOTLIGHT and GLOW) by visit and health state

	Pre-progression			Post-progression		
Analysis visit*	Number of expected responses	Number of observed responses	Completion rates	Number of expected responses	Number of observed responses	Completion rates
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pre-progression			Post-progression		
Analysis visit*	Number of expected responses	Number of observed responses	Completion rates	Number of expected responses	Number of observed responses	Completio n rates
Week 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 67	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 82	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 106	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 109	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pre-progression			Post-progression		
Analysis visit*	Number of expected responses	Number of observed responses	Completion rates	Number of expected responses	Number of observed responses	Completio n rates
Week 118	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 121	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 124	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 127	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 130	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 133	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 136	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 139	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 142	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 145	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 148	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 157	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 160	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 163	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 166	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 169	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 172	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 175	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 178	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pre-progression			Post-progression		
Analysis visit*	Number of expected responses	Number of observed responses	Completion rates	Number of expected responses	Number of observed responses	Completio n rates
Week 181	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 184	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 187	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 190	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 193	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 196	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 199	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 202	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 205	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 208	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 211	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 214	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 217	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 220	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 223	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Week in table refers in day one of each cycle in GLOW and day one or day 22 of each cycle in SPOTLIGHT

The EQ-5D index change from baseline is presented section 14.1.3. Table 93 presents the summary statistics by visit.

Table 93 HRQoL EQ-5D index (DK) summary statistics

Analysis	Zolbetuximab + chemotherapy		Placebo + chemotherapy		Zolbetuximab vs PBO
visit*	N	Mean (95%CI)	N	Mean (95%CI)	Mean (95%CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Analysis	Zolbetuximab + chemotherapy		Placebo + chemotherapy		Zolbetuximab vs PBO
visit*	N	Mean (95%CI)	N	Mean (95%CI)	Mean (95%CI)
Week 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 67	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 82	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 106	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Analysis visit*	Zolbetuximab + chemotherapy		Placebo + chemotherapy		Zolbetuximab vs PBO
	N	Mean (95%CI)	N	Mean (95%CI)	Mean (95%CI)
Week 109	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 118	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 121	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 124	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 127	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 130	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 133	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 136	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 139	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 142	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 145	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 148	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 157	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 160	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 163	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 166	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 169	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 172	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 175	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 178	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 181	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 184	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 187	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 D SFU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90 D FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations 30 D SFU 30-days safety follow-up; 90 D FU 90-days follow-up; CI confidence interval
* Week in table refers in day one of each cycle in GLOW and day one or day 22 of each cycle in SPOTLIGHT.
Mean only calculated for visits with 5 or more complete questionaires

F.2.5 Estimation results

The descriptive statistics for Denmark, and the estimation results based on the GEE model and the mixed effects model are presented in Table 94. Based on the descriptive analysis, the utility values were 0.875 for pre-progression and 0.820 for post-progression using pooled data. All three methods consistently demonstrate the utility for pre-progression state is higher than post-progression state. The differences between the two health states ranges from [redacted] to [redacted], contingent on method.

Table 94. Estimation results for Denmark (Integrated dataset; final OS data-cut)

	Descriptive statistics		GEE		Mixed effects model	
	Mean	SE	Mean	SE	Mean	SE
Pre-progression	0.875	0.002	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	0.820	0.007	[redacted]	[redacted]	[redacted]	[redacted]
Difference	0.054	-	[redacted]	[redacted]	[redacted]	[redacted]

Appendix G. Probabilistic sensitivity analyses

Table 95. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Extrapolation curves. OS Zolbetuximab (log-log)				
Scale	69.88	63.53	76.22	Multivariate normal
Shape	1.69	1.55	1.83	
Extrapolation curves. OS Chemo (gamma)				
Shape	1.51	1.33	1.69	Multivariate normal
Rate	0.020	0.017	0.023	
Extrapolation curves. PFS Zolbetuximab (log-log)				
Scale	45.33	40.69	49.97	Multivariate normal
Shape	1.63	1.48	1.77	
Extrapolation curves. PFS Chemo (log-log)				
Scale	34.81	31.79	37.82	Multivariate normal
Shape	1.81	1.65	1.96	
Extrapolation curves. TTD Zolbetuximab + Capox (gamma)				
Shape	0.63	0.54	0.73	Multivariate normal
Rate	0.02	0.01	0.02	
Extrapolation curves. TTD CAPOX (gamma)				
Shape	1.29	1.09	1.49	Multivariate normal
Rate	0.05	0.04	0.06	
Extrapolation curves. TTD Zolbetuximab + CAPOX (gamma)				
Shape	0.67	0.57	0.77	Multivariate normal
Rate	0.01	0.01	0.02	
Extrapolation curves. TTD FOLFOX (log)				
Scale	26.96	23.93	29.99	Multivariate normal
Shape	1.76	1.58	1.95	

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Dosing				
BSA	1.81	1.78	1.84	Simultaneous distribution estimated from N:5000 bootstrap samples from SPOTLIGHT (with replacement) stratified by race (non-Asian, Asian)
Zolbetuximab vials per infusion. Loading dose	14.9	14.7	15.2	
Zolbetuximab vials per infusion. Maintenance dose (600mg)	11.3	11.2	11.5	
Zolbetuximab vials per infusion. Maintenance dose (400mg)	7.7	7.6	7.8	
Zolbetuximab. Skipped infusions	1.0%	0.8%	1.3%	Beta
Population				
Age	58.5	57.0	60.0	Normal
Percent female	37.9%	35.0%	40.8%	Beta
HSUV				
PF	0.875	0.871	0.879	Simultaneous distribution estimated from N:5000 samples using difference method (Ren et al. 2018). PF, PD sampled from beta distribution. Difference in logit transformed HSUV sampled from gamma distribution.
PD	0.820	0.805	0.833	
Direct medical cost				
Subsequent treatment cost. Zol	6,148.92	4,919.11	7,378.72	Gamma
Subsequent treatment cost. Che	6,889.06	5,511.22	8,266.90	Gamma
Monitoring costs. PF	36,726.00	29,380.67	44,071.33	Gamma
Monitoring costs. PD	7,164.00	5,731.17	8,596.83	Gamma

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
CDLN18.2 test costs	2,051.77	1,641.41	2,462.13	Gamma
Patients costs				
Additional IV infusion time (zolbetuximab) (h)	3.0	2.9	3.1	Gamma
CT-scan (h per visit)	1.0	0.8	1.2	Gamma
Outpatient visit (h per visit)	1.0	0.8	1.2	Gamma
Nurse visit (h per visit)	0.5	0.4	0.6	Gamma
Transport cost (DKK per visit)	140.00	112.00	168.00	Gamma
Side-effects				
Incidence rates (zolbetuximab). Neutropenia	18.2%	14.9%	21.5%	Beta
Neutrophil count decreased	17.8%	14.6%	21.1%	Beta
Vomiting	14.3%	11.3%	17.2%	Beta
Nausea	12.6%	9.8%	15.4%	Beta
Anaemia	9.6%	7.1%	12.1%	Beta
Decreased appetite	6.2%	4.1%	8.2%	Beta
Hypokalaemia	5.6%	3.7%	7.6%	Beta
Asthenia	5.1%	3.2%	6.9%	Beta
Diarrhoea	5.1%	3.2%	6.9%	Beta
Incidence rates (Chemo alone). Neutropenia	13.7%	10.7%	16.6%	Beta
Neutrophil count decreased	17.6%	14.4%	20.9%	Beta
Vomiting	4.7%	2.9%	6.5%	Beta
Nausea	4.6%	2.8%	6.3%	Beta
Anaemia	10.2%	7.7%	12.8%	Beta
Decreased appetite	2.5%	1.1%	3.8%	Beta
Hypokalaemia	4.9%	3.1%	6.8%	Beta
Asthenia	1.9%	0.7%	3.1%	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Diarrhoea	5.1%	3.2%	7.0%	Beta
AE duration (zolbetuximab).				
Neutropenia	1.9	1.5	2.3	Log-Normal
Neutrophil count decreased	2.4	1.9	2.9	Log-Normal
Vomiting	1.0	0.8	1.2	Log-Normal
Nausea	1.0	0.8	1.2	Log-Normal
Anaemia	2.1	1.7	2.6	Log-Normal
Decreased appetite	0.0	0.0	0.0	Log-Normal
Hypokalaemia	0.5	0.4	0.6	Log-Normal
Asthenia	1.0	0.8	1.2	Log-Normal
Diarrhoea	1.0	0.8	1.2	Log-Normal
AE duration (Chemo alone).				
Neutropenia	1.9	1.5	2.3	Log-Normal
Neutrophil count decreased	2.4	1.9	2.9	Log-Normal
Vomiting	1.0	0.8	1.2	Log-Normal
Nausea	1.0	0.8	1.2	Log-Normal
Anaemia	2.1	1.7	2.6	Log-Normal
Decreased appetite	0.0	0.0	0.0	Log-Normal
Hypokalaemia	0.5	0.4	0.6	Log-Normal
Asthenia	1.0	0.8	1.2	Log-Normal
Diarrhoea	1.0	0.8	1.2	Log-Normal
AE disutility.				
Neutropenia	-0.090	-0.108	-0.072	Normal
Neutrophil count decreased	-0.050	-0.060	-0.040	Normal
Vomiting	-0.103	-0.124	-0.082	Normal
Nausea	-0.103	-0.124	-0.082	Normal
Anaemia	-0.120	-0.144	-0.096	Normal
Decreased appetite	0.000	0.000	0.000	Normal
Hypokalaemia	-0.070	-0.084	-0.056	Normal
Asthenia	-0.115	-0.138	-0.092	Normal

Appendix H. Literature searches for the clinical assessment Appendix I.

I.1 Efficacy and safety of the intervention and comparator(s)

A systematic literature review (SLR) was conducted by Astellas in order obtain the most up to date information about the published evidence on efficacy and safety of different treatments in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction cancer. Below, find a brief description of the SLR. Details are available in appendix H and the full SLR report. [24] The objective was to identify published evidence on efficacy and safety of treatments for patients with locally advanced unresectable or metastatic G/GEJC.

The SLR prepared by Astellas included all treatment regimens for G/GEJC (various chemo regimens and PD-(L)1 inhibitors). The most relevant comparators to zolbetuximab in Denmark in this assessment are pembrolizumab, nivolumab and chemotherapy (CAPOX and mFOLFOX6). The comparison of zolbetuximab to chemotherapy (CAPOX/mFOLFOX6) is based on the pivotal trials for zolbetuximab (SPOTLIGHT and GLOW). Hence, focus in the Danish literature search is to obtain information about the efficacy and safety of zolbetuximab, nivolumab and pembrolizumab, respectively. Below a description of the SLR conducted by Astellas is presented. Details are available in the full SLR report[24]

Table 96 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	OVID platform	1980 to present	22nd September 2020 for the original review, 11th August 2022 for first SLR update, 30th October 2023 for the second SLR update and 4th March 2024 for third SLR update
Medline	OVID platform	1946 to present	
Cochrane	OVID platform	To present	

Table 97 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Reference list	Search of reference lists to identified studies in the search presented in Table 96	Manual search	October 5 2020; September 8 2022; November 1 2023

Source name	Location/source	Search strategy	Date of search
	Conference proceedings (ASCO, ESMO, ISPOR, IGCC) and clinical trials registers (Clinicaltrials.gov, "International Clinical Trials Registry")		

Table 98 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Clinical Oncology (ASCO) – Annual Meeting International Conference on Malignant Lymphoma (ICML)	Conference website	Manual search	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer	October 8 2020; September 8 2022; October 31 2023
European Society for Medical Oncology (ESMO)	Conference website	Manual search	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer	October 8 2020; September 8 2022; November 11 2023
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	Conference website	Manual search	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer	October 8 2020; September 8 2022; October 31 2023
International Gastric Cancer Association (IGCC) – Biennial	Conference website	Manual search	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer	October 8 2020; September 8 2022; October 31 2023
ASCO- Gastrointestinal Cancers Symposium	Conference website	Manual search	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer	October 8 2020; September 8

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
				2022; October 31 2023

I.1.1 Search strategies

The search strategy for the latest update of the literature search March 4th 2024 is presented below.

Table 99 of search strategy table for EMBASE (data of search March 4th 2024)

No.	Query	Results
#	Query	Results from 4 Mar 2024
1	exp stomach cancer/	156,671
2	((stomach or gastric) adj4 (neoplas* or cancer* or carcinom* or tumo?r* or malign* or adenocarcin*)).mp.	217,114
3	((gastroesophag* or gastro-?esophag* or ?esophagogastric or ?esophago-gastric or cardia or GEJ or GOJ or OGJ) adj4 (neoplas* or cancer* or carcinom* or tumo?r* or malign* or adenocarcin*)).mp.	14,347
4	exp gastroesophageal junction/	8,839
5	or/1-4	229,497
6	((stage adj1 (three or "3" or 3A or 3B or III or IIIA or IIIB or four or "4" or IV)) or advanced or metasta* or progress* or refractory or recurren* or unresectable).mp.	4,839,989
7	5 and 6	103,472
8	exp capecitabine/ or (capecitabine or Xeloda or CAPOX or CapeOx or CAPE-OX or XELOX).mp.	42,685
9	exp zolbetuximab/ or (zolbetuximab or IMAB362 or claudiximab).mp.	216
10	exp irinotecan/ or (irinotecan or Campto or Camptosar or Onivyde or CPT-11).mp.	49,980
11	exp fluorouracil/ or exp fluoropyrimidine/ or (fluorouracil or 5-FU or 5FU or 5-fluracil or fluoro uracil or flouracil or fluoropyridine or fluoropyrimidine or Adrucil or S-1 or S1 or Teysuno).mp.	373,830
12	exp docetaxel/ or (docetaxel or Taxceus or Taxotere).mp.	78,143
13	exp cisplatin/ or (cisplatin or cisplatinum or CDDP or Platin).mp.	238,308

No.	Query	Results
14	exp oxaliplatin/ or (oxaliplatin or Eloxatin).mp.	58,378
15	(FOLFOX* or mFOLFOX* or DCF or ECF or EOX or ECX or FLOT or FOLFIRI).mp.	21,419
16	exp epirubicin/ or (epirubicin or Pharmorubicin).mp.	34,356
17	exp nivolumab/ or (nivolumab or opdivo).mp.	42,358
18	exp pembrolizumab/ or (pembrolizumab or keytruda).mp.	42,040
19	exp ipilimumab/ or (ipilimumab or yervoy).mp.	27,151
20	exp Pamiparib/ or (Pamiparib or DB14769).mp.	194
21	exp bemarituzumab/ or (bemarituzumab or FPA144).mp.	80
22	exp tislelizumab/ or (tislelizumab or BGB-A317 or Tisle).mp.	1,932
23	exp Avelumab/ or (avelumab or Bavencio).mp.	7,049
24	exp ramucirumab/ or (ramucirumab or Cyramza).mp.	5,240
25	S-1.mp.	143,280
26	exp gimeracil plus oteracil potassium plus tegafur/	6,863
27	exp durvalumab/ or (durvalumab or Imfinzi).mp.	11,820
28	exp Toripalimab/ or (Toripalimab or Tuoyi or "JS 001").mp.	1,729
29	exp Sintilimab/ or (Sintilimab or Tyvyt or IBI308).mp.	2,374
30	exp Spartalizumab/ or (Spartalizumab or PDR001).mp.	613
31	exp Camrelizumab/ or (Camrelizumab or SHR1210).mp.	2,443
32	or/8-31	721,934
33	Clinical trial/	1,079,353
34	Randomized controlled trial/	809,180
35	controlled clinical trial/	472,477
36	multicenter study/	385,933
37	Phase 3 clinical trial/	74,135
38	Phase 4 clinical trial/	6,908

No.	Query	Results
39	exp RANDOMIZATION/	99,383
40	Single blind procedure/	53,765
41	Double blind procedure/	216,361
42	Crossover procedure/	77,100
43	Placebo/	409,545
44	Randomi?ed controlled trial$.tw.	339,185
45	Rct.tw.	56,476
46	(random$ adj2 allocat$).tw.	56,571
47	single blind$.tw.	32,696
48	double blind$.tw.	249,760
49	((treble or triple) adj blind$).tw.	2,049
50	Placebo$.tw.	375,599
51	Prospective study/	907,180
52	Clinical study/	165,930
53	Longitudinal study/	207,486
54	Cohort analysis/	1,124,967
55	(Cohort adj (study or studies)).mp.	502,686
56	(follow up adj (study or studies)).tw.	75,411
57	single arm.tw.	30,423
58	(observational adj (study or studies)).tw.	269,337
59	or/33-58	4,380,249
60	Case study/	99,387
61	Case report.tw.	560,335
62	letter/	1,228,597
63	Editorial.pt.	796,568
64	review.pt.	3,190,233

No.	Query	Results
65	Note.pt.	975,211
66	or/60-65	6,800,406
67	59 not 66	3,865,848
68	7 and 32 and 67	6,363
69	limit 68 to yr="2024 -Current"	122
70	limit 68 to dd=20231030-20240304	107
71	(Nov* 2023 or Dec* 2023).dp.	164,869
72	68 and 71	88
73	69 or 70 or 72	224

Table 100 of search strategy table for MEDLINE (data of search March 4th 2024)

No.	Query	Results
1	exp Stomach Neoplasms/	113,047
2	((stomach or gastric) adj4 (neoplas* or cancer* or carcinom* or tumo?r* or malign* or adenocarcin*)).mp.	155,746
3	((gastroesophag* or gastro-?esophag* or ?esophagogastric or ?esophago-gastric or cardia or GEJ or GOJ or OGJ) adj4 (neoplas* or cancer* or carcinom* or tumo?r* or malign* or adenocarcin*)).mp.	8,072
4	exp Esophagogastric Junction/	10,541
5	1 or 2 or 3 or 4	165,380
6	((stage adj1 (three or "3" or 3A or 3B or III or IIIA or IIIB or four or "4" or IV)) or advanced or metasta* or progress* or refractory or recurren* or unresectable).mp.	3,330,630
7	5 and 6	63,266
8	exp capecitabine/ or (capecitabine or Xeloda or CAPOX or CapeOx or CAPE-OX or XELOX).mp.	9,473
9	(zolbetuximab or IMAB362 or claudiximab).mp.	65
10	exp irinotecan/ or (irinotecan or Campto or Camptosar or Onivyde or CPT-11).mp.	13,625

No.	Query	Results
11	exp fluorouracil/ or (fluorouracil or 5-FU or 5FU or 5-furacil or fluoro uracil or fluouracil or fluoropyridine or fluoropyrimidine or Adrucil or S-1 or S1 or Teysuno).mp.	178,917
12	exp docetaxel/ or (docetaxel or Taxceus or Taxotere).mp.	20,512
13	exp cisplatin/ or (cisplatin or cisplatinum or CDDP or Platin).mp.	91,516
14	exp oxaliplatin/ or (oxaliplatin or Eloxatin).mp.	15,778
15	(FOLFOX* or mFOLFOX* or DCF or ECF or EOX or ECX or FLOT or FOLFIRI).mp.	12,542
16	exp epirubicin/ or (epirubicin or Pharmorubicin).mp.	8,007
17	exp nivolumab/ or (nivolumab or opdivo).mp.	10,301
18	(pembrolizumab or keytruda).mp.	9,656
19	exp ipilimumab/ or (ipilimumab or yervoy).mp.	5,798
20	(Pamiparib or DB14769).mp.	29
21	(bemarituzumab or FPA144).mp.	18
22	(tislelizumab or BGB-A317 or Tisle).mp.	272
23	(avelumab or Bavencio).mp.	1,016
24	S-1.mp.	68,101
25	(ramucirumab or Cyramza).mp.	1,321
26	(durvalumab or Imfinzi).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	1,718
27	(Toripalimab or Tuoyi or "JS 001").mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	288
28	(Sintilimab or Tyvyt or IBI308).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	524

No.	Query	Results
29	(Spartalizumab or PDR001).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	37
30	(Camrelizumab or SHR1210).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	607
31	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	315,643
32	Randomized controlled trials as Topic/	167,283
33	Randomized controlled trial/	609,673
34	Random allocation/	107,101
35	Double blind method/	177,672
36	Single blind method/	33,286
37	Clinical trial/	539,542
38	exp Clinical Trials as Topic/	388,553
39	(clinic$ adj trial$1).tw.	498,147
40	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	202,361
41	Placebos/	35,934
42	Placebo$.tw.	252,944
43	Randomly allocated.tw.	37,735
44	(allocated adj2 random).tw.	844
45	clinical trial, phase i.pt.	25,702
46	clinical trial, phase ii.pt.	40,984
47	clinical trial, phase iii.pt.	22,523
48	clinical trial, phase iv.pt.	2,479
49	controlled clinical trial.pt.	95,571

No.	Query	Results
50	randomized controlled trial.pt.	609,673
51	multicenter study.pt.	343,724
52	clinical trial.pt.	539,542
53	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52	1,958,177
54	Letter/	1,242,730
55	Historical article/	369,384
56	Case study/	2,376,918
57	Case report.tw.	412,211
58	editorial.pt.	676,160
59	54 or 55 or 56 or 57 or 58	4,472,027
60	53 not 59	1,883,697
61	7 and 31 and 60	2,981
62	animals/ not (humans/ and animals/)	5,166,243
63	61 not 62	2,977
64	limit 63 to yr="2024 -Current"	38
65	limit 63 to dt=20231030-20240304	52
66	(2023 Nov* or 2023 Dec*).dp.	152,664
67	63 and 66	16
68	64 or 65 or 67	61

Table 101 of search strategy table for COCHRANE (data of search March 4th 2024)

No.	Query	Results
1	exp stomach cancer/	3,983
2	((stomach or gastric) adj4 (neoplas* or cancer* or carcinom* or tumo?r* or malign* or adenocarcin*)).mp.	11,028
3	((gastroesophag* or gastro-?esophag* or ?esophagogastric or ?esophago-gastric or cardia or GEJ or GOJ or OGJ) adj4 (neoplas* or cancer* or carcinom* or tumo?r* or malign* or adenocarcin*)).mp.	1,853

No.	Query	Results
4	exp gastroesophageal junction/	701
5	1 or 2 or 3 or 4	11,948
6	((stage adj1 (three or "3" or 3A or 3B or III or IIIA or IIIB or four or "4" or IV)) or advanced or metasta* or progress* or refractory or recurren* or unresectable).mp.	291,119
7	5 and 6	6,367
8	(capecitabine or Xeloda or CAPOX or CapeOx or CAPE-OX or XELOX).mp.	5,295
9	(zolbetuximab or IMAB362 or claudiximab).mp.	46
10	(irinotecan or Campto or Camptosar or Onivyde or CPT-11).mp.	4,119
11	exp fluorouracil/ or (fluorouracil or 5-FU or 5FU or 5-fluracil or fluoro uracil or fluouracil or fluoropyridine or fluoropyrimidine or Adrucil or S-1 or S1 or Teysuno).mp.	23,458
12	(docetaxel or Taxceus or Taxotere).mp.	8,723
13	exp cisplatin/ or (cisplatin or cisplatinum or CDDP or Platin).mp.	16,939
14	(oxaliplatin or Eloxatin).mp.	5,694
15	(FOLFOX* or mFOLFOX* or DCF or ECF or EOX or ECX or FLOT or FOLFIRI).mp.	4,041
16	exp epirubicin/ or (epirubicin or Pharmorubicin).mp.	3,422
17	exp nivolumab/ or (nivolumab or opdivo).mp.	2,952
18	(pembrolizumab or keytruda).mp.	3,054
19	(ipilimumab or yervoy).mp.	1,872
20	(Pamiparib or DB14769).mp.	9
21	(bemarituzumab or FPA144).mp.	22
22	(tislelizumab or BGB-A317 or Tisle).mp.	252
23	(avelumab or Bavencio).mp.	408
24	(ramucirumab or Cyramza).mp.	678
25	S-1.mp.	6,130
26	(durvalumab or Imfinzi).mp. [mp=ti, ot, ab, fx, sh, hw, kw, tx, ct]	1,141

No.	Query	Results
27	(Toripalimab or Tuoyi or "JS 001").mp. [mp=ti, ot, ab, fx, sh, hw, kw, tx, ct]	155
28	(Sintilimab or Tyvyt or IBI308).mp. [mp=ti, ot, ab, fx, sh, hw, kw, tx, ct]	198
29	(Spartalizumab or PDR001).mp. [mp=ti, ot, ab, fx, sh, hw, kw, tx, ct]	61
30	(Camrelizumab or SHR1210).mp. [mp=ti, ot, ab, fx, sh, hw, kw, tx, ct]	230
31	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	55,476
32	7 and 31	3,328
33	limit 32 to yr="2023 -Current" [Limit not valid in DARE; records were retained]	164

I.1.2 Systematic selection of studies

The original 2020 review, first SLR update, second SLR update and third SLR update were carried out using an identical methodology. Identified studies were independently assessed by two reviewers for inclusion at each stage of study selection. First, the title and abstracts of the references identified from the electronic bibliographic databases were screened by two independent reviewers. Any disputes between the inclusion and exclusion decisions were resolved by a third independent reviewer. The full-texts of included titles and abstracts, where available, were then further assessed by two independent reviewers. For both phases, the reviewers determined the eligibility according to pre-specified inclusion and exclusion criteria for the review based on PICOS set out in the scope of the appraisal.

Relevant information was extracted into the data extraction template by a reviewer. A second reviewer checked the data extraction, and any inconsistencies were resolved through discussion or by a third reviewer.

Below an overview of eligibility criteria in the global SLR is presented along with local adaptation.

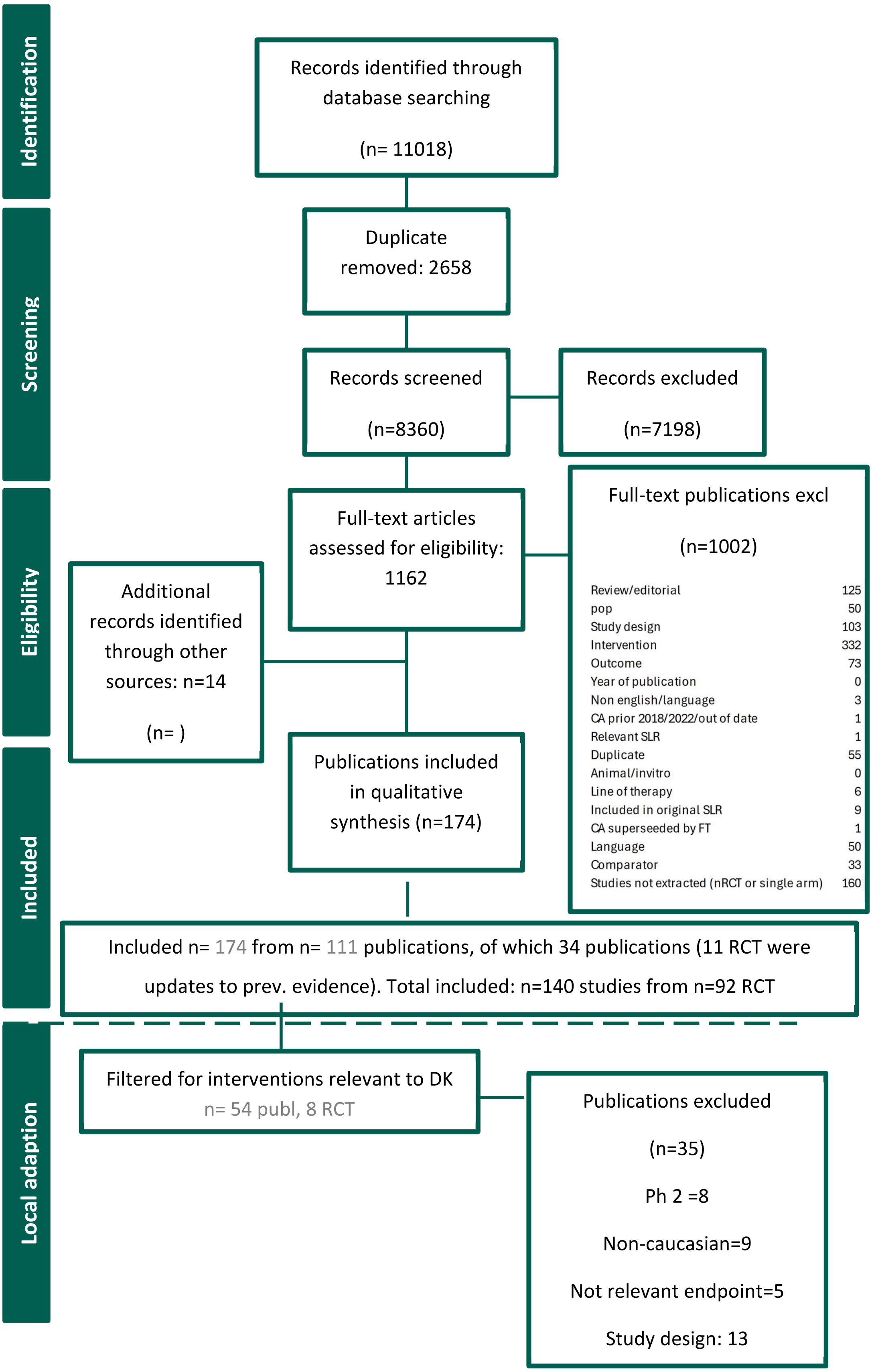
Table 102 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Adult patients (≥18 years) with pathologically confirmed metastatic or locally advanced unresectable, or recurrent gastric or GEJ adenocarcinoma, who: • have not received any previous first-line	• <18 years of age • HER2-positive status Studies with mixed patient populations will be included if	No

	treatment (chemotherapy or targeted agent) for gastric or GEJ cancer (prior adjuvant or neo-adjuvant therapy is permitted), • have HER2-negative status	≥80% of patients are eligible, or if eligible subgroups are reported	
Interventions and comparators	Treatments currently used or in development for advanced or metastatic GC: • Avelumab (Bavencio®) • Bemarituzumab • Camrelizumab† • CAPOX (capecitabine + oxaliplatin) • Cisplatin + 5-FU (fluorouracil) • Cisplatin + capecitabine (CX) • DCF (docetaxel, cisplatin, 5-FU) • Durvalumab† • ECF (epirubicin, cisplatin, fluorouracil) • ECX (epirubicin, cisplatin, capecitabine) • EOF (epirubicin, oxaliplatin, fluorouracil) • EOX (epirubicin, oxaliplatin, capecitabine) • FLOT (folinic acid, fluorouracil, oxaliplatin, docetaxel) • FOLFIRI (folinic acid, fluorouracil, irinotecan) • Ipilimumab (Yevroy®) • mFOLFOX6 • Nivolumab (OPDIVO®) • Oxaliplatin + 5-FU (fluorouracil) • Pamiparib • Pembrolizumab • Placebo • Sintilimab† • Spartalizumab† • Tislelizumab • Toripalimab† • Zolbetuximab • BSC	• Treatments not listed • Non-pharmacological therapies	Nivolumab Pembrolizumab Zolbetuximab
Outcomes	**Baseline characteristics** Patient and study characteristics (including age, race, country, % males, CLDN18.2 status etc.) **Efficacy** • Overall survival • Progression-free survival • Time to progression • Duration of response • Event-free survival	Outcome(s) not listed	Only publications with endpoints of relevance for the Danish assessment are included

	• Response rates (complete response, partial response, stable disease) • Objective response rate • Disease control rate • Duration of treatment; duration of treatment beyond progression **Safety** • All-grade treatment related AE • Treatment related Grade 3 or 4 AEs • Treatment related SAEs Tolerability: dose reductions and interruptions, discontinuation (all-cause; due to AEs)		
Study design/ setting	RCTs, any duration (irrespective of blinding)	Other study designs	Only Phase 3 RCTs included
Language of publication	English language publications	Non-English language studies	No
Geography	No restriction	-	Publications presenting data only for subgroup of patients with non-Caucasian origin or the publication only include data for subgroup of patients with non-caucasian origin are excluded
Date of publication	Original SLR: Last 20 years (2000– 22nd September 2022) First SLR update: 22nd September 2022– 11thAugust 2022) Second SLR update: 11th August 2022- 30th October 2023 Third SLR update: 30th October 2023- 4th March 2024	Studies published prior to 2000	No

PRISMA diagram



The included trials for zolbetuximab are the two pivotal clinical trials SPOTLIGHT and GLOW. The included trials for nivolumab and pembrolizumab are the pivotal trials CheckMate 649 and KEYNOTE 859. This study selection for nivolumab and pembrolizumab align with the recent assessment of nivolumab and pembrolizumab in G/GEJC by DMC. [1, 2]

Table 103 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
SPOTLIGHT /NCT03504397	To compare the efficacy and safety of zolbetuximab given in addition to chemotherapy vs chemotherapy alone	Phase 3, multicentre double-blind, RCT	Patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma	Zolbetuximab plus mFOLFOX6 (n=283) Placebo plus mFOLFOX6 (n=282)	PFS The median follow-up for PFS was 18.0 months in the zolbetuximab group and 17.9 months in the placebo group.	OS Median follow-up time was 33.28 months in the zolbetuximab+ FOLFOX arm and 31.38 months in the placebo + FOLFOX arm
GLOW/ NCT03653507	To compare the efficacy and safety of zolbetuximab given in addition to chemotherapy vs chemotherapy alone	Phase 3, multicentre double-blind RCT	Patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma	Zolbetuximab plus CAPOX (n=254) Placebo plus CAPOX (n=253)	PFS The median follow-up for PFS was 20.6 months in the zolbetuximab group and 23.5 months in the placebo group	OS Median duration of follow-up (months) 31.70 months in the zolbetuximab + CAPOX arm and 32.95 months in the placebo+ CAPOX arm
CheckMate 649/ NCT02872116	To compare the efficacy and safety of nivolumab	Phase 3, multi-centre, randomised, open-label,	Patients with locally advanced or metastatic non-HER2	nivolumab plus XELOX/FOLFOX (n=789) and	Dual primary: OS in PD-L1 positive	Dual primary: PFS in PD-L1 positive

Study/ID	Aim	Study design	Patient population	Intervention and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	given in addition to chemotherapy vs chemotherapy alone	active-controlled study	positive G/GEJ adenocarcinoma	XELOX/FOLFOX (n=792) (a total of 955 (60%) were PD-L1 positive with a CPS ≥ 5)	(CPS ≥5) patients At the latest data cut, efficacy inputs were based on data with minimum follow-up time of 4 years	(CPS ≥5) patients At the latest data cut, efficacy inputs were based on data with minimum follow-up time of 4 years
KEYNOTE 859/NCT03675737	To compare the efficacy and safety of pembrolizumab given in addition to chemotherapy vs chemotherapy alone	Phase 3, multicentre, double-blind, placebo-controlled, RCT	Patients with locally advanced or metastatic HER2-negative G/GEJ adenocarcinoma.	Pembro + CAPOX/FOLFOX (n = 790) CAPOX/FOLFOX (n = 789)	OS in All Participants, OS In Participants With CPS ≥1, OS In Participants With CPS ≥10 Median duration of follow up 13 months. Interim analysis: Oct 3, 2022. Final analysis not published	PFS in All Participants, OS In Participants With CPS ≥1, OS In Participants With CPS ≥10 Median duration of follow up 13 months. Interim analysis: Oct 3, 2022. Final analysis not published

After the global SLR was conducted, the following additional references have been identified for the identified pivotal clinical trials for zolbetuximab, nivolumab and pembrolizumab via hand search:

Zolbetuximab (pivotal trials: GLOW and SPOTLIGHT):

- Shitara K, Shah MA, Lordick F, Van Cutsem E, Ilson DH, Klempner SJ, et al. Zolbetuximab in Gastric or Gastroesophageal Junction Adenocarcinoma. N Engl J Med. 2024;391(12):1159-62.
- Lordick F, Van Cutsem E, Shitara K, Xu RH, Ajani JA, Shah MA, et al. Health-related quality of life in patients with CLDN18.2-positive, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma: results from the SPOTLIGHT and GLOW clinical trials. ESMO open. 2024;9(8):103663.

Pembrolizumab (pivotal trial: KEYNOTE 859) and Nivolumab (pivotal trial: CheckMate 649)

- No new publications were identified

In addition, the EPAR assessment reports for zolbetuximab, nivolumab and pembrolizumab have been included. [18, 28, 32]Furthermore, a previous assessment of pembrolizumab by DMC has been included. [2]

I.1.3 Excluded fulltext references

For a detailed overview of all excluded references in the global SLR, we refer to the full global SLR attached to the application. [24]

For the Danish adaptation, the global SLR included 8 RCTs and 54references for zolbetuximab, nivolumab and pembrolizumab. The exclusion criteria presented above in Table 102 were considered for the Danish adaptation. Reason for exclusion (Danish adaptation) is presented below

Zolbetuximab
A total of 10 publications were identified in the global SLR describing a total of three RCTs which investigated zolbetuximab based treatment regimens. These included: FAST/ NCT01630083 (primary reference: Sahin et al 2021 [41]) , SPOTLIGHT/NCT03504397 (primary reference: Shitara et al 2023 [11]), and GLOW/NCT03653507 (primary reference: Shah et al 2023.[10]). Below find the references excluded for the Danish adaptation.

Reason for exclusion (DK)	Publication included in global SLR
Phase 2	Sahin U, Tureci O, Manikhas G, Lordick F, Rusyn A, Vynnychenko I, et al. FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. Ann Oncol. 2021;32(5):609-19.
Phase 2	Morlock R, Turnbul J, Blahut S, Krukas-Hampel MR, Hawryluk E, Tureci O. Health-related quality-of-life (HRQoL) results from the FAST study, a phase 2 trial of epirubicin, oxaliplatin and capecitabine with or without IMAB362 in patients with advanced CLDN18.2+ gastric (GA) and gastroesophageal junction (GEJ) adeno-carcinoma. Journal of Clinical Oncology Conference. 2018;36(15 Supplement 1).
Phase 2	Morlock R, Krukas-Hampel MR, Tureci O. Patient reported outcomes (PRO) results from phase II MONO and FAST zolbetuximab (IMAB362) trials in patients with advanced CLDN18.2+ gastric and gastroesophageal junction adenocarcinoma (GA/GEJA). Annals of oncology: official journal of the European Society for Medical Oncology. 2018;29(Supplement 8):viii221.
Phase 2	Lordick F, Al-Batran SE, Ganguli A, Morlock R, Sahin U, Tureci O. Patient-reported outcomes from the phase II FAST trial of zolbetuximab plus EOX compared to EOX alone as first-line treatment of patients with metastatic CLDN18.2+ gastroesophageal adenocarcinoma. Gastric Cancer. 2021;24(3):721-30.
Phase 2	Sahin U, Tureci O, Manikhas GM, Lordick F, Rusyn A, Vynnychenko I, et al. Zolbetuximab combined with EOX as first-line therapy in advanced CLDN18.2+ gastric (G) and gastroesophageal junction (GEJ) adenocarcinoma: updated results from the FAST trial. Journal of clinical oncology. 2019;37.

The references based on the phase 2 clinical trial, FAST, were excluded since FAST is a phase 2 study. The abstract and posters by Ajani et al (2023)[51]; Lordick et al, 2023 [52]and Lordick et al, 2023 [53] are included, but not presented in the current submission since the later hand search identified a later full text publications representing same data or data from a later data cut.

The primary publications included for zolbetuximab from the global SLR are:

- Shah MAS, K.; Ajani, J. A.; Bang, Y. J.; Enzinger, P.; Ilson, D.; Lordick, F.; Van Cutsem, E.; Gallego Plazas, J.; Huang, J.; Shen, L.; Oh, S. C.; Sunpaweravong, P.; Soo Hoo, H. F.; Turk, H. M.; Oh, M.; Park, J. W.; Moran, D.; Bhattacharya, P.; Arozullah, A.; Xu, R. H. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nature Medicine. 2023;29(8):2133-41 (*Primary reference*).
- Shitara KL, F.; Bang, Y. J.; Enzinger, P.; Ilson, D.; Shah, M. A.; Van Cutsem, E.; Xu, R. H.; Aprile, G.; Xu, J.; Chao, J.; Pazo-Cid, R.; Kang, Y. K.; Yang, J.; Moran, D.; Bhattacharya, P.; Arozullah, A.; Park, J. W.; Oh, M.; Ajani, J. A. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. The Lancet 2023;401:1 655-68 (*Primary reference*).

The later hand search identified Shitara (2024), where final data for SPOTLIGHT and GLOW is presented in detail in a publication.[26] Furthermore, a recent publication by Lordick and collagues (2024) presenting detailed results on HRQoL from SPOTLIGHT and GLOW was identified and included. [25]

<u>PD-(L)1 inhibitors:</u>

Nivolumab
A total of 25 publications for a total of three clinical studies were included for nivolumab in the global SLR for the following three RCTs: ATTRACTION-4/NCT02746796, Moonlight/NCT03647969 and CheckMate-649/ NCT02872116.

Below find the references excluded for the Danish adaptation.

Reason for exclusion (DK)	**Publication included in global SLR**
Non caucasian	Boku N, Ryu MH, Kato K, Chung HC, Minashi K, Lee KW, et al. Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastro-esophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4). Annals of Oncology. 2019;30(2):250-8.
Non caucasian	Kang YK, Chen LT, Ryu MH, Oh DY, Oh SC, Chung HC, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2022;23(2):234-47.

Phase 2	Pauligk CG, T. O.; Thuss-Patience, P. C.; Riera-Knorrenschild, J.; et al. Modified FOLFOX versus modified FOLFOX plus nivolumab and ipilimumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction - Safety Results from AIO-STO-0417: A randomized phase II trial of the German Gastric Group of the AIO. Annals of Oncology. 2020;31((Supplement 4)):S908.
Non caucasian	Shen LB, Y.; Lin, X.; Li, W.; et al. First-Line (1L) nivolumab (NIVO) plus chemotherapy (chemo) versus chemo in patients (pts) with advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): CheckMate 649 Chinese subgroup analysis. Cancer Research Conference: AACR Annual Meeting. 2021;81(13 SUPPL).
Non caucasian	Shen LB, Y.; Lin, X.; Li, W.; et al. P-86 First-line nivolumab (NIVO) plus chemotherapy (chemo) vs chemo in patients with advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): CheckMate 649 Chinese subgroup analysis 2-year follow-up. Annals of Oncology. 2022;33((Supplement 4)):S279.
Not relevant endpoint	Sugarman RB, M.; Rusibamayila, N. A quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis of patients in CheckMate 649: Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC). Journal of Clinical Oncology Conference. 2022;40(4 SUPPL).
Not relevant endpoint	Sugarman RN, S.; Betts, K. A.; Nie, X.; Nguyen, H. Number needed to treat (NNT) analysis of patients in CheckMate 649 (CM 649): Nivolumab plus chemotherapy versus chemotherapy as first-line (1L) treatment for advanced gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC/GEJ/EAC). Journal of Clinical Oncology Conference. 2022;40(4 SUPPL).
Phase 2	Lorenzen S. FOLFOX versus FOLFOX plus nivolumab and ipilimumab administered in parallel or sequentially versus FLOT plus nivolumab administered in parallel in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction: A randomized phase 2 trial of the AIO. Journal of Clinical Oncology Conference. 2022;40 ((16)_Suppl 4):4043.
Non caucasian	Boku N, Ryu MH, Oh DY, Oh SC, Chung HC, Lee KW, et al. LBA7_PR Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study. Annals of Oncology. 2020;31:S1192.
Not relevant endpoint	Janjigian YYS, K.; Ajani, J.; Moehler, M.; et al. Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: checkMate 649 biomarker analyses. Cancer research and treatment. 2023;83.
Non caucasian	Liu TB, Y.; Lin, X.; Li, W.; et al. First-line nivolumab plus chemotherapy vs chemotherapy in patients with advanced gastric, gastroesophageal junction and esophageal adenocarcinoma: CheckMate 649 Chinese subgroup analysis. International Journal of Cancer. 2023;152(4):749-60.
Not relevant endpoint	Sugarman RB, K. A.; Nie, X.; Hartman, J.; Nguyen, H. Nivolumab Plus Chemo-therapy for Advanced Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinoma: Analysis of Number Needed To Treat and Number Needed To Harm. Clinical Therapeutics. 2023
Phase 2	Lorenzen ST-P, P. C.; Folprecht, G.; Riera Knorrenschild, J.; Heinemann, V.; et al. FOLFOX plus nivolumab and ipilimumab versus FOLFOX induction followed by nivolumab and ipilimumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction: Results

	from the randomized phase II Moonlight trial of the AIO. Annals of Oncology. 2022;33(7):s1099.
Non caucasian	Shen LB, Y.; Lin, X.; Li, W.; et al. First-line (1L) nivolumab (NIVO) plus chemotherapy (chemo) vs chemo in patients (pts) with advanced gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC/GEJC/EAC): CheckMate 649 Chinese subgroup analysis 4-year (yr) follow-up. Journal of Clinical Oncology. 2024;42.

All references for the clinical trials ATTRACTION-4 were excluded since these studies were not in a Caucasian population (the study was conducted in Japan, Korea and Taiwan). The references for Moonlight were excluded since this was a phase 2 trial. The references by Shen et al (2021, 2022 and 2023) and Liu et al (2024) were excluded since these considered a subgroup of Chinese patients, i.e. not Caucasian population. The abstracts and publications by Sugarman (2022, 2022 and 2023) and Janjigian et al, 2023 were excluded since these did not present data endpoints relevant for the Danish assessment.

The publication by Elimova (2021)[54] and the poster by Moehler (2020 and 2021) [55, 56] were included, but these are not presented further, since a full publication by Moehler was published in 2023 with detailed HRQoL data.

Finally, the abstracts and publications by Janjigian (2023, 2023 and 2021)[40, 57, 58], Shitara (2022 and 2022)[59, 60] were included but are not presented further since these included data, where the later hand search identified later full text publications representing same data or data from a later data cut.

Hence, the key references included for nivolumab are:

- Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27-40. (*primary reference*)
- Shitara KM, M. H.; Ajani, J. A.; Shen, L.; Garrido, M.; Gallardo, C.; Wyrwicz, L. S.; Yamaguchi, K.; Cleary, J. M.; Elimova, E.; Maya, R. E. B.; Karamouzis, M.; Skoczylas, T.; Bragagnoli, A.; Liu, T.; Tehfe, M.; Feeney, K.; Wang, R.; Nathani, R.; Janjigian, Y. Y. Nivolumab (NIVO) + chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 4 year (yr) follow-up of CheckMate 649. Journal of Clinical Oncology. 2024;42 (*latest datacut*)
- Moehler MX, H.; Blum, S. I.; Elimova, E.; Cella, D.; Shitara, K.; Ajani, J. A.; Janjigian, Y. Y.; Garrido, M.; Shen, L.; Yamaguchi, K.; Liu, T.; Schenker, M.; Kowalyszyn, R.; Bragagnoli, A. C.; Bruges, R.; Montesarchio, V.; Pazo-Cid, R.; Hunter, S.; Davenport, E.; Wang, J.; Kondo, K.; Li, M.; Wyrwicz, L. Health-Related Quality of Life With Nivolumab Plus Chemotherapy Versus Chemotherapy in Patients With Advanced Gastric/Gastroesophageal Junction Cancer or Esophageal Adenocarcinoma From CheckMate 649. Journal of Clinical Oncology. 2023;41:5388-99 (*HRQoL publication*)

Pembrolizumab

A total of 19 references were included for a total of 2 clinical trials for pembrolizumab: KEYNOTE 062 and KEYNOTE 859 in the global SLR. Below find the references excluded for the Danish adaptation.

Reason for exclusion (DK)	Publication included in global SLR
Study design	Shitara K, Van Cutsem E, Bang YJ, Fuchs C, Wyrwicz L, Lee KW, et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer: The KEYNOTE-062 Phase 3 Randomized Clinical Trial. JAMA oncology. 2020;03.
Study design	Chao J, Fuchs CS, Shitara K, Tabernero J, Muro K, Van Cutsem E, et al. Pembro-lizumab (pembro) in microsatellite instability-high (MSI-H) advanced gastric/-gastroesophageal junction (G/GEJ) cancer by line of therapy. Journal of Clinical Oncology Conference. 2020;38(4 Supplement).
Study design	Chung HC, Bang YJ, Tabernero J, Van Cutsem E, Fuchs CS, Wyrwicz L, et al. Pem-brolizumab + chemotherapy for advanced G/GEJ adenocarcinoma (GC): The phase III KEYNOTE-062 study. Annals of Oncology. 2019;30 (Supplement 9):ix43-ix4.
Study design	Satake H, Lee KW, Chung HC, Lee J, Yamaguchi K, Chen JS, et al. Pembrolizumab (pembro) versus standard of care chemotherapy (chemo) in patients with advanced gastric or gastroesophageal junction adenocarcinoma: Asian subgroup analysis of KEYNOTE-062. Journal of Clinical Oncology Conference. 2020;38(15).
Study design	Shitara K, Van Cutsem E, Bang YJ, Fuchs CS, Wyrwicz L, Lee KW, et al. Pembro-lizumab with or without chemotherapy vs chemotherapy in patients with advanced G/GEJ cancer (GC) including outcomes according to Microsatellite Instability-High (MSI-H) status in KEYNOTE-062. Annals of oncology. 2019;878(30).
Study design	Tabernero J, Van Cutsem E, Bang YJ, Fuchs CS, Wyrwicz L, Lee KW, et al. Pembro-lizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: the phase III KEYNOTE-062 study. Journal of clinical oncology. 2019;37.
Study design	Tabernero J, Van Cutsem E, Bang Y, Fuchs C, Wyrwicz L, Lee K, et al. Pembro-lizumab with or without chemotherapy versus chemotherapy for first-line treatment of advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: the phase 3 KEYNOTE-062 Study. Annals of oncology. 2019;30.
Study design	Van Cutsem E, Valderrama A, Bang YJ, Fuchs C, Shitara K, Janjigian YY, et al. Health-related quality of life (HRQoL) impact of pembrolizumab (P) versus chemotherapy (C) as first-line (1L) treatment in PD-L1-positive advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. Annals of Oncology. 2019;30 (Supplement 5):v879.
Study design	Lee KW, Van Cutsem E, Bang YJ, Fuchs CS, Kudaba I, Garrido M, et al. Association of Tumor Mutational Burden with Efficacy of Pembrolizumab+/-Chemotherapy as First-Line Therapy for Gastric Cancer in the Phase III KEYNOTE-062 Study. Clin Cancer Res. 2022;28(16):3489-98.
Study design	Van Cutsem E, Valderrama A, Bang YJ, Fuchs CS, Shitara K, Janjigian YY, et al. Quality of life with first-line pembrolizumab for PD-L1-positive advanced gastric/gastroesophageal junction adenocarcinoma: results from the randomised phase III KEYNOTE-062 study. ESMO Open. 2021;6(4):100189.
Study design	Wainberg ZA, Fuchs CS, Tabernero J, Shitara K, Muro K, Van Cutsem E, et al. Efficacy of Pembrolizumab Monotherapy for Advanced Gastric/Gastroesophageal Junction Cancer with Programmed Death Ligand 1 Combined Positive Score >/=10. Clin Cancer Res. 2021;27(7):1923-31 .
Study design	Wainberg ZAS, K.; Van Cutsem, E.; Wyrwicz, L.; et al. Pembrolizumab with or without chemotherapy versus chemotherapy alone for patients with PD-L1-positive advanced gastric or gastroesophageal junction adenocarcinoma: Update from the phase 3 KEYNOTE-062 trial. Journal of Clinical Oncology Conference. 2022;40.
Non caucasian	Muro KS, K.; Yamaguchi, K.; Yoshikawa, T.; et al.. Efficacy of Pembrolizumab Monotherapy in Japanese Patients with Advanced Gastric or Gastroesophageal Junction Cancer. Journal of Gastrointestinal Cancer. 2023 .

Study design	Satake HL, K. W.; Chung, H. C.; Lee, J.; et al. Pembrolizumab or pembrolizumab plus chemotherapy versus standard of care chemotherapy in patients with advanced gastric or gastroesophageal junction adenocarcinoma: Asian subgroup analysis of KEYNOTE-062. Japanese Journal of Clinical Oncology. 2023;53(3):221-9.
Not relevant endpoint	Wyrwicz LO, D.; Weber, P.; Bai, Y.; et al.. Additional data from the KEYNOTE-859 study of pembrolizumab plus chemotherapy versus placebo plus chemotherapy for advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) cancer. Annals of Oncology. 2023;34(1):s181.
Non caucasian	Oh DYB, Y.; Ryu, M. H.; Lee, J.; et al. 138MO Pembrolizumab (Pembro) or placebo (Pbo) plus chemotherapy (Chemo) for advanced HER2-negative gastric/gastroesophageal junction (G/GEJ) adenocarcinoma (KEYNOTE-859): Asia subgroup analysis. Annals of Oncology. 2023;34.

The references based on the KEYNOTE 62 study were excluded since KEYNOTE 062 due to study design. In addition, the references by Oh (2023) and Muro et al, 2023 were excluded since this considered data for subgroup of patients with non-caucasian origin. The abstract by Wyrwicz was excluded since this considered endpoint which was not relevant for the Danish assessment.

The abstract by Lowery et al (2023) [61]was included. The abstract presented HRQoL data for pembrolizumab +chemo vs chemotherapy for the ITT population. The conclusion was that there was no difference between treatment arms. The abstract is not further discussed since it considers the ITT population and hence not a population of interest for the Danish assessment. The abstract by Wainberg (2024) [62] presents data from KEYNOTE 590 and KEYNOTE 859 for the subgroup of patients with GEJC. In KEYNOTE 859, among patients with a CPS≥1, the median OS for patients with GEJC was 14.2 in the pembro + chemo arm vs 12 months in the chemo arm (HR: 0.71 (0.55-0.93)).

The primary publication included for pembrolizumab is:

- Rha SYO, D. Y.; Yanez, P.; Bai, Y.; Ryu, M. H.; Lee, J.; Rivera, F.; Alves, G. V.; Garrido, M.; Shiu, K. K.; Fernandez, M. G.; Li, J.; Lowery, M. A.; Cil, T.; Cruz, F. M.; Qin, S.; Luo, S.; Pan, H.; Wainberg, Z. A.; Yin, L.; Bordia, S.; Bhagia, P.; Wyrwicz, L. S. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2023;19 (*primary reference)*.

The included trials for nivolumab and pembrolizumab align with the recent assessment of nivolumab and pembrolizumab in G/GEJC by DMC. [1, 2]

I.1.4 Quality assessment

The global literature search by Astellas represents an up-to-date overview of the clinical data for the treatment of G/GEJ adenocarcinoma. The global SLR represents a detailed and comprehensive overview of the available evidence for the treatment of G/GEJC worldwide.

The systematic literature review is based on systematic search based on predefined criteria in peer-reviewed literature as well as searches in conference materials. In addition, Astellas has searched clinical trial registries to identify completed but unpublished trials with available results. The selection and data extraction is strengthened by the fact that it was carried out by two independent researchers.

The SLR is not focused solely on relevant treatments for G/GEJC in Europe or in Denmark specifically, and hence the current assessment only focusses on selected treatments of relevance for Danish clinical practice and for the decision problem.

It should also be noted that despite the fact that the SLR is updated recently (March 2024), two additional publications of zolbetuximab have become available after the search (Shitara et al. 2024 [26] and Lordick et al 2024)[25]. This study presents the final data for SPOTLIGHT and GLOW as well as integrated analysis.

I.1.5 Unpublished data

Unpublished data were included for EQ-5D VAS results from SPOTLIGHT and GLOW and for EQ-5D Index and EQ-5D based HSUVs sourced from the integrated analysis of SPOTLIGHT and GLOW (see section 14).

Appendix J. Literature searches for health-related quality of life

Not applicable

Appendix K. Literature searches for input to the health economic model

Not applicable

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