Zolbetuximab (Vyloy®) with chemotherapy for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

General information [1]

Drug description

The active substance of Vyloy® is zolbetuximab, an antineoplastic agent. Zolbetuximab is a chimeric (mouse/human) IgG1 antibody directed against the tight junction molecule CLDN18.2, a tissue-specific cell surface molecule that is expressed in normal gastric tissue as well as in many human cancers.

Indication

Zolbetuximab (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 GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.

Incidence

- In Austria, in 2022, a total of 1,173 persons were newly diagnosed with gastric cancer. The age-standardised[1] incidence rate was 17.5/100,000 in men and 8.4/100,000 in women [2]
- In an assessment of 286 gastric cancer/GEJ tissue samples (North America, n=100; Asia, n=100; Europe, n=98), 30% (n = 86/286) were CLDN18.2^{high} (moderate-to-strong CLDN18.2 membrane staining in ≥75% of tumour cells). CLDN18.2^{high} prevalence ranged from 24% (n = 22/92) in Asian samples to 34% (n = 33/97) in American samples [3].

Current treatment [4]

Onkopedia provides the following information regarding the first-line treatment of stage IV tumours that are Claudin 18.2 positive:

- In 2023, data from the multinational phase III Spotlight study were presented. These show that in patients with advanced irresectable gastric cancer and claudin18.2 expression in ≥ 75% of tumour cells, zolbetuximab, a chimeric monoclonal IgG1 antibody directed against claudin18.2, in combination with FOLFOX chemotherapy prolongs overall survival (median 18.23 vs. 15.54 months, HR 0.750, p = 0.0053). The main side effects of zolbetuximab are nausea and vomiting, especially during the first application.
- The results of the Spotlight study are primarily confirmed by the multinational phase III GLOW study, in which the chemotherapy doublet was used as a control therapy or combination partner for zolbetuximab.

Regulatory status

EMA [1]	FDA
Approval status for this indication: On 25 July 2024, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Vyloy® for the following indication: ❖ 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 GEJ adenocarcinoma whose tumours are CLDN 18.2 positive. **Other indications**: none ✓ **Orphan designation**	**Approval status for this indication**: not approved On 31 May 2024, the manufacturer of zolbetuximab (Astellas Pharma Inc.) announced that the FDA had acknowledged the company's resubmission of the Biologics License Application for zolbetuximab for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive [5]. **Other indications**: none

Manufacturer

The manufacturer of Vyloy® is Astellas Pharma Inc.

Costs

[1] European Standard Population 2013.

Currently, there is no cost information available.

Warnings and precautions

Currently, there is no EMA EPAR available for Vyloy®.

Study characteristics: SPOTLIGHT trial [6, 7]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up for PFS	Characteristics	Biomarker	Funding	Publication(s)
SPOTLIGHT NCT03504397	565 (1:1)	zolbetuximab (800 mg/m^2 loading dose followed by 600 mg/m^2 every 3 weeks) + mFOLFOX6 (every 2 weeks)	placebo + mFOLFOX6	PFS by IRC	12.94 months vs. 12.65 months	ongoing[2], global, randomised, placebo-controlled, double-blind, phase 3 trial	-	Astellas Pharma Global Development, Inc	SPOTLIGHT trial [6]

Inclusion criteria[3]

- Female subjects are eligible to participate if she is not pregnant and at least one of the following conditions applies:
  - Not a WOCBP OR
  - WOCBP who agrees to follow the contraceptive guidance throughout the treatment period and for at least nine months after the final administration of oxaliplatin and six months after the final administration of all other study drugs.
  - Female patients must agree not to breastfeed starting at screening and throughout the study period, and for six months after the final study drug administration.
  - Female patient must not donate ova starting at screening and throughout the study period, and for nine months after the final administration of oxaliplatin and six months after the final administration of all other study drugs.
- A sexually active male subject with a female partner(s) who is of child-bearing potential must agree to use contraception during the treatment period and for at least 6 months after the final study drug administration.
- Male subject must agree not to donate sperm starting at screening and throughout the study period, and for 6 months after the final study drug administration.

Exclusion criteria

- Prior systemic chemotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma.
- Previous radiotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma ≤ 14 days prior to randomisation and has not recovered from any related toxicity.
- Previous systemic immunosuppressive therapy, including systemic corticosteroids within 14 days prior to randomisation.
- Patient has received other investigational agents or devices within 28 days prior to randomisation.
- Prior severe allergic reaction or intolerance to known ingredients of zolbetuximab or other monoclonal antibodies, including humanised or chimeric antibodies.
- Known immediate or delayed hypersensitivity, intolerance or contraindication to any component of study treatment.
- Prior severe allergic reaction or intolerance to any component of mFOLFOX6.
- Known dihydropyrimidine dehydrogenase deficiency.
- Complete gastric outlet syndrome or a partial gastric outlet syndrome with persistent/recurrent vomiting.
- Significant gastric bleeding and/or untreated gastric ulcers that would exclude the subject from participation.
- Known history of a positive test for HIV infection or known active hepatitis B or C infection.

Patient characteristics at baseline (n=283 vs. 282)

- Age: 62.0 (51.0–69.0) vs. 60.0 (50.0–69.0) years
- Male sex: 62% vs. 62%
- Region
  - Asia: 31% vs. 32%
  - Non-Asia: 69% vs. 68%
- Ethnicity
  - Hispanic or Latino: 13% vs. 13%
  - Not Hispanic or Latino: 80% vs. 76%
  - Missing: 8% vs. 11%
- Organs with metastases
  - 0–2: 77% vs. 78%
  - ≥3: 23% vs. 22%
- Location of metastases:
  - Lymph node: 36% vs. 39%
  - Peritoneum: 33% vs. 27%
  - Liver: 22% vs. 27%
  - Lung: 13% vs. 12%
  - Bone: 10% vs. 8%
  - Abdominal cavity: 7% vs. 6%
  - Ovary: 6% vs. 7%
- Previous gastrectomy:
  - Yes: 30% vs. 29%
  - No: 70% vs. 71%

[2] The SPOTLIGHT trial is currently ongoing; estimated study completion date is 03/2025.
[3] For detailed in-and exclusion criteria, please see trial protocol.

❖ Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for 6 months after the final study drug administration. ❖ Histologically confirmed diagnosis of Gastric or GEJ adenocarcinoma. ❖ Radiologically confirmed locally advanced unresectable or metastatic disease within 28 days prior to randomisation. ❖ Radiologically evaluable disease (measurable and/or non-measurable disease according to RECIST 1.1), per local assessment, ≤ 28 days prior to randomisation. ❖ Tumor expresses CLDN18.2 in ≥ 75% of tumour cells demonstrating moderate to strong membranous staining as determined by central immunohistochemistry testing. ❖ HER2-Negative tumour as determined by local or central testing on a gastric or GEJ tumour specimen. ❖ ECOG performance status 0 to 1. ❖ Predicted life expectancy ≥ 12 weeks. ❖ Patient must meet all of the following criteria based on the centrally or locally analysed laboratory tests collected within 14 days prior to randomisation: • Haemoglobin ≥ 9 g/dL. • ANC ≥ 1.5 x 10^9/L • Platelets ≥ 100 x 10^9/L • Albumin ≥ 2.5 g/dL • Total bilirubin ≤ 1.5 x ULN without liver metastases • AST and ALT ≤ 2.5 x ULN without liver metastases • Estimated creatinine clearance ≥ 30 mL/min • Prothrombin time/ INR and partial thromboplastin time (≤ 1.5 x ULN).	❖ For patients who are negative for HBs Ag, but hepatitis B core antibody positive, an HB DNA test will be performed and if positive, the subject will be excluded. ❖ Active autoimmune disease that has required systemic treatment within the past 3 months prior to randomisation. ❖ Active infection requiring systemic therapy that has not completely resolved within 7 days prior to randomisation. ❖ Significant cardiovascular disease, including any of the following: • Congestive heart failure, myocardial infarction, unstable angina, coronary angioplasty, stenting, coronary artery bypass graft, cerebrovascular accident or hypertensive crisis within 6 months prior to randomisation. • History of clinically significant ventricular arrhythmias. • QTc interval > 450 msec for male subjects; QTc interval > 470 msec for female subjects. • History or family history of congenital long QT syndrome. • Cardiac arrhythmias requiring anti-arrhythmic medications. ❖ History of central nervous system metastases and/or carcinomatous meningitis from gastric/GEJ cancer. ❖ Known peripheral sensory neuropathy > Grade 1 unless the absence of deep tendon reflexes is the sole neurological abnormality. ❖ Major surgical procedure ≤ 28 days prior to randomisation. ❖ Patient is without complete recovery from a major surgical procedure ≤ 14 days prior to randomisation. ❖ Patient has psychiatric illness or social situations that would preclude study compliance. ❖ Another malignancy for which treatment is required. ❖ Any concurrent disease, infection or comorbid condition that interferes with the ability of the subject to participate in the study, which places the subject at undue risk or complicates the interpretation of data.	❖ Primary site: • Stomach: 77% vs. 74% • GEJ: 23% vs. 26% ❖ Lauren classification: • Diffuse: 29% vs. 41% • Intestinal: 25% vs. 23% • Mixed: 11% vs. 5% • Unknown: 17% vs. 14% • Other: 18% vs. 15% • Missing: <1% vs. 1% ❖ ECOG PS score: • 0: 44% vs. 41% • 1: 54% vs. 58% • 2: <1% vs. 0 • Missing: 1% vs. 1% ❖ Measurable disease: • Yes: 75% vs. 75% • No: 25% vs. 25%

Efficacy (I vs. C)	**Safety** (I vs. C)
Median PFS: 10.61 months (95% CI, 8.90–12.48) vs. 8.67 months (8.21–10.28); HR 0.75 (95% CI, 0.60–0.94); p=0.0066 **Estimated 12-month PFS:** 49% (95%, CI 42–55) vs. 35% (28–42) **24-month PFS**: 24% (95% CI, 17–32) vs. 15% (9–22) **Patients who had died by the interim analysis**: 53% vs. 63% **HR for death**: 0.75 (95% CI, 0.60–0.94; p=0.0053) **Median OS[4]:** 18.23 months (95% CI, 16.43–22.90) vs. 15.54 months (13.47–16.53) **Estimated 12-month OS:** 68% (95% CI, 61–73) vs. 60% (54–66)	**All TEAE:** >99% vs. >99% **All TEAEs grade ≥3**: 87% vs. 78% **Serious TEAEs:** 45% vs. 44% **TEAEs leading to discontinuation of any study drug:** 43% vs. 38% **TRAEs leading to discontinuation of any study drug:** 38% vs. 29**%**

[4] The median follow-up for OS was 22.14 months in the zolbetuximab group vs. 20.93 months in the placebo group.

24-month OS: 39% (32–46) vs. 28% (22–35) **ORR** (in the full analysis set, CR or PR): 48% (95% CI 42–54) vs. 48%, 42–54 **Median DoR**: 9.00 months (95% CI, 6.87–10.25) vs. 8.05 months (6.47–10.81) **ORR in patients with measurable disease**: 61% (95% CI 54–67) vs. 62% (55–69) **Median DoR**: 8.51 months (95%, CI 6.80–10.25) vs. 8.11 months (6.47–11.37) **ORR by the investigator**: 53% (95% CI 47–59) vs. 44%) **Median DoR**: 9.00 months (95% CI, 7.49–10.25) vs. 6.80 months (6.21–8.31) **Subsequent anticancer therapies:** 48% vs. 53%	**TEAEs leading to discontinuation of zolbetuximab or placebo:** 20% vs. 11% **TRAES leading to discontinuation of zolbetuximab or placebo:** 14% vs. 2% **TEAEs leading to death:** 8% vs. 9% **TRAEs leading to death:** 2% vs. 1%

Patient-reported outcomes

According to the authors, patient-reported outcome data will be disclosed in a subsequent publication.

ESMO-MCBS version 1.1 [8]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	≤12 months	OS: +2.69 months	0.75 (0.60-0.94)	HR≤0.65 AND gain ≥2.0-<3months	3	-	NA	-	3
Adapted	NC	2A	≤12 months	OS: +2.69 months	0.75 (0.60-0.94)	HR≥0.70 OR gain <1.5 months	1	-	NA	-	1

Risk of bias (RCT) [9]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	yes low risk	unclear[5] unclear risk	yes[6] high risk	unclear

Study characteristics: GLOW trial [10, 11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up for PFS	Characteristics	Biomarker	Funding	Publication(s)
GLOW trial NCT03653507	507 (1:1)	zolbetuximab 800 mg/m^2 (cycle 1, day 1) followed by 600 mg/m^2 (day 1 of subsequent cycles) + CAPOX[7]	Placebo+ CAPOX	PFS	12.62 months versus 12.09 months	ongoing[8], global, randomised, double-blind, phase 3 study	-	Astellas Pharma Inc	GLOW trial [10]

Inclusion criteria[9]	Exclusion criteria	Patient characteristics at baseline, ITT population (n=254 vs. n=253)
❖ Written informed consent ❖ ≥18 years of age ❖ Female patients: • Not pregnant • Not a WOCBP	❖ Prior systemic chemotherapy for local advanced unresectable or metastatic gastric/GEJ adenocarcinoma. ❖ Previous radiotherapy for locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma ≤14 days before randomisation and has not recovered from any related toxicity.	❖ Median age (range): 61.0 (22–82) vs. 59.0 (21–83) years ❖ Male sex: 62.6% vs. 61.7% ❖ Region: • Asia: 61.8% vs. 62.5% • Non-Asia: 38.2% vs. 37.5%

[5] Trial is currently ongoing.
[6] The funder of the study was involved in the study design, data collection, data analysis, data interpretation, and writing of the report.
[7] CAPOX=oral capecitabine, 1,000 mg/m^2, twice daily on days 1–14 of each cycle; intravenous infusion of oxaliplatin, 130 mg/m^2, day 1 of each cycle) for eight 21-day cycles.
[8] The GLOW trial is currently ongoing; estimated study completion date is 03/2025.
[9] For detailed in-and exclusion criteria, please see trial protocol.

• OR WOCBP who agrees to follow the contraceptive guidance as defined in Protocol throughout the treatment period and for 9 months after the final administration of oxaliplatin and 6 months after the final administration of all other study drugs. • not to breastfeed starting at screening and throughout the study period and for 6 months after the final study treatment administration • must not donate ova starting at screening and throughout the study period and for 9 months after the final administration of oxaliplatin and for 6 months after the final administration of all other study drugs. ❖ Male patient with female partner(s) of childbearing potential: • must agree to use contraception as detailed in Protocol during the treatment period and for 6 months after the final study treatment administration. • must not donate sperm during the treatment period and for 6 months after the final study treatment administration. • must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for 6 months after the final study treatment administration. ❖ Histologically confirmed diagnosis of gastric/GEJ adenocarcinoma. ❖ radiologically confirmed locally advanced unresectable or metastatic disease within 28 days before randomisation. ❖ Radiologically evaluable disease according to RECIST version 1.1, ❖ tumour expresses CLDN18.2 in ≥75% of tumour cells, demonstrating moderate-to-strong CLDN18 membranous staining as determined by central immunohistochemistry testing. ❖ HER2-negative tumour ❖ ECOG PS score 0 or 1. ❖ Predicted life expectancy ≥12 weeks ❖ Haemoglobin ≥9 g dl−1. ❖ ANC ≥1.5 × 10^9/l ❖ Platelets ≥100 × 10^9/l ❖ Albumin ≥2.5 g dl−1 ❖ Total bilirubin ≤1.5× ULN ❖ AST and ALT ≤2.5× ULN without liver metastases ❖ Estimated creatinine clearance ≥30 ml min−1 ❖ Prothrombin time/international normalised ratio and partial thromboplastin time ≤1.5× ULN (except for patients receiving anti-coagulation therapy).	❖ Previous treatment with herbal medications or other treatments that have known anti-tumour activity within 28 days before randomisation. ❖ Previous systemic immunosuppressive therapy, including systemic corticosteroids, within 14 days before randomisation. ❖ Previous other investigational agents or devices within 28 days before randomisation. ❖ Prior severe allergic reaction or intolerance to known ingredients of zolbetuximab or other monoclonal antibodies, including humanised or chimeric antibodies. ❖ Patient has known immediate or delayed hypersensitivity, intolerance or contraindication to any component of study treatment. ❖ Prior severe allergic reaction or intolerance to any component of CAPOX. ❖ Known dihydropyrimidine dehydrogenase deficiency. ❖ Patient has a complete gastric outlet syndrome or a partial gastric outlet syndrome with persistent/recurrent vomiting. ❖ Per investigator judgment, patient has significant gastric bleeding and/or untreated gastric ulcers that exclude the patient from participation. ❖ Known history of a positive test HIV infection or known active hepatitis B or hepatitis C infection. ❖ For patients who are negative for HBs Ag but HB core antibody (HBc Ab) positive, an HB DNA test will be performed, and, if positive, the patient will be excluded. ❖ Positive HCV serology but negative HCV RNA test are eligible. ❖ Active autoimmune disease that has required systemic treatment within the past 3 months before randomisation. ❖ Active infection requiring systemic therapy that has not completely resolved within 7 days before randomisation. ❖ Significant cardiovascular disease, including any of the following. ❖ Congestive heart failure, myocardial infarction, unstable angina, coronary angioplasty, coronary stenting, coronary artery bypass graft, cerebrovascular accident or hypertensive crisis within 6 months before randomisation. ❖ History of clinically significant ventricular arrhythmias. ❖ QTc interval >450 ms for male patients; QTc interval >470 ms for female patients. ❖ History or family history of congenital long QT syndrome. ❖ Cardiac arrhythmias requiring anti-arrhythmic medications. ❖ History of CNS metastases and/or carcinomatous meningitis from gastric/GEJ cancer. ❖ Patient has known peripheral sensory neuropathy grade >1 unless the absence of deep tendon reflexes is the sole neurological abnormality. ❖ Patient has had a major surgical procedure ≤28 days before randomisation.	• Organs with metastases: o 0–2: 74.4% vs. 74.3% o ≥3: 25.6% vs. 25.7% ❖ Prior gastrectomy: • Yes: 29.5% vs. 29.6% • No: 70.5% vs. 70.4% ❖ Primary site: • Stomach: 86.2% vs. 82.6% • GEJ: 13.8% vs. 17.4% ❖ Lauren classification: • Diffuse: 34.4% vs. 39.5% • Intestinal: 14.2% vs. 16.2% • Mixed: 7.9% vs. 8.3% • Unknown: 30.0% vs. 25.3% • Other: 13.4% vs. 10.7% • Missing: n=1 vs. 0 ❖ ECOG PS score: • 0: 42.7% vs. 43.2% • 1: 57.3% vs. 56.8% • Missing: n=1 vs. n=3 ❖ Measurable disease: • Yes: 76.8% vs. 81.0% • No: 23.2% vs. 19.0%

	❖ Patient without complete recovery from a major surgical procedure ≤14 days before randomisation. ❖ Psychiatric illness or social situations that would preclude study compliance, per investigator judgment. ❖ Another malignancy for which treatment is required. ❖ Any concurrent disease, infection or comorbid condition that interferes with the ability of the patient to participate in the study, which places the patient at undue risk or complicates the interpretation of data.	

Efficacy (I vs. C)	**Safety** (I vs. C), safety analysis set (n=254 vs. n=249)
Data cutoff 7 October 2022, median follow-up 12.62 vs. 12.09 months for PFS; and 17.71 vs. 18.43 months for OS: **Median PFS:** 8.21 months vs. 6.80 months; HR 0.687 (95% CI, 0.544–0.866); p= 0.0007 **Estimated 12-month PFS rates**: 35% vs. 19% **Estimated 24-month PFS rates**: 14% vs. 7% **Median PFS per investigator assessment:** 7.79 months vs. 6.08 months; HR 0.678 (95% CI, 0.546–0.841); p=0.0002 **Median OS**: 14.39 months vs. 12.16 months; HR 0.771 (95% CI, 0.615–0.965); p=0.0118 **Estimated 12-month OS rates**: 58% vs. 51% **Estimated 24-month OS rates:** 29% vs. 17% **Subsequent anticancer therapies administered**: 46.5% vs. 55.3% **ORR in the ITT population by IRC**: 42.5% (95% CI, 36.36–48.85) vs. 40.3% (95% CI, 34.22–46.64) **DOR**: 6.14 months (95% CI, 5.03–8.08) vs. 6.08 months (95% CI, 4.44–6.34) **ORR in patients with measurable lesions by IRC**: 53.8% (95% CI, 46.58–60.99) vs. 48.8% (95% CI, 41.76–55.84); CR: 3.1% vs. 1.5%; PR: 50.8% vs. 47.3% **Median DOR in patients with measurable lesions:** 6.28 months (95% CI, 5.39–8.28) vs. 6.18 months (95% CI, 4.53–6.41)	**All-grade TEAEs:** 98.8% vs. 98.0% **Grade ≥3 TEAEs:** 72.8% vs. 69.9% **Serious TEAEs:** 47.2% vs. 49.8% **TEAEs leading to discontinuation of any study drug:** 31.1% vs. 25.3% **TRAEs leading to discontinuation of any study drug:** 21.7% vs. 15.7% **TEAEs leading to discontinuation of zolbetuximab or placebo:** 20.1% vs. 14.5% **TRAEs leading to discontinuation of zolbetuximab or placebo:** 7.1% vs. 4.4% **TEAEs leading to death:** 10.6% vs. 12.9% **TRAEs leading to death:** 2.4% vs. 2.8%

Patient-reported outcomes

According to the authors, patient-reported outcomes will be reported in a future publication.

ESMO-MCBS version 1.1 [8]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	>12 months ≤24 months	OS: + 2.23 months	HR 0.771 (0.615–0.965)	HR≤0.70 AND gain ≥1.5-<3months	2	-	NA	-	2
Adapted	NC	2A	>12 months ≤24 months	OS: + 2.23 months	HR 0.771 (0.615–0.965)	HR>0.70 -0.75 AND gain ≥1.5 months	1	-	NA	-	1

Risk of bias (RCT) [9]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	Yes low risk	unclear[10] unclear risk	yes[11] high risk	unclear

[10] The GLOW trial is currently ongoing.
[11] Industry-funded.

Ongoing trials [12]		
NCT number/trial name	Description	Estimated study completion date
NCT03653507 / GLOW	Please see above.	03/2025
NCT03504397 / SPOTLIGHT	Please see above.	03/2025

Available assessments

- In February 2022, NIHR published a Health Technology Briefing "Zolbetuximab for previously untreated advanced gastric or gastro-oesophageal junction adenocarcinoma "[13]
- No assessments were identified via NICE (project in development), CDA-AMC (reimbursement review in development), G-BA and ICER.

Other aspects and conclusions

- In July 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Vyloy® in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN 18.2 positive. This indication has not been **approved by the FDA**.
- **SPOTLIGHT trial**
  - SPOTLIGHT (NCT03504397) is an **ongoing**, randomised, placebo-controlled, double-blind, **phase 3 trial** assessing **zolbetuximab plus mFOLFOX6** in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. Eligible patients were ≥ 18 years old with radiologically evaluable disease according to RECIST version 1.1; an ECOG PS score of 0 or 1, and adequate organ function.
  - The primary endpoint is **PFS**, which is assessed by IRC. Median PFS was 10.61 months (95% CI, 8.90–12.48) in the zolbetuximab group vs. 8.67 months (8.21–10.28) in the placebo group.
  - Results of patient-reported outcomes are currently **not available**.
  - The original and adapted **ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit of **3 and 1**, respectively.
  - Due to the ongoing status of the trial, the **risk of bias was considered unclear**. However, it is increased by the sponsor's involvement throughout the study.
- **GLOW trial**
  - GLOW (NCT03653507) is an **ongoing,** double-blind, **phase 3 study** evaluating zolbetuximab plus CAPOX as first-line treatment for CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. Eligible patients were ≥18 years old with radiologically evaluable disease according to RECIST version 1.1. Patients had an ECOG PS score of 0 or 1 and adequate organ function.
  - The primary endpoint was **PFS**; median PFS was 8.21 months in the zolbetuximab plus CAPOX group vs. 6.80 months in the placebo plus CAPOX group, HR was 0.687 (95% CI, 0.544–0.866); p= 0.0007.
  - Results of patient-reported outcomes are currently **not available**.
  - The original and adapted **ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit of **2 and 1**, respectively.
  - Due to the ongoing status of the trial, the **risk of bias was considered unclear**. However, it is increased by the industry-funded background of the trial.
- For the assessed indication, besides SPOTLIGHT and GLOW, **no further ongoing phase 3 trials** were identified via ClinicalTrials.gov.
- **Final phase 3 data and patient-reported outcome data** are required to determine the role of zolbetuximab with chemotherapy for the first-line therapy in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive. When interpreting the results of the SPOTLIGHT and GLOW trials, it has to be **considered** that the **prevalence of CLDN18.2 positivity was 38.4% across both trials**.

First published: 08/2024

Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase C=comparator, CAPOX=capecitabine and oxaliplatin, CDA-AMC=Canada's Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLDN=Claudin, CNS= central nervous system, DNA=deoxyribonucleic acid, DoR=duration of response, ECOG PS=Eastern Cooperative Oncology Group Performance status, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GEJ= gastroesophageal junction, HB=hepatitis B, HCV=hepatitis C virus, HER2=human epidermal growth factor receptor 2, HIV= for human immunodeficiency virus HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, INR= international normalised ratio , Int.=intention, IRC=independent review committee, ITT=intention-to-treat, MG=median gain, mFOLFOX6=modified folinic acid (or levofolinate), fluorouracil, and oxaliplatin regimen, n=number of patients, NICE=National Institute for Health Care Excellence, ORR=objective response rate, OS=overall

survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RECIST=Response Evaluation Criteria In Solid Tumors, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event, ULN= upper limit of normal, WOCBP= woman of child-bearing potential

References:

1. European Medicines Agency (EMA). Medicines. Vyloy. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vyloy].
2. Statistik Austria. Krebserkrankungen. Krebsinzidenz nach ausgewählten Lokalisationen und Geschlecht. [Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen].
3. Moran D, et al. Prevalence of CLDN18.2, HER2 and PD-L1 in gastric cancer samples. Annals of Oncology. 2018; Volume 29, SUPPLEMENT 8, VIII32.
4. Onkopedia, Lordick F, et al. Onkopedia Guidelines. Gastric Cancer. [Available from: https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/gastric-cancer/@@guideline/html/index.html].
5. Astellas Pharma Inc. U.S. FDA ACKNOWLEDGES ASTELLAS' RESUBMISSION OF BIOLOGICS LICENSE APPLICATION FOR ZOLBETUXIMAB AND SETS NEW ACTION DATE [Available from: https://www.astellas.com/en/news/29186].
6. Shitara K, Lordick F, Bang Y-J, 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.
7. U.S. National Library of Medicine, ClinicalTrials.gov. A Phase 3 Efficacy, Safety and Tolerability Study of Zolbetuximab (Experimental Drug) Plus mFOLFOX6 chemotherapy Compared to Placebo Plus mFOLFOX6 as Treatment for Gastric and Gastroesophageal Junction (GEJ) Cancer (Spotlight). [Available from: https://clinicaltrials.gov/study/NCT03504397#more-information].
8. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology. 2017;28(10):2340-2366.
9. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].
10. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophagealjunction adenocarcinoma: the randomised, phase 3 GLOW trial. Nature Medicine Volume 29, August 2023, 2133–2141 2133.
11. U.S. National Library of Medicine, ClinicalTrials.gov. A Study of Zolbetuximab (IMAB362) Plus CAPOX Compared With Placebo Plus CAPOX as First-line Treatment of Subjects With Claudin (CLDN) 18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (GLOW). [Available from: https://www.clinicaltrials.gov/study/NCT03653507].
12. U.S. National Library of Medicine, ClinicalTrials.gov. [Available from: https://clinicaltrials.gov/].
13. National Institute for Health Research (NIHR). Zolbetuximab for previously untreated advanced gastric or gastro-oesophageal junction adenocarcinoma. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/03/26905-Zolbetuximab-for-Gastric-Cancer-or-Gastro-Oesophageal-Junction-Cancer-Feb-2022-NON-CONF-v1.0.pdf].