Updates in perioperative management of localized esophageal cancer

ESOPEC Trial

Perioperative Chemotherapy (FLOT) vs Neoadjuvant Chemoradiation (CROSS) for Resectable Esophageal Adenocarcinoma

Trial Conduct

- Phase 3 randomized trial
- Locally advanced esophageal/GEJ adeno
- Enrolled Feb 2016 to April 2020
- Total of 438 patients (25 sites in Germany)
- Randomly assigned (221 FLOT; 217 Cross)
- Follow-up carried out to Nov 2023

Inclusion Criteria

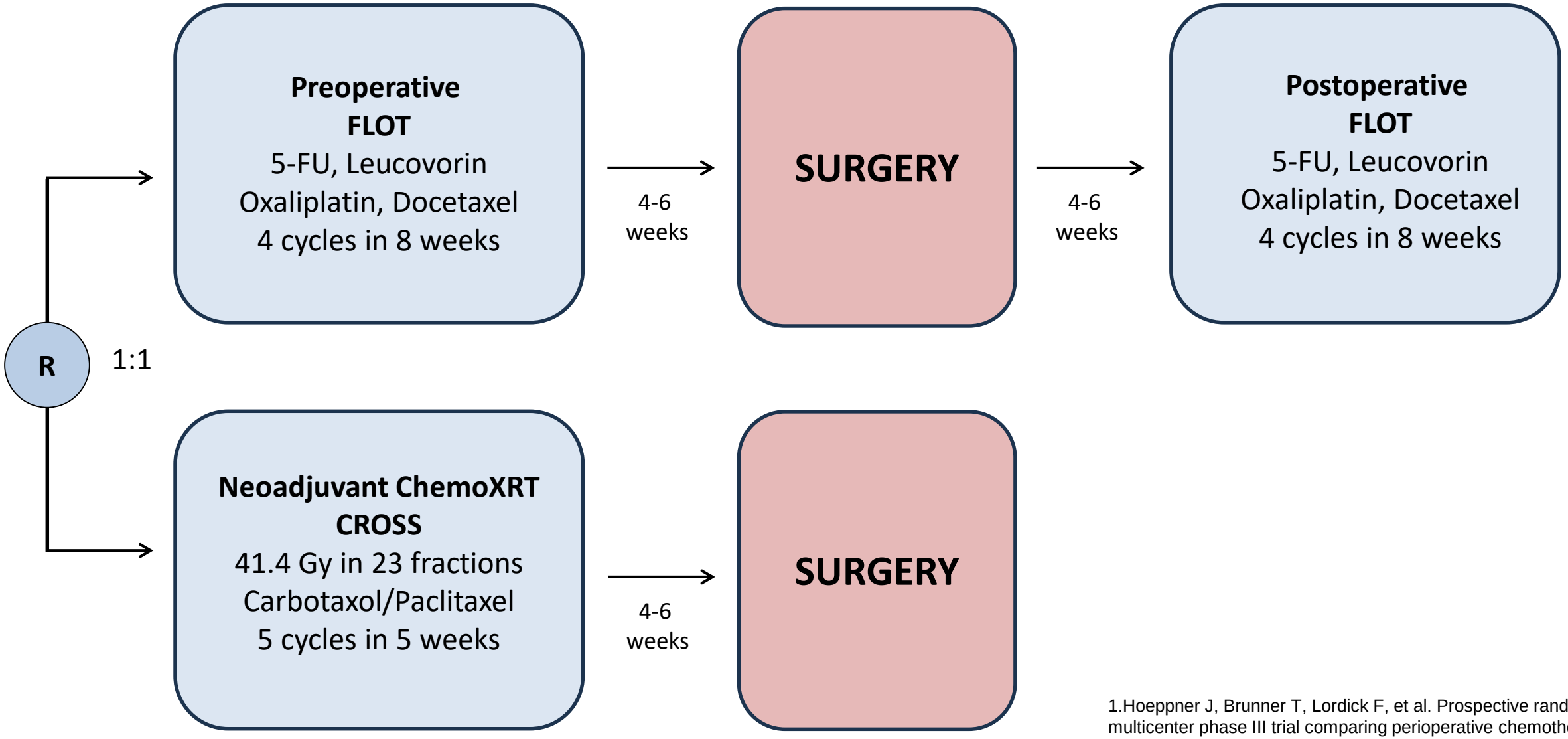
- Histology: Adenocarcinoma
- Esophageal cancer UICC (TNM7)
- Clinical stage cT1N+ or cT2-4a, cN0/+, cM0

Exclusion Criteria

- Squamous or non-adenocarcinoma histology
- Gastric cancer
- Clinical stage cT1cN0 and cT4b
- Metastatic disease

1.Hoeppner J, Brunner T, Lordick F, et al. Prospective randomized multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (ESOPEC trial).*J Clin Oncol*. 2024;42(suppl 17):LBA1. doi:10.1200/JCO.2024.42.17_suppl.LBA1

ESOPEC - Trial Scheme



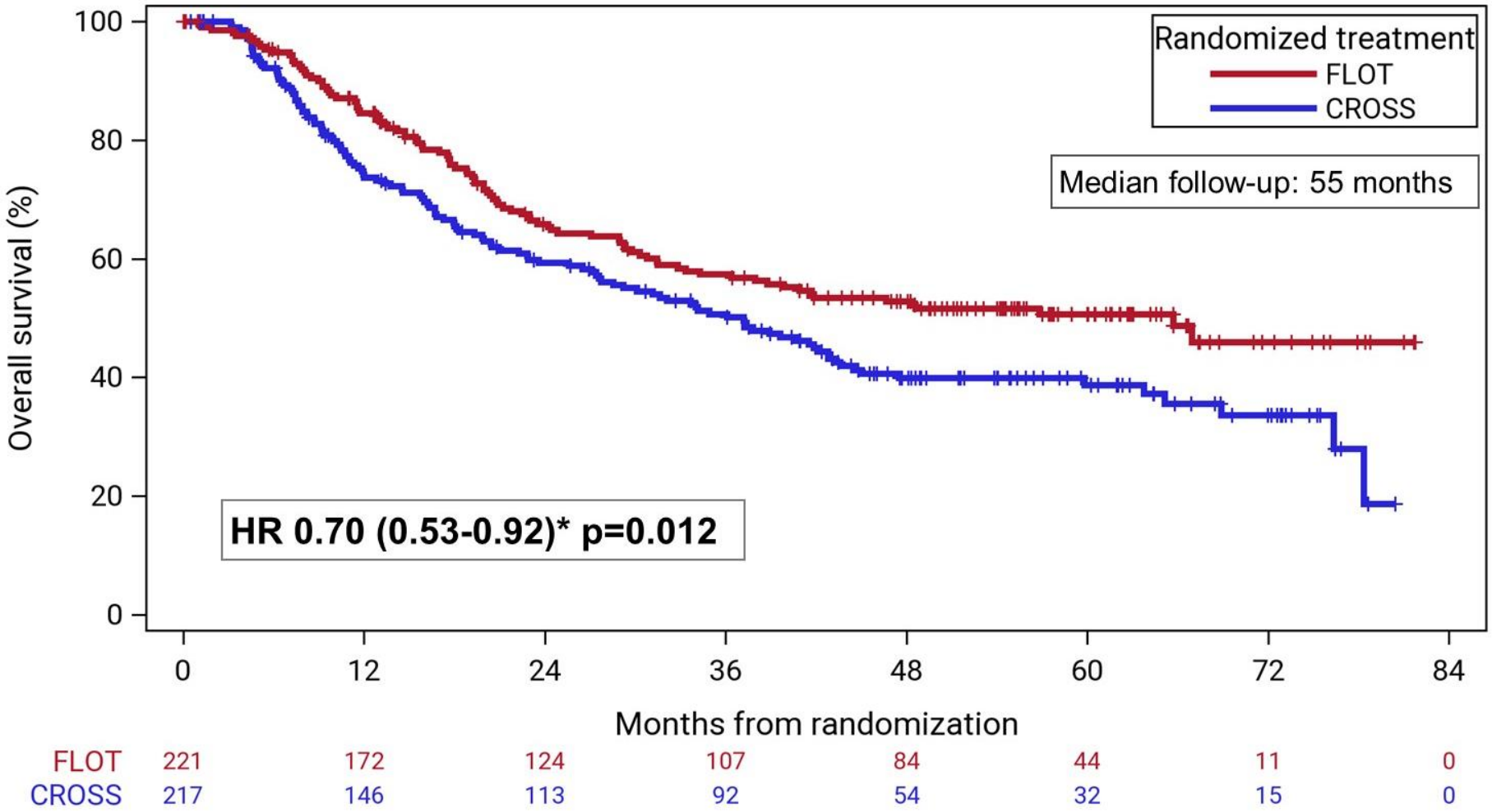
1.Hoeppner J, Brunner T, Lordick F, et al. Prospective randomized multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (ESOPEC trial).*J Clin Oncol*. 2024;42(suppl 17):LBA1. doi:10.1200/JCO.2024.42.17_suppl.LBA1

ESOPEC - Trial Patient Characteristics

	FLOT Group	CROSS Group
N	221	217
Age mean (SD) in years	63.1 (8.6)	62.6 (9.8)
Sex male	89.1 %	89.4 %
ECOG		
> 0	26.7%	28.1%
Clinical T-stage		
cT1-2	19.5%	17.1%
cT3-4	79.1%	81.9%
Clinical N-stage		
cN0	22.2%	18.4%
cN+	77.8%	81.6%

1.Hoeppner J, Brunner T, Lordick F, et al. Prospective randomized multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (ESOPEC trial).*J Clin Oncol*. 2024;42(suppl 17):LBA1. doi:10.1200/JCO.2024.42.17_suppl.LBA1

ESOPEC - OS



	FLOT	CROSS
Events	97	121
Median OS time (months)	66 95% CI 36 – n.e	37 95% CI 28 – 43
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

- After a median follow-up of 55 months mOS was 66 months for FLOT patients vs. 37 months for CROSS patients
- Perioperative FLOT improved median OS by 29 months compared to neoadjuvant CROSS

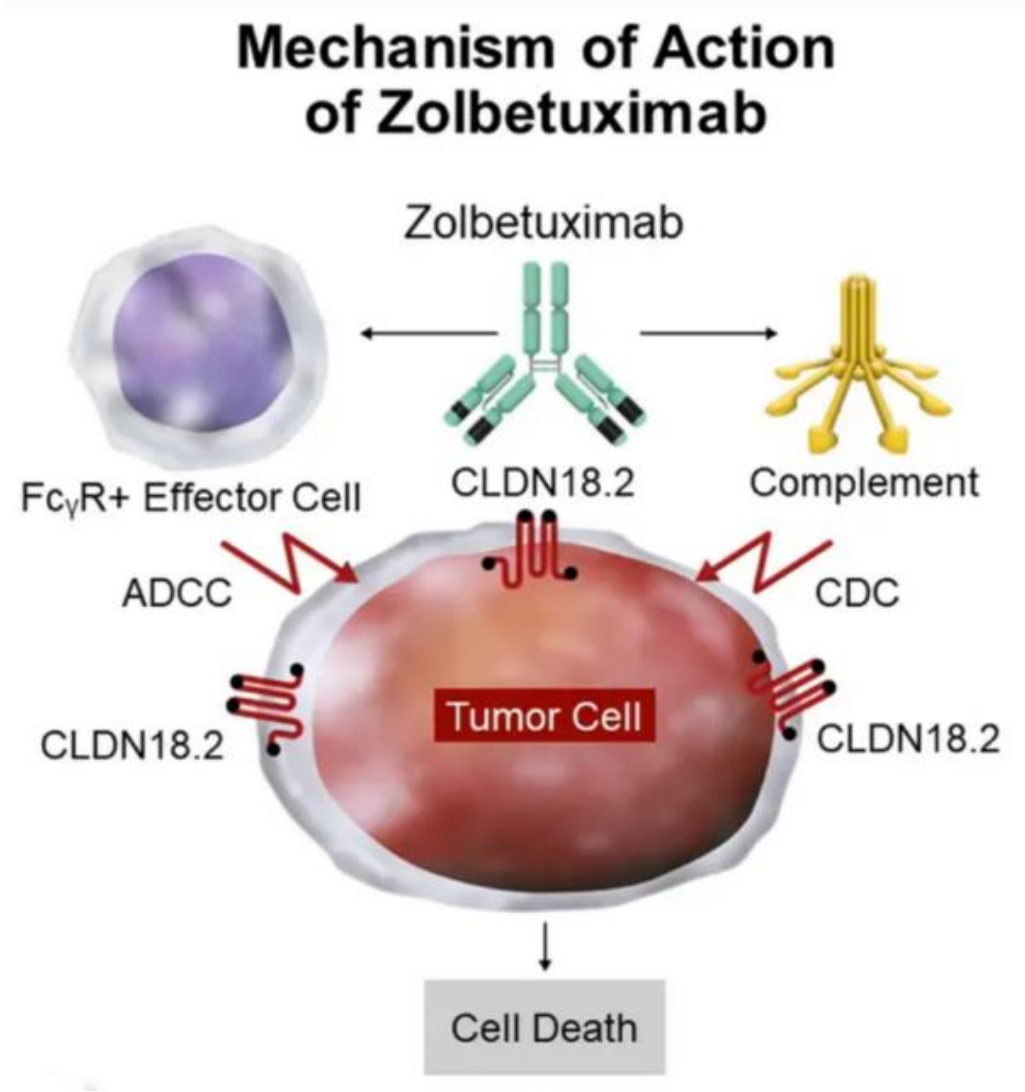
ESOPEC

- Perioperative chemotherapy (FLOT) plus surgery improves OS compared to chemoradiation (CROSS) for patients with cT1cN+ and cT2-4a, cN-/+ M0 esophageal adenocarcinoma by 29 months
- 3 year OS was 57% for FLOT and 51% for CROSS
- New approaches were developed during the conduct of ESOPEC including adjuvant immunotherapy (CheckMate 577)
- Prior studies (including Neo-AEGIS) compared CROSS with perioperative treatment consisting of either FLOT, epirubicin plus cisplatin, or oxaliplatin plus fluorouracil or capecitabine. No OS different leading to conclusion of clinical equipose
- FLOT is reserved for medically fit patients
- More patients completed FLOT 87.3% vs. CROSS 67.7%
- pCR was 16.8% in the FLOT arm vs. 10% in the CROSS arm
- pCR was lower than expected in the CROSS arm (radiation dose?)
- Preoperative RT: 41.4–50.4 Gy (1.8–2.0 Gy/day) (total 23–28 fractions)
- CROSS could offer an organ sparing approach to treatment for complete responders
- Future possibility of combined modality chemo and chemoradiation as per CALBG 80803

1. Hoeppner J, Brunner T, Lordick F, et al: Prospective randomized multicener phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (ESOPEC trial). 2024 ASCO Annual Meeting. Abstract LBA1. Presented June 2, 2024.
2. Reynolds JV, Preston SR, O'Neill B, et al: Trimodality therapy versus perioperative chemotherapy in the management of locally advanced adenocarcinoma of the oesophagus and oesophagogastric junction (Neo-AEGIS): An open-label, randomised, phase 3 trial. Lancet Gastroenterol Hepatol 8:1015-1027, 2023.
3. Kelly RJ, Ajani JA, Kuzdzal J, et al: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 384:1191-1203, 2021.
4. Goodman KA, Ou FS, Hall NC, et al. Randomized phase II study of PET response-adapted combined modality therapy for esophageal cancer: mature results of the CALGB 80803 (Alliance) Trial. *J Clin Oncol*. 2021;39(25):2803-2815.

Emerging therapeutic targets in gastroesophageal cancer treatment

EMERGING THERAPEUTIC TARGET IN GASTRIC and GEJ ADENOCARCINOMA – CLDN18.2



- CLDN18.2 is a tight junction protein normally expressed in gastric mucosa cells
- CLDN18.2 may become expose on the surface of G/GEJ adeno cells, making it a potential target
- Zolbetuximab is a chimeric IgG1 monoclonal antibody that targets CLDN18.2 and induces ADCC/CDC
- It is estimated that 35% of gastric/GEJ tumor express CLDN18.2

Antibody-dependent cellular cytotoxicity (ADCC)
Complement-dependent cytotoxicity (CDC)

EMERGING THERAPEUTIC TARGET IN GASTRIC and GEJ ADENOCARCINOMA – CLDN18.2

SPOTLIGHT

Zolbetuximab + mFOLFOX6
vs.
Placebo + mFOLFOX 6

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 Shitara, Kohei et al. The Lancet, Volume 401, Issue 10389, 1655 - 1668

Key Eligibility Criteria

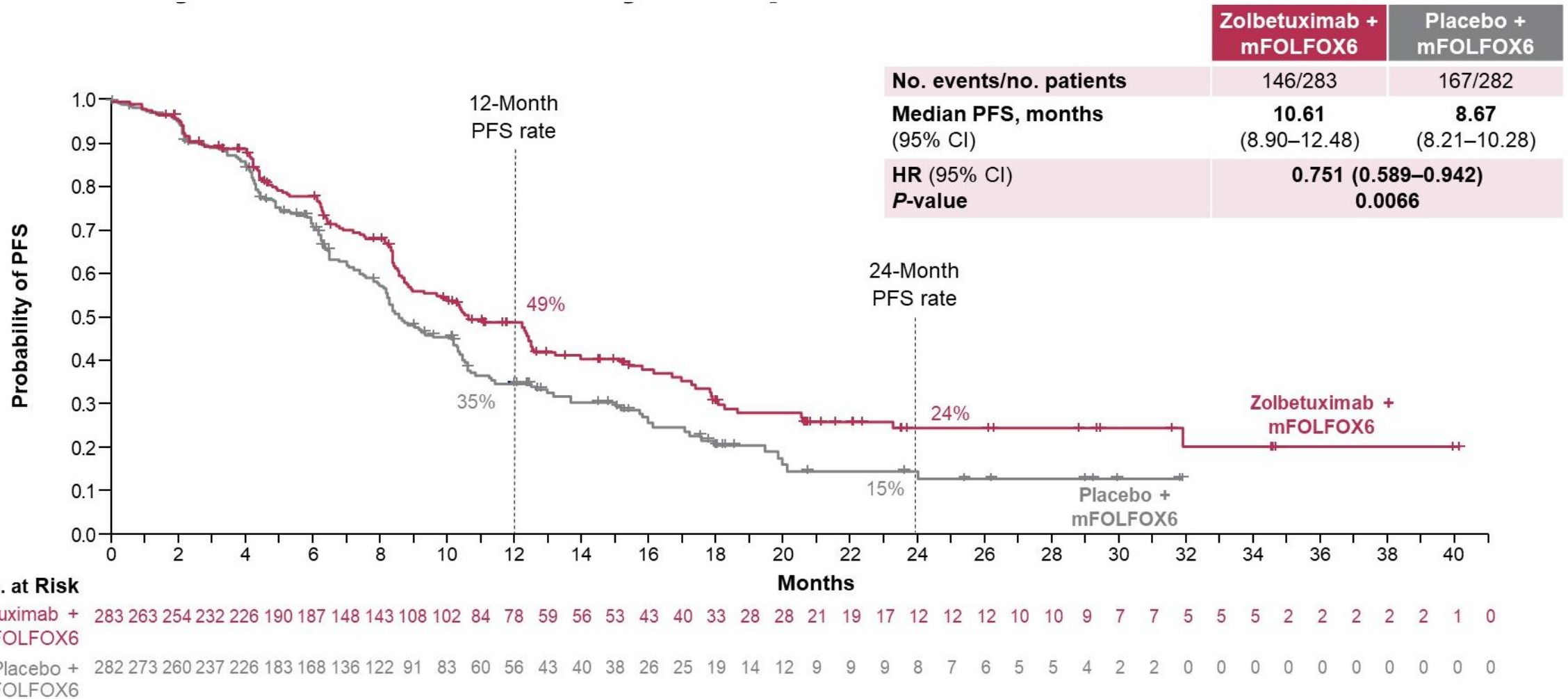
- Previously untreated LA
- Unresectable mG/GEJ adeno
- CLDN18.2+ (>/= 75% of tumor cells with moderate to strong membranous CLD18.2 staining
- HER2-
- ECOG PS 0-1

GLOW

Zolbetuximab + CAPOX
vs.
Placebo + CAPOX

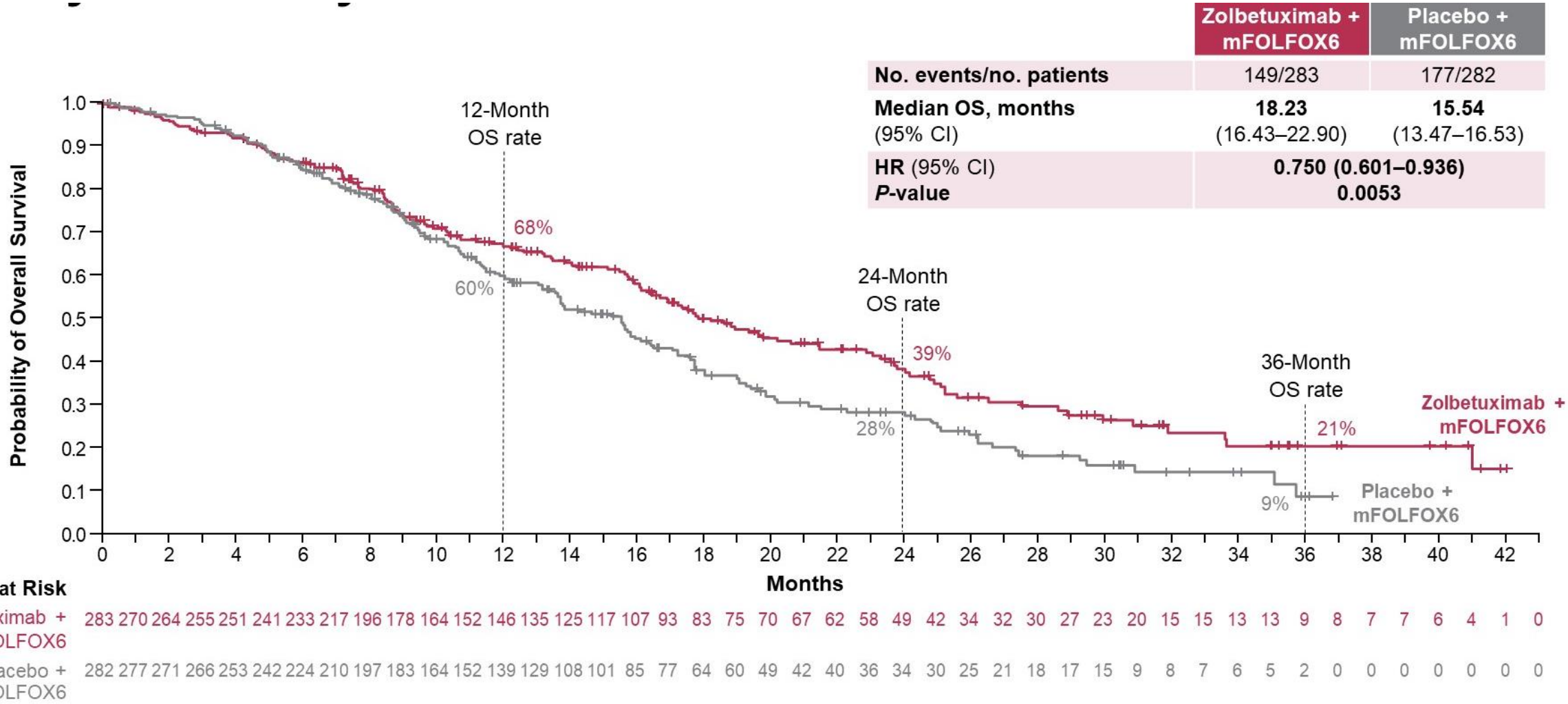
Shah, M.A., Shitara, K., Ajani, J.A. *et al.* Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med* **29**, 2133–2141 (2023). https://doi.org/10.1038/s41591-023-02465-7

SPOTLIGHT - PFS

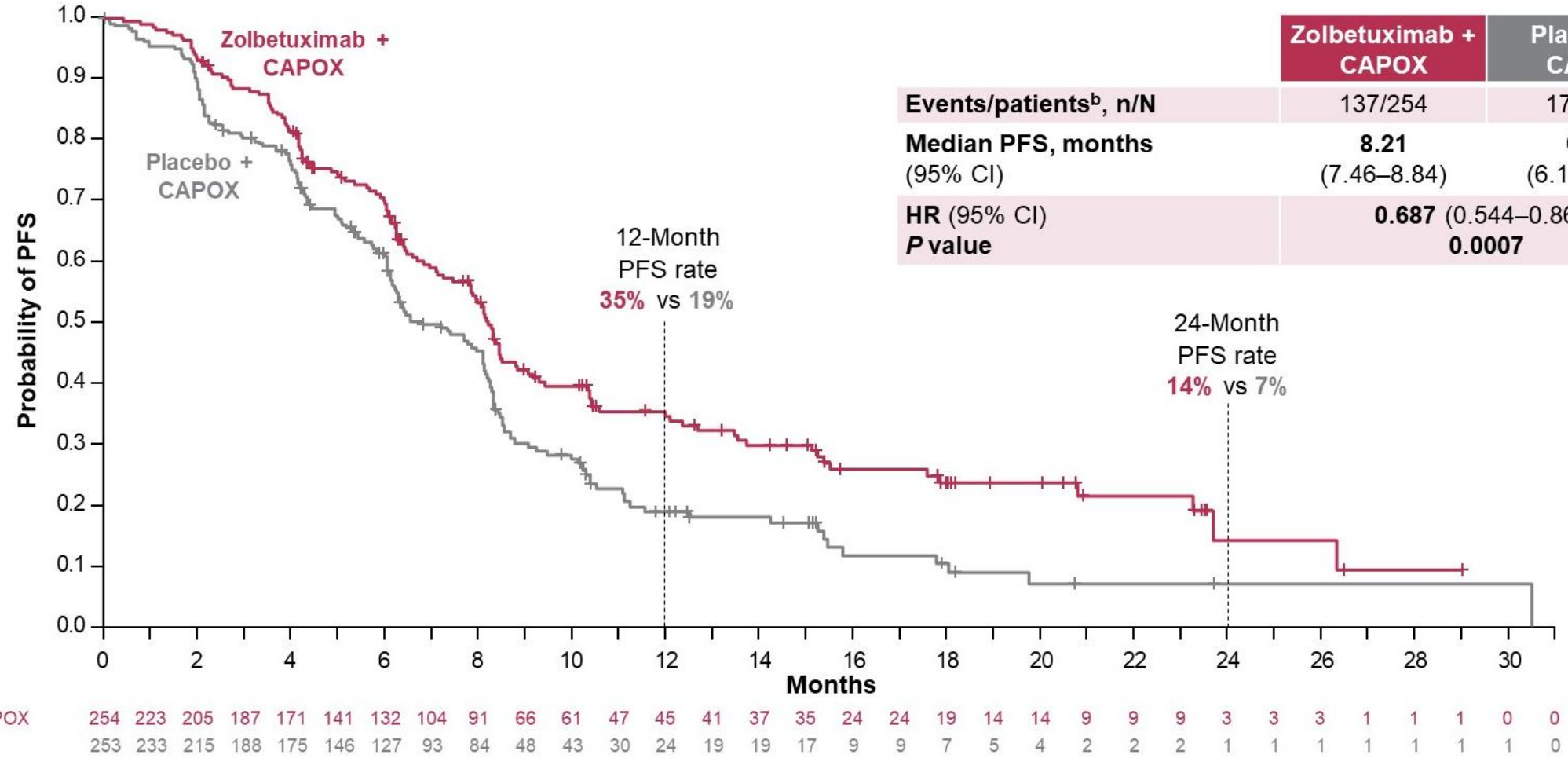


	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	146/283	167/282
Median PFS, months (95% CI)	**10.61** (8.90–12.48)	**8.67** (8.21–10.28)
HR (95% CI)	**0.751 (0.589–0.942)**	
***P*-value**	**0.0066**	

SPOTLIGHT - OS



GLOW - PFS

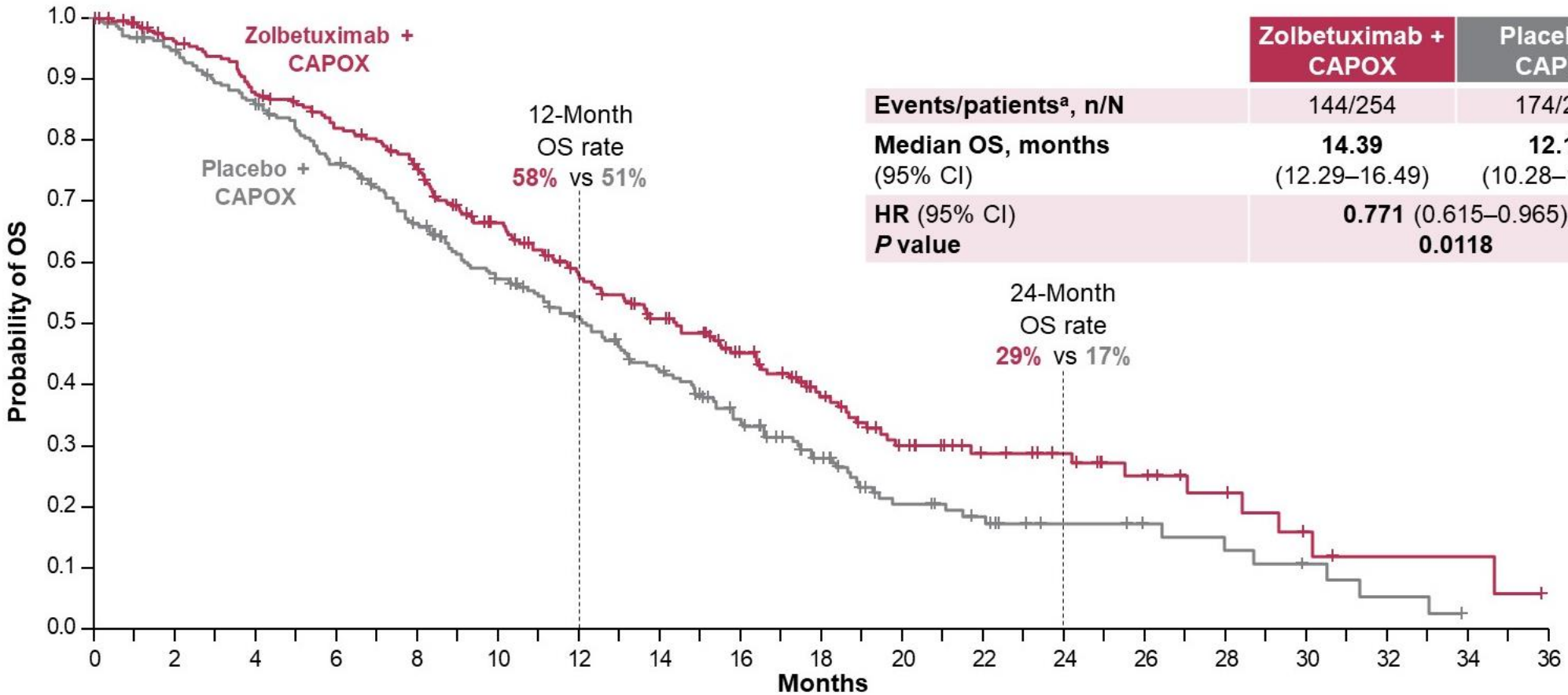


	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[b], n/N	137/254	172/253
Median PFS, months (95% CI)	**8.21** (7.46–8.84)	**6.80** (6.14–8.08)
HR (95% CI)	**0.687** (0.544–0.866)	
***P* value**	**0.0007**	

No. at Risk

Zolbetuximab + CAPOX	254	223	205	187	171	141	132	104	91	66	61	47	45	41	37	35	24	24	19	14	14	9	9	9	3	3	3	1	1	1	0	0
Placebo + CAPOX	253	233	215	188	175	146	127	93	84	48	43	30	24	19	19	17	9	9	7	5	4	2	2	2	1	1	1	1	1	1	1	0

GLOW - OS



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[a], n/N	144/254	174/253
Median OS, months (95% CI)	**14.39** (12.29–16.49)	**12.16** (10.28–13.67)
HR (95% CI)	**0.771** (0.615–0.965)	
***P* value**	**0.0118**	

No. at Risk

Zolbetuximab + CAPOX	254	243	233	226	211	203	193	187	171	150	138	125	108	100	87	80	68	61	47	38	31	27	22	21	18	13	12	9	8	6	4	2	2	2	2	1	0
Placebo + CAPOX	253	243	235	220	210	197	181	168	152	136	125	115	104	92	82	70	59	49	40	27	22	20	16	12	10	10	8	7	6	5	4	3	2	2	0	0	0

SPOLIGHT - AEs

Treatment-emergent events* by preferred terms				
Nausea	230 (82%)	45 (16%)	169 (61%)	18 (6%)
Vomiting	188 (67%)	45 (16%)	99 (36%)	16 (6%)
Decreased appetite	131 (47%)	16 (6%)	93 (33%)	9 (3%)
Diarrhoea	110 (39%)	12 (4%)	122 (44%)	9 (3%)
Peripheral sensory neuropathy	106 (38%)	11 (4%)	118 (42%)	15 (5%)
Neutropenia	102 (37%)	79 (28%)	94 (34%)	65 (23%)
Anaemia	100 (36%)	24 (9%)	104 (37%)	26 (9%)
Constipation	99 (35%)	3 (1%)	112 (40%)	2 (1%)
Neutrophil count decreased	95 (34%)	69 (25%)	91 (33%)	69 (25%)
Fatigue	78 (28%)	17 (6%)	91 (33%)	14 (5%)
Asthenia	74 (27%)	20 (7%)	64 (23%)	7 (3%)
Abdominal pain	67 (24%)	12 (4%)	82 (29%)	6 (2%)
Stomatitis	58 (21%)	7 (3%)	57 (21%)	3 (1%)
Weight decreased	55 (20%)	5 (2%)	54 (19%)	2 (1%)
Pyrexia	54 (19%)	1 (<1%)	48 (17%)	1 (<1%)
White blood cell count decreased	50 (18%)	8 (3%)	46 (17%)	16 (6%)
Hypokalaemia	50 (18%)	16 (6%)	41 (15%)	10 (4%)
Oedema peripheral	49 (18%)	2 (1%)	26 (9%)	0
Aspartate aminotransferase increased	49 (18%)	4 (1%)	44 (16%)	7 (3%)
Abdominal pain upper	47 (17%)	4 (1%)	32 (12%)	0
Paraesthesia	44 (16%)	6 (2%)	46 (17%)	4 (1%)
Hypoalbuminaemia	43 (15%)	11 (4%)	17 (6%)	2 (1%)
Dysgeusia	41 (15%)	1 (<1%)	40 (14%)	0
Platelet count decreased	40 (14%)	3 (1%)	49 (18%)	6 (2%)
Dizziness	36 (13%)	0	27 (10%)	1 (<1%)
Alanine aminotransferase increased	34 (12%)	2 (1%)	47 (17%)	7 (3%)
Back pain	34 (12%)	0	30 (11%)	0
Headache	31 (11%)	2 (1%)	35 (13%)	1 (<1%)
Hypertension	31 (11%)	15 (5%)	22 (8%)	10 (4%)
Hypocalcaemia	30 (11%)	6 (2%)	9 (3%)	0
Insomnia	29 (10%)	1 (<1%)	25 (9%)	0
Thrombocytopenia	28 (10%)	4 (1%)	45 (16%)	4 (1%)
Cough	28 (10%)	0	28 (10%)	0
Dyspnoea	20 (7%)	3 (1%)	32 (12%)	6 (2%)

GLOW - AEs

TEAEs[a] by preferred terms[b]	All grade	Grade ≥3	All grade	Grade ≥3
Nausea	174 (68.5)	22 (8.7)	125 (50.2)	6 (2.4)
Vomiting	168 (66.1)	31 (12.2)	77 (30.9)	9 (3.6)
Decreased appetite	105 (41.3)	17 (6.7)	84 (33.7)	4 (1.6)
Anemia	90 (35.4)	27 (10.6)	91 (36.5)	28 (11.2)
Diarrhea	80 (31.5)	15 (5.9)	86 (34.5)	18 (7.2)
Neutrophil count decreased	70 (27.6)	26 (10.2)	59 (23.7)	24 (9.6)
Aspartate aminotransferase increased	63 (24.8)	6 (2.4)	72 (28.9)	7 (2.8)
Platelet count decreased	61 (24.0)	19 (7.5)	60 (24.1)	20 (8.0)
Hypoalbuminemia	57 (22.4)	8 (3.1)	35 (14.1)	4 (1.6)
Peripheral sensory neuropathy	56 (22.0)	1 (0.4)	56 (22.5)	6 (2.4)
White blood cell count decreased	51 (20.1)	5 (2.0)	39 (15.7)	9 (3.6)
Neutropenia	50 (19.7)	18 (7.1)	35 (14.1)	7 (2.8)
Weight decreased	50 (19.7)	1 (0.4)	25 (10.0)	1 (0.4)
Alanine aminotransferase increased	48 (18.9)	2 (0.8)	52 (20.9)	7 (2.8)
Palmar-plantar erythrodysesthesia syndrome	41 (16.1)	4 (1.6)	49 (19.7)	9 (3.6)
Abdominal pain	40 (15.7)	1 (0.4)	54 (21.7)	4 (1.6)
Constipation	39 (15.4)	–	52 (20.9)	–
Hypokalemia	36 (14.2)	14 (5.5)	36 (14.5)	16 (6.4)
Fatigue	34 (13.4)	7 (2.8)	42 (16.9)	9 (3.6)
Pyrexia	34 (13.4)	1 (0.4)	23 (9.2)	0
Asthenia	33 (13.0)	7 (2.8)	32 (12.9)	3 (1.2)
Malaise	31 (12.2)	1 (0.4)	22 (8.8)	0
Hypoesthesia	30 (11.8)	1 (0.4)	30 (12.0)	0
Thrombocytopenia	28 (11.0)	7 (2.8)	31 (12.4)	7 (2.8)
Insomnia	27 (10.6)	–	16 (6.4)	–
Edema peripheral	26 (10.2)	1 (0.4)	6 (2.4)	0

GUIDANCE ON THE MANAGEMENT OF NAUSEA AND VOMITING WITH VYLOY® (zolbetuximab-clzb) ADMINISTRATION

Based on Expert Guidance: Anticipate, Administer, and Manage

What to Expect With Zolbetuximab Use?

- Administer first followed by chemotherapy[1]
  - Do not co-administer using the same infusion line[1]
- First infusion (cycle 1 day 1 [C1D1]) to take a minimum of ~3.5 hrs (range, 3.33-4.5 hrs)[1,2]
- Subsequent infusions[a] to take a minimum of ~2.5 hrs (range, 2.38-4.5 hrs)[1,2]
- **Timing does not take into consideration the potential infusion interruptions/rate modifications[1,2]**
- **Diluted infusion should not be kept for >6 hrs[b] at room temperature or >16 hrs[b] under refrigeration[1]**
- Any baseline nausea and/or vomiting should be resolved to Grade ≤1 (≤ mild)[c] before starting the first infusion[1]
- In two global Phase 3 trials:
  - Nausea and vomiting were the most frequently reported all-grade TEAEs[3,4]
    - **~3 out of 4** patients experienced nausea
    - **~2 out of 3** patients experienced vomiting
  - Occurrences of nausea/vomiting was highest during cycle 1 (C1) and decreased significantly thereafter[2]
    - **Median time to first occurrence of nausea/vomiting[d] was <1 hr[2]**
    - In some instances, vomiting occurred suddenly without prior nausea[2,e]

Infusion Modifications for Zolbetuximab-Related Adverse Reactions Management, Including Nausea and Vomiting

- No dose reduction recommended[1]
  - Nausea and vomiting are managed by reducing infusion rate, infusion interruption, withholding the dose, and/or permanent discontinuation[1]
- Zolbetuximab should not be discontinued without first attempting to modify or temporarily interrupt the infusion and/or without providing additional treatment for nausea and vomiting[5]

Hypersensitivity or IRR	Anaphylaxis	Immediately stop and permanently discontinue	
	Grade 3 or 4[c]		
	Grade 2[c]	Interrupt the infusion (until recovery to Grade ≤1[c])	• Resume infusion at a reduced rate for the remaining infusion • For next infusion, **premedicate** and administer per infusion rate recommendations
Nausea	Grade ≥2[c,f]		
Vomiting	Grade 2 or 3[c]		
	Grade 4[c]	Immediately stop and permanently discontinue	

Grade 1: mild; Grade 2: moderate; Grade 3: severe or medically significant but not immediately life-threatening; Grade 4: life-threatening consequences[6,c]

Management of Nausea and/or Vomiting

Zolbetuximab Infusion Rates Recommendations Per PI

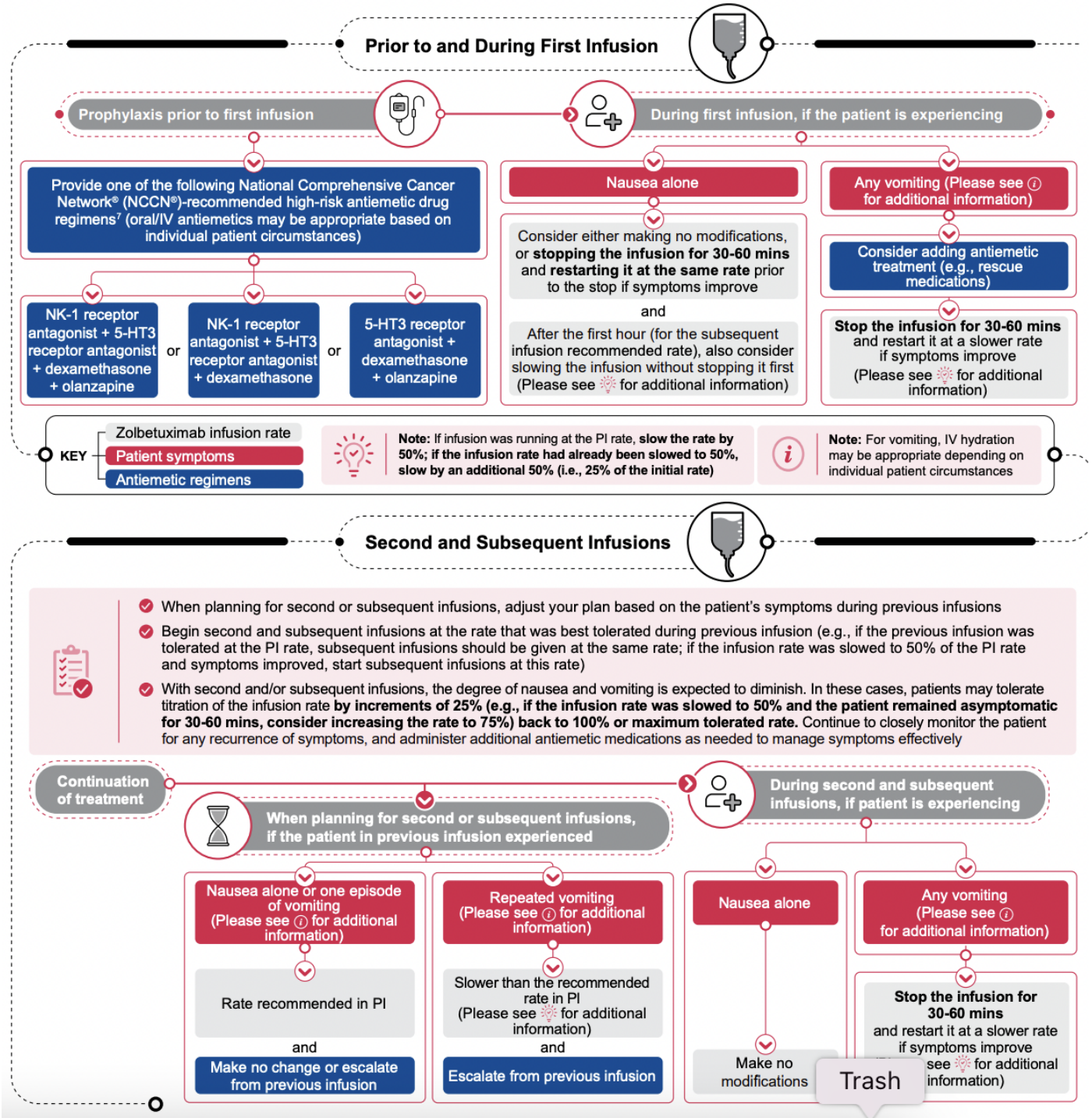
- Start at a slower rate (100 mg/m²/hr) for the first infusion and then adjust as tolerated[1]
- Subsequent infusions can be at a rate of 100-265 mg/m²/hr (after the first 30-60 mins) as tolerated[1]

Zolbetuximab Dose		Infusion Rate	
		Initial Infusion Rate First 30-60 mins	Subsequent Infusion Rate
First	800 mg/m²	100 mg/m²/hr	200-265 mg/m²/hr
Subsequent	600 mg/m² every 3 weeks or 400 mg/m² every 2 weeks	75 mg/m²/hr or 50 mg/m²/hr	150-265 mg/m²/hr or 100-200 mg/m²/hr

Antiemetic Prophylaxis Prior to Each Zolbetuximab Infusion

- Zolbetuximab is emetogenic and may cause severe nausea and/or vomiting[1]
- Premedicate with antiemetics (e.g., NK-1 receptor blockers and/or 5-HT3 receptor blockers, as well as other drugs per local and institutional guidelines)[1]
- The most commonly used prophylactic antiemetic regimens during C1D1 were:[2]
  - 5-HT3 receptor blocker + NK-1 receptor blocker (~26%)
  - 5-HT3 receptor blocker + NK-1 receptor blocker + others (~13%)
  - 5-HT3 receptor blocker + NK-1 receptor blocker + steroids (~12%)
- Patients who received prophylactic corticosteroids had similar PFS and OS benefits as those in the overall population[2,g,h]

astellas


Prior to and During First Infusion
Prophylaxis prior to first infusion
During first infusion, if the patient is experiencing
Provide one of the following National Comprehensive Cancer Network® (NCCN®)-recommended high-risk antiemetic drug regimens[7] (oral/IV antiemetics may be appropriate based on individual patient circumstances)
NK-1 receptor antagonist + 5-HT3 receptor antagonist + dexamethasone + olanzapine
or
NK-1 receptor antagonist + 5-HT3 receptor antagonist + dexamethasone
or
5-HT3 receptor antagonist + dexamethasone + olanzapine
Nausea alone
Consider either making no modifications, or stopping the infusion for 30-60 mins and restarting it at the same rate prior to the stop if symptoms improve
and
After the first hour (for the subsequent infusion recommended rate), also consider slowing the infusion without stopping it first (Please see for additional information)
Any vomiting (Please see for additional information)
Consider adding antiemetic treatment (e.g., rescue medications)
Stop the infusion for 30-60 mins and restart it at a slower rate if symptoms improve (Please see for additional information)
KEY
Zolbetuximab infusion rate
Patient symptoms
Antiemetic regimens
Note: If infusion was running at the PI rate, slow the rate by 50%; if the infusion rate had already been slowed to 50%, slow by an additional 50% (i.e., 25% of the initial rate)
Note: For vomiting, IV hydration may be appropriate depending on individual patient circumstances
Second and Subsequent Infusions
When planning for second or subsequent infusions, adjust your plan based on the patient's symptoms during previous infusions
Begin second and subsequent infusions at the rate that was best tolerated during previous infusion (e.g., if the previous infusion was tolerated at the PI rate, subsequent infusions should be given at the same rate; if the infusion rate was slowed to 50% of the PI rate and symptoms improved, start subsequent infusions at this rate)
With second and/or subsequent infusions, the degree of nausea and vomiting is expected to diminish. In these cases, patients may tolerate titration of the infusion rate by increments of 25% (e.g., if the infusion rate was slowed to 50% and the patient remained asymptomatic for 30-60 mins, consider increasing the rate to 75%) back to 100% or maximum tolerated rate. Continue to closely monitor the patient for any recurrence of symptoms, and administer additional antiemetic medications as needed to manage symptoms effectively
Continuation of treatment
When planning for second or subsequent infusions, if the patient in previous infusion experienced
During second and subsequent infusions, if patient is experiencing
Nausea alone or one episode of vomiting (Please see for additional information)
Rate recommended in PI
and
Make no change or escalate from previous infusion
Repeated vomiting (Please see for additional information)
Slower than the recommended rate in PI (Please see for additional information)
and
Escalate from previous infusion
Nausea alone
Make no modifications
Any vomiting (Please see for additional information)
Stop the infusion for 30-60 mins and restart it at a slower rate if symptoms improve (Please see for additional information)
Trash

CONCLUSIONS

SPOTLIGHT

- Zolbetuximab + mFOLFOX6
- Significant improvement survival benefit
- mPFS: 10.61 vs 8.67 months (HR=0.751, P=0.0066)
- mOS: 18.23 vs 15.54 months (HR=0.750, P=0.0053)
- Nausea and vomiting were the most common AE
- Typically occurred in the first cycle

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 Shitara, Kohei et al. The Lancet, Volume 401, Issue 10389, 1655 - 1668

GLOW

- Zolbetuximab + CAPOX
- Significant improvement survival benefit
- mPFS: 8.21 vs 6.80 months (HR=0.687, P=0.0007)
- mOS: 14.39 vs 12.16 months (HR=0.771, P=0.0118)
- Nausea and vomiting were the most common AE
- Typically occurred in the first and second cycle

Shah, M.A., Shitara, K., Ajani, J.A. *et al.* Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med* **29**, 2133–2141 (2023). https://doi.org/10.1038/s41591-023-02465-7

FDA approves zolbetuximab-clzb with chemotherapy for gastric or gastroesophageal junction adenocarcinoma

On October 18, 2024, the Food and Drug Administration approved zolbetuximab-clzb (Vyloy, Astellas Pharma US, Inc.), a claudin 18.2 (CLDN18.2)-directed cytolytic antibody, with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are CLDN18.2 positive, as determined by an FDA-approved test.

Today, FDA also approved the VENTANA CLDN18 (43-14A) RxDx Assay (Ventana Medical Systems, Inc./Roche Diagnostics) as a companion diagnostic device to identify patients with gastric or GEJ adenocarcinoma who may be eligible for treatment with zolbetuximab.