

Adebrelimab plus apatinib and SOX (AASOX) as conversion therapy for borderline resectable gastric cancer: a single-arm, single-centre, exploratory phase II study

Jiayi Li

Shandong First Medical University

Haichuan Wu

Shandong First Medical University

Weishuai Weishuai Song

Shandong First Medical University

Changqing Jing

Shandong Provincial Hospital

Feng Tian

Shandong Provincial Hospital

Jizhun Zhang

Shandong Provincial Hospital

Shubo Tian

Shandong Provincial Hospital

Tao Xu

`xutao@email.sdfmu.edu.cn`

Shandong Provincial Hospital

Wenchen Wang

Shandong Provincial Hospital

Research Article

Keywords: Gastric cancer, borderline resectable, conversion therapy, addebrelimab, apatinib, SOX regimen, PD-L1 inhibitor

Posted Date: July 25th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10176838/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Borderline resectable gastric cancer—clinical T4b disease with bulky locoregional lymphadenopathy, oligometastatic liver involvement, or both—remains a major therapeutic challenge because upfront curative resection is often infeasible. We evaluated the efficacy and safety of adebrelimab (anti-PD-L1) plus apatinib (anti-VEGFR-2) and SOX (AASOX) as conversion therapy in this population.

Methods

This single-arm, single-centre, exploratory phase II study enrolled patients with histologically confirmed borderline resectable gastric or gastro-oesophageal junction adenocarcinoma and PD-L1 CPS ≥ 1 . Patients received four 21-day preoperative cycles of AASOX (adebrelimab 200 mg and oxaliplatin 130 mg/m² intravenously on day 1; S-1 40 mg/m² orally twice daily on days 1–14; apatinib 250 mg orally once daily, stopped 28 days before surgery). The primary endpoint was the intention-to-treat (ITT) R0 resection rate (A'Hern single-stage design; one-sided $\alpha = 0.05$; power = 0.80). Secondary endpoints included pathological complete response, objective response rate (ORR), survival, and safety.

Results

Between January 12, 2024, and January 15, 2026, 31 patients were enrolled. At data cutoff (March 31, 2026), median follow-up was 15.0 months. Eleven patients underwent curative-intent surgery, all achieving R0 resection (ITT R0 rate, 35.5%; 95% CI, 19.2–54.6; one-sided $P = 0.033$), meeting the primary endpoint. ORR was 61.3%. Median OS was not reached, but survival data were immature (7 deaths). Grade ≥ 3 treatment-related adverse events occurred in 19 patients (61.3%), most commonly neutropenia (38.7%). No treatment-related deaths or Clavien–Dindo grade $\geq III$ perioperative complications occurred.

Conclusions

AASOX met its primary endpoint, achieving an ITT R0 resection rate of 35.5% with manageable toxicity. Survival outcomes remain immature; these hypothesis-generating findings warrant multicentre randomised evaluation.

Trial registration

The study has been submitted to the Chinese Clinical Trial Registry (ChiCTR) and is currently under review.

Background

Gastric cancer remains a major global health burden ^{1,2}. In China, many patients are diagnosed at advanced or locally advanced stages, which limits opportunities for upfront curative surgery ³. Borderline

resectable gastric cancer is a clinically important subgroup, defined by cT4b disease with bulky regional nodal involvement, oligometastatic liver disease without peritoneal spread, or both ^{3,4}. Conversion therapy aims to downstage tumours and enable R0 resection ⁵. Retrospective series suggest that long-term survival may be achievable in selected patients after conversion surgery, particularly when R0 resection is achieved ^{6,7}. For patients with liver metastases, pooled evidence also supports a potential role for surgery in selected candidates within multimodal strategies ⁸.

The SOX regimen (S-1 plus oxaliplatin) is widely used in East Asia and is supported by phase III evidence ^{9,10}. Oxaliplatin may also induce immunogenic cell death, providing a rationale for combination with checkpoint inhibition ¹¹.

In parallel, VEGF/VEGFR-driven vascular abnormalities are associated with an immunosuppressive tumour microenvironment ¹², and the concept of vascular normalisation offers a mechanistic basis for combining antiangiogenic therapy with immunotherapy ^{12,13}. Apatinib, which has demonstrated a survival benefit in previously treated advanced gastric cancer ¹⁴, is therefore a rational antiangiogenic partner in such combinations. The PD-1/PD-L1 pathway is an established therapeutic target in upper gastrointestinal cancers. Early evidence from KEYNOTE-059 and KEYNOTE-590 demonstrated the activity of checkpoint-based strategies in previously treated gastric/GEJ cancer and in first-line advanced oesophageal cancer, respectively ^{15,16}. Subsequent phase III trials in advanced gastric/GEJ adenocarcinoma, including CheckMate-649, ORIENT-16, and ATTRACTION-4, further supported checkpoint inhibitor–chemotherapy combinations in this setting ^{17–19}. Adebrelimab (SHR-1316), a humanised anti–PD-L1 antibody, has shown activity in combination regimens ^{20,21}.

Despite growing interest in immunotherapy-based multimodal strategies, prospective evidence for PD-L1 inhibitor–based conversion therapy in borderline resectable gastric cancer remains scarce, particularly in rigorously defined, MDT-selected populations. Accordingly, we conducted this single-arm, single-centre, exploratory phase II study to evaluate the efficacy and safety of AASOX as conversion therapy in patients with borderline resectable gastric or GEJ adenocarcinoma.

Methods

Study design and oversight

This was a single-arm, single-centre, exploratory phase II trial conducted at the Shandong Provincial Hospital Affiliated to Shandong First Medical University (Jinan, China). The study evaluated addebrelimab plus apatinib and SOX (AASOX) as conversion therapy for borderline resectable gastric cancer.

The study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice, and applicable Chinese regulations. The protocol and amendments were approved by the institutional ethics committee before study initiation (SWYX:NO.2023-1041). The study has been submitted to the Chinese Clinical Trial Registry (ChiCTR) and

is currently under review. All participants provided written informed consent before any study-specific procedures.

Participants

Eligible patients were aged 18–75 years and had histologically/cytologically confirmed gastric or gastro-oesophageal junction (GEJ) adenocarcinoma classified as borderline resectable by multidisciplinary team (MDT) assessment. Borderline resectable disease was defined as one of the following:

1. cT4b disease with bulky confluent regional lymphadenopathy and no distant metastasis;
2. synchronous oligometastatic liver disease (≤ 3 lesions, each ≤ 5 cm) without peritoneal or extrahepatic dissemination;
3. coexistence of both patterns.

Additional inclusion criteria were: at least one measurable lesion per RECIST v1.1, ECOG performance status 0–1, life expectancy ≥ 12 weeks, available pretreatment tumour tissue for biomarker testing with a PD-L1 combined positive score (CPS) ≥ 1 , no prior antitumour therapy, and adequate haematologic, hepatic, renal, coagulation, thyroid, and cardiac function within 7 days before treatment initiation.

Key exclusion criteria included severe malnutrition (body mass index < 18.5 kg/m² or $\geq 10\%$ weight loss within 2 months), recent gastrointestinal perforation/fistula, prior checkpoint inhibitor therapy, recent investigational treatment, active autoimmune disease requiring systemic treatment, uncontrolled cardiovascular disease, active severe infection, interstitial lung disease/non-infectious pneumonitis, active tuberculosis, pregnancy, or lactation.

Women of childbearing potential were required to have a negative pregnancy test within 72 hours before the first dose and to use highly effective contraception during treatment and for 180 days after the last chemotherapy dose.

Treatment

Treatment included three phases: preoperative conversion therapy, surgery, and postoperative therapy.

Preoperative conversion therapy: four 21-day cycles of AASOX:

- adabrelinab 200 mg intravenously on day 1 (q3w);
- oxaliplatin 130 mg/m² intravenously on day 1 (q3w);
- S-1 40 mg/m² orally twice daily on days 1–14 (q3w);
- apatinib 250 mg orally once daily, stopped 28 days before planned surgery.

Surgery: restaging was performed within 4 weeks after completion of cycle 4. The MDT reviewed resectability and determined surgical timing and approach according to Japanese Gastric Cancer Treatment Guidelines (6th edition). R0 resection was the surgical goal.

Postoperative therapy: patients with R0 resection and adequate recovery received four cycles of adjuvant SOX (same dose schedule), initiated 4–8 weeks after surgery. Four weeks after adjuvant chemotherapy, maintenance adebrelimab (200 mg q3w) plus apatinib (250 mg once daily) was started and continued until progression, unacceptable toxicity, withdrawal of consent, or 2 years, whichever occurred first.

Dose modification and treatment discontinuation

Dose adjustments were based on worst treatment-related toxicity and CTCAE v5.0.

- **Adebrelimab:** no dose reduction allowed; interruption/discontinuation followed predefined immune-related adverse event (irAE) algorithms.
- **Apatinib:** one reduction to 250 mg every other day was allowed for grade ≥ 3 related toxicity or clinically significant grade 2 hypertension refractory to combination antihypertensive therapy.
- **Oxaliplatin/S-1:** modified per institutional standards for haematologic, neurologic, hepatic, and gastrointestinal toxicities.

If one drug was permanently discontinued, other agents could continue at investigator discretion if clinically appropriate. All changes were documented in case report forms.

Assessments

A 28-day screening period preceded treatment initiation. Baseline assessments included demographics, medical history, physical examination, ECOG status, laboratory tests, ECG, echocardiography, tumour markers, viral serology, and cross-sectional imaging. Clinical staging was assigned according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system.

During preoperative treatment, tumour imaging (contrast-enhanced CT or MRI when CT was contraindicated) was performed at baseline and every 6 weeks (± 7 days), using consistent modality and protocol across time points. Response was assessed locally by RECIST v1.1. No blinded independent central review was performed.

Safety evaluations were conducted before each cycle and included blood counts, chemistry tests, and ECG. Thyroid function, urinalysis, and stool occult blood were assessed every two cycles. Blood pressure was self-monitored daily during apatinib exposure.

Surgical specimens were evaluated using Becker tumour regression grade (TRG). Pathological complete response (pCR) was defined as ypT0N0 (TRG 1a), and major pathological response (MPR) as $\leq 10\%$ viable tumour cells (TRG 1a–1b). Two gastrointestinal pathologists independently reviewed specimens, with consensus adjudication for discrepancies.

Pretreatment biomarkers included PD-L1 combined positive score (CPS), mismatch repair status, MSI (when applicable), EBV status, HER2 status, and tumour-infiltrating lymphocyte density.

Endpoints

The primary endpoint was the ITT R0 resection rate (microscopically margin-negative resection among all enrolled and treated patients; patients who did not undergo surgery were counted as non-responders).

Secondary endpoints were pCR rate (reported in ITT, per-protocol [PP], and R0-resected populations), objective response rate (ORR), disease control rate (DCR), overall survival (OS), disease-free survival (DFS; assessed in R0-resected patients), and safety (AEs, serious AEs, irAEs, dose modification/discontinuation events, and perioperative complications by Clavien–Dindo grade).

Exploratory endpoints included associations between baseline biomarkers and efficacy outcomes.

Safety reporting

Adverse events were recorded from consent until 90 days after the last study-drug dose (or 30 days after surgery, whichever was later) and graded using CTCAE v5.0. Serious adverse events were reported within protocol-defined timelines. irAEs were adjudicated clinically after the exclusion of alternative aetiologies and were managed using predefined treatment algorithms.

Statistical analysis

The sample size was based on A'Hern's single-stage exact binomial design for the primary endpoint (ITT R0 resection rate), with a null hypothesis $P_0 = 0.20$, an alternative hypothesis $P_1 = 0.45$, a one-sided $\alpha = 0.05$, and a power of 0.80. Twenty-one evaluable patients were required, and ≥ 7 R0 resections among these patients were prespecified to reject H_0 (exact one-sided $\alpha = 0.043$; power = 0.803). Allowing for approximately 10% attrition, the planned enrolment was 24; 31 patients were ultimately enrolled. The primary efficacy analysis was conducted in the ITT population, with all enrolled and treated patients included in the denominator and patients without curative-intent surgery counted as non-responders.

The ITT population was the primary efficacy set. The PP population excluded major protocol deviations and required at least two preoperative cycles plus at least one post-baseline response assessment. The safety set included all patients receiving at least one dose.

For primary and other categorical efficacy endpoints, patients without curative-intent surgery were counted as non-responders in ITT analyses. Prespecified sensitivity analyses used the PP population.

The primary endpoint was tested using a one-sided exact binomial test. Categorical outcomes were summarised with exact Clopper–Pearson 95% confidence intervals (CIs). OS and DFS were estimated using the Kaplan–Meier method, and the median follow-up was estimated using the reverse Kaplan–Meier method. Because R0 status is a post-baseline outcome, the OS comparison by R0 status was descriptive; prespecified bias-mitigation analyses included a 6-month landmark analysis and a Firth-penalised Cox model with R0 as a time-dependent covariate. Analyses were performed in R 4.3.0

(packages: clinfun, binom, survival, survminer, coxphf). The primary endpoint used a one-sided $\alpha = 0.05$; secondary and exploratory analyses were interpreted descriptively with two-sided 95% CIs. A post-hoc sensitivity analysis of the primary endpoint was additionally performed excluding patients enrolled outside the protocol-specified age range, using the same one-sided exact binomial test and exact Clopper–Pearson 95% confidence interval.

Results

Patient disposition and baseline characteristics

Between January 12, 2024, and January 15, 2026, 31 patients were enrolled and received at least one dose of AASOX, forming the ITT and safety populations (Figure 1). At data cutoff (March 31, 2026), three patients (9.7%) discontinued before the first post-baseline tumour assessment (lost to follow-up, $n = 2$; consent withdrawal, $n = 1$) and were excluded from the PP population. The PP population therefore comprised 28 patients.

Among the PP patients, 25 completed all four preoperative cycles. Three did not, owing to death from progressive disease during treatment ($n = 1$), MDT-directed early surgery before completion of cycle 4 ($n = 1$), and intolerable toxicity ($n = 1$).

Baseline characteristics are summarised in Table 1. The median age was 68 years (range, 44–81), and 22/31 patients (71.0%) were male. ECOG performance status was 0 in 20/31 (64.5%). According to the AJCC eighth edition clinical staging system, clinical stage was IVA in 25/31 patients (80.6%) and IVB in 6/31 (19.4%). Borderline resectable patterns were cT4bN+ without distant metastasis (25/31, 80.6%), liver oligometastases only (4/31, 12.9%), and both patterns (2/31, 6.5%). Poorly differentiated or undifferentiated histology was present in 25/31 (80.6%). Consistent with the eligibility criterion, all 31 patients had PD-L1 CPS ≥ 1 ; the CPS distribution was 1–4 in 20/31 (64.5%), 5–9 in 5/31 (16.1%), and ≥ 10 in 6/31 (19.4%). Most patients had proficient mismatch repair (pMMR; 29/31, 93.5%), with deficient mismatch repair (dMMR) in the remaining 2/31 (6.5%). HER2 was positive in 6/31 (19.4%). Two patients older than 75 years were enrolled and recorded as documented protocol deviations.

Primary endpoint: R0 resection rate

The primary endpoint was met. In the ITT population, 11/31 patients underwent curative-intent surgery, and all achieved R0 resection, yielding an ITT R0 resection rate of 35.5% (95% CI, 19.2–54.6). The one-sided exact binomial test against H_0 ($P \leq 0.20$) was significant ($P = 0.033$), and the prespecified threshold (≥ 7 R0 resections) was reached.

In the prespecified PP sensitivity analysis, the R0 resection rate was 39.3% (11/28; 95% CI 21.5–59.4; one-sided $P = 0.015$).

In a post-hoc sensitivity analysis excluding the two patients aged >75 years (recorded protocol deviations), neither of whom underwent R0 resection, the ITT R0 resection rate was 37.9% (11/29; 95%

CI, 20.7–57.7; one-sided $P = 0.020$), confirming that the primary result was robust to these deviations.

Among the 11 R0-resected patients, the surgical procedures were total gastrectomy (3/11, 27.3%), proximal gastrectomy (5/11, 45.5%), and distal gastrectomy (3/11, 27.3%). One additional patient underwent palliative bypass (with no curative intent) and was not counted in the R0 numerator.

Among the 20/31 ITT patients who did not undergo curative-intent resection at data cutoff, the reasons were ongoing systemic treatment with planned MDT reassessment ($n = 9$), death during preoperative therapy ($n = 1$), insufficient downstaging or progression with subsequent death without surgery ($n = 6$), loss to follow-up or consent withdrawal ($n = 3$), and palliative bypass only ($n = 1$).

Secondary efficacy outcomes

Radiologic response

In the ITT population, the best overall response was complete response (CR) in 2/31 (6.5%), partial response (PR) in 17/31 (54.8%), stable disease (SD) in 7/31 (22.6%), progressive disease (PD) in 2/31 (6.5%), and non-evaluable in 3/31 (9.7%). ORR was 61.3% (19/31; 95% CI, 42.2–78.2), and DCR was 83.9% (26/31; 95% CI, 66.3–94.5) (Figure 2). In the PP population, ORR was 67.9% (19/28; 95% CI, 47.6–84.1), and DCR was 92.9% (26/28; 95% CI, 76.5–99.1). The median time to first documented response among responders was 2.0 months (IQR, 1.4–2.8).

Pathological response

pCR (ypT0N0; Becker TRG 1a) occurred in 2/11 resected patients. The pCR rates were 6.5% in the ITT population (2/31; 95% CI, 0.8–21.4), 7.1% in the PP population (2/28; 95% CI, 0.9–23.5), and 18.2% among resected patients (2/11; 95% CI, 2.3–51.8). MPR (TRG 1a–1b) was also observed in 2/11 (18.2%), with no TRG 1b-only cases. T-stage downstaging to ypT0–2 occurred in 8/11 (72.7%), and nodal downstaging to ypN0 in 4/11 (36.4%) (Table 2).

Survival outcomes

The treatment exposure and clinical course of all 31 patients, including the timing of radiologic responses, surgery, progression, and death, are summarised in the swimmer plot (Figure 3). At data cutoff, the median follow-up in the ITT population was 15.0 months (95% CI, 8.7–19.5; reverse Kaplan–Meier). Seven of 31 patients (22.6%) had died, all in the non-R0 subgroup.

Overall survival

Median OS in ITT was not reached (95% CI 15.3 months to not reached) (Figure 4A). Landmark OS rates were 92.1% at 6 months (95% CI 72.1–98.0), 82.3% at 12 months (95% CI 58.9–93.1), 68.6% at 18 months (95% CI 41.5–85.1), and 58.8% at 24 months (95% CI 29.6–79.3). These estimates are based on only 7 events with limited follow-up and should be regarded as preliminary.

Descriptive analyses by R0 status

By surgical status, median OS was not reached in R0-resected patients (n = 11; 0 events) and was 15.6 months in non-R0 patients (n = 20; 7 events; 95% CI, 8.1 to not reached; log-rank P = 0.010) (Figure 4B). Because this comparison is susceptible to immortal-time and selection bias, it was prespecified as descriptive only. In prespecified supportive analyses, the 6-month landmark model yielded a Firth-penalised hazard ratio (HR) of 0.09 (95% CI, 0.001–0.81; P = 0.028), and the time-dependent Cox model yielded an HR of 0.08 (95% CI, 0.001–0.68; P = 0.016).

Disease-free survival in R0-resected patients

Among the 11 R0-resected patients, the median postoperative follow-up was 13.2 months (IQR, 7.0–15.7). One DFS event (recurrence) occurred at approximately 12 months after surgery; the patient was alive at data cutoff. Median DFS was not reached; the 12-month DFS estimate was 85.7% (95% CI, 33.4–98.0) but was based on only one event and should be interpreted with caution (Figure 4C). The 2-year DFS estimate was immature at the time of this analysis.

Safety

All 31 treated patients were evaluable for safety. TRAEs of any grade occurred in 31/31 patients (100%), and grade ≥ 3 TRAEs occurred in 19/31 (61.3%; 95% CI, 42.2–78.2) (Table 3; Figure 5). No grade 5 TRAEs or treatment-related deaths occurred.

The most common any-grade TRAEs were neutropenia (22/31, 71.0%), nausea or vomiting (17/31, 54.8%), fatigue (16/31, 51.6%), anaemia (14/31, 45.2%), and thrombocytopenia (12/31, 38.7%). The most common grade ≥ 3 TRAEs were neutropenia (12/31, 38.7%), anaemia (6/31, 19.4%), AST elevation (5/31, 16.1%), bilirubin elevation (4/31, 12.9%), thrombocytopenia (4/31, 12.9%), and GGT elevation (3/31, 9.7%).

irAEs occurred in 5/31 patients (16.1%): grade 3 hyperglycaemia (n = 2), hypothyroidism (n = 2; grade 1, n = 1; grade 2, n = 1), and grade 1 pneumonitis (n = 1). All irAEs were managed with standard treatment, and none led to permanent discontinuation of adebrelimab.

Apatinib-related events were consistent with known class effects. Hypertension occurred in 7/31 patients (22.6%), all grade 1–2 and controlled medically. No grade ≥ 3 hypertension, proteinuria, major haemorrhage, or thromboembolic events were observed.

Dose reduction of at least one agent occurred in 8/31 patients (25.8%), and treatment delay of more than seven days in 6/31 (19.4%). One patient (3.2%) permanently discontinued protocol therapy because of toxicity. Among the 11 R0-resected patients, no Clavien–Dindo grade $\geq$ III perioperative complications or perioperative deaths were reported.

Discussion

In this single-arm, exploratory phase II study, the combination of adebrelimab, apatinib, and SOX met its prespecified primary endpoint, achieving an ITT R0 resection rate of 35.5% (one-sided $P = 0.033$) in patients with borderline resectable gastric or GEJ adenocarcinoma. The regimen also produced encouraging radiologic activity (ORR 61.3%, DCR 83.9%) and meaningful pathological downstaging, with a toxicity profile that, although substantial, was manageable. To our knowledge, this is among the first prospective trials to evaluate a PD-L1 inhibitor–based regimen specifically in an MDT-defined borderline resectable population—a group situated between conventionally resectable locally advanced disease and frankly unresectable stage IV disease.

A central interpretive point is that efficacy should be anchored to the ITT denominator rather than to the 100% R0 rate observed among operated patients, because surgery was undertaken only after MDT-confirmed conversion. The 35.5% ITT R0 rate therefore represents the probability that an eligible, MDT-selected patient entering this approach will ultimately reach margin-negative resection, and it is this metric—not per-protocol surgical success—that is relevant for treatment decision-making. We emphasize this distinction because conversion-therapy reports that present R0 rates within the operated subgroup risk substantially overstating clinical benefit.

Our results are broadly consistent with the existing evidence for checkpoint inhibitor–chemotherapy combinations in gastric cancer. In first-line phase III trials in advanced disease, adding PD-1 blockade to chemotherapy improved the objective response rate—from 45% to 60% in CheckMate-649 and from 48.4% to 58.2% in ORIENT-16^{17,18}—values comparable to the 61.3% observed here despite our more advanced, conversion-oriented population. The most directly relevant comparator is the randomised neoadjuvant trial by Lin et al. of camrelizumab plus apatinib and chemotherapy in locally advanced gastric cancer, which reported an ORR of 66.0% and a major pathological response rate of 33.3% (pCR 16.3%)²²; their higher pathological response is expected, given that their cohort was resectable at baseline, whereas ours comprised cT4b bulky-nodal disease and oligometastatic liver involvement that carry a lower a priori chance of pathological clearance. Similarly, the perioperative DANTE trial of atezolizumab plus FLOT in resectable oesophagogastric cancer reported improved pathological regression with the addition of checkpoint blockade²³, reinforcing the value of immunochemotherapy across the resectability spectrum. These data collectively support the rationale for immunochemotherapy in this disease, while our findings suggest specifically that a meaningful fraction of borderline resectable patients can be converted to curative-intent surgery.

The biological rationale rests on three complementary mechanisms: oxaliplatin-induced immunogenic cell death¹¹, antiangiogenic reprogramming of the immunosuppressive tumour microenvironment with apatinib^{12–14}, and PD-L1 blockade with adebrelimab²⁴. The convergence of these effects offers a plausible explanation for the depth of response observed, although the trial was not designed to dissect the contribution of any single agent.

Grade ≥ 3 treatment-related adverse events occurred in 61.3% of patients, predominantly haematologic. This is higher than with doublet chemotherapy alone but in line with other intensive

immunochemotherapy combinations in gastric cancer^{17,22}. This safety profile is also broadly consistent with prior studies combining checkpoint blockade, antiangiogenic therapy, and chemotherapy in gastric cancer, in which grade 3–4 toxicities were similarly frequent despite acceptable perioperative feasibility²². Reassuringly, immune-related events were infrequent and low-grade, no grade ≥ 3 hypertension or major bleeding occurred despite apatinib exposure, and there were no treatment-related deaths or Clavien–Dindo grade $\geq III$ perioperative complications. The prespecified discontinuation of apatinib 28 days before surgery likely contributed to this favourable perioperative profile by allowing recovery of VEGF-dependent wound healing, and supports the feasibility of incorporating antiangiogenic agents into conversion regimens.

Survival findings should be interpreted with caution. Although median OS was not reached and all seven deaths occurred in the non-R0 subgroup, the apparent OS advantage for R0-resected patients is intrinsically vulnerable to immortal time and selection bias, because R0 status is a post-baseline outcome achievable only by patients who both survived to surgery and were biologically selected for response. We therefore treated this comparison as descriptive and supported by prespecified bias-mitigation analyses; the results are hypothesis-generating only and should not be read as evidence that surgery itself confers survival benefit. Moreover, with only 7 OS events and a single DFS event, both the Kaplan–Meier estimates and the penalised and time-dependent Cox models are statistically fragile and could change materially with longer follow-up; accordingly, no survival benefit should be inferred from the present data. Our exploratory biomarker analysis was underpowered and could not establish robust associations between PD-L1 CPS, MMR status, EBV, HER2, or tumour-infiltrating lymphocyte density and outcome. Because enrolment was restricted to PD-L1 CPS ≥ 1 , responses were observed across the full CPS range studied and in a predominantly pMMR cohort (93.5%); however, the absence of CPS-negative patients precludes any inference about activity in PD-L1–unselected or PD-L1–negative disease. Prospective, biomarker-stratified designs will be needed to refine patient selection beyond MDT clinical judgement.

Several limitations temper interpretation. First, the single-arm, single-centre design without a randomised control group fundamentally limits causal inference: the observed activity cannot be attributed specifically to the addition of apatinib and addebrelimab over chemotherapy alone, nor can the relative contribution of any individual component be determined. Confounding by indication and centre-specific MDT practice cannot be excluded, and the findings may not be generalisable to other institutions or to patients managed under different resectability criteria. Second, the small sample ($N = 31$) yields wide confidence intervals across all endpoints, so all point estimates—particularly pCR, DFS, and the bias-mitigation hazard ratios—should be regarded as imprecise and exploratory rather than confirmatory. Third, enrolment was restricted to patients with PD-L1 CPS ≥ 1 . Consequently, the efficacy and safety of AASOX in patients with PD-L1–negative borderline resectable gastric cancer remain unknown, and the generalisability of these findings to an unselected population is limited. In addition, although 6 patients had HER2-positive disease, the protocol did not include HER2-directed therapy. Whether HER2-targeted treatment should be incorporated into future conversion regimens for this subgroup warrants further

investigation. Fourth, response was assessed by local investigators without blinded independent central review, which may introduce assessment bias. Collectively, these design constraints position the study as hypothesis-generating, and the results require confirmation in an adequately powered, multicentre randomised trial before any change in clinical practice can be justified. Fifth, follow-up remains immature, so long-term DFS and OS—the outcomes that ultimately matter for a conversion strategy—cannot yet be reliably estimated. Finally, the definition of borderline resectable gastric cancer is not yet standardised; our MDT-based criteria, while pragmatic and reproducible within our institution, may differ from those used elsewhere and warrant consensus refinement.

These considerations also inform where this approach fits in practice. Given the intensity and toxicity burden of the regimen, it may be most appropriate for carefully selected patients with good performance status who are considered potential candidates for curative-intent conversion surgery after MDT evaluation, rather than for unselected stage IV disease.

From a real-world feasibility perspective, the regimen is resource-intensive and demands sustained multidisciplinary coordination: it combines triplet systemic therapy with a prolonged postoperative course of adjuvant chemotherapy followed by up to two years of maintenance adebrelimab plus apatinib. The associated treatment burden, cumulative toxicity, cost, and requirement for repeated MDT re-evaluation may limit applicability outside high-volume specialised centres, and long-term adherence to maintenance therapy in routine practice remains uncertain. These practical considerations should inform the design of future pragmatic trials.

In conclusion, within these limitations, the combination demonstrated promising conversion efficacy and acceptable safety in borderline resectable gastric/GEJ adenocarcinoma, supporting the concept that an intensive immunotherapy–antiangiogenic–chemotherapy strategy can render a meaningful proportion of these high-risk patients amenable to R0 resection. These hypothesis-generating results should be confirmed in adequately powered multicentre randomised trials incorporating central radiologic review, prospective biomarker stratification, and longer follow-up.

Conclusion

AASOX achieved a promising ITT R0 resection rate with manageable toxicity in borderline resectable gastric/GEJ adenocarcinoma. Survival outcomes remain immature, and no conclusions regarding long-term efficacy can yet be drawn. These hypothesis-generating data support further validation in randomised multicentre studies.

Declarations

Ethics approval and consent to participate: Approved by the Institutional Review Board/Ethics Committee of the Shandong Provincial Hospital Affiliated to Shandong First Medical University

(SWYX:NO.2023-1041). Written informed consent was obtained from all participants.

Consent for publication: Not applicable.

Trial registration: The study has been submitted to the Chinese Clinical Trial Registry (ChiCTR) and is currently under review.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author (Tao Xu) upon reasonable request. The data are not publicly available due to privacy and ethical restrictions related to patient confidentiality.

Competing interests: The authors declare that they have no competing interests.

Funding Statement: This study was supported by the Youth Science Special Foundation of the Chen Xiao-Ping Foundation for the Development of Science and Technology of Hubei Province (Grant No. CXPJJH125001-25110). The funding body had no role in the design of the study; collection, analysis, and interpretation of data; or writing of the manuscript.

Authors' contributions: Jiayi Li and Haichuan Wu collected and curated the clinical data. Jiayi Li performed the statistical analyses and drafted the manuscript. Weishuai Song, Changqing Jing, Feng Tian, Jizhun Zhang, and Shubo Tian participated in patient management, data collection, and data verification. Tao Xu and Wenchen Wang conceived and supervised the study, interpreted the data, and critically revised the manuscript. All authors reviewed, approved the final manuscript, and agreed to be accountable for all aspects of the work.

Acknowledgements: The authors thank the patients, families, and study staff.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71(3):209–249.
2. Cao W, Chen H-D, Yu Y-W, Li N, Chen W-Q. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chin Med J (Engl)* 2021;134(7):783–791.
3. Wang F-H, Zhang X-T, Li Y-F, et al. The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer, 2021. *Cancer Commun* 2021;41(8):747–795.
4. Yoshida K, Yamaguchi K, Okumura N, Tanahashi T, Kodera Y. Is conversion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. *Gastric Cancer Off J Int Gastric Cancer Assoc Jpn Gastric Cancer Assoc* 2016;19(2):329–338.
5. Li Z, Shan F, Wang Y, et al. Correlation of pathological complete response with survival after neoadjuvant chemotherapy in gastric or gastro-oesophageal junction cancer treated with radical

- surgery: A meta-analysis. *PloS One* 2018;13(1):e0189294.
6. Fukuchi M, Ishiguro T, Ogata K, et al. Prognostic Role of Conversion Surgery for Unresectable Gastric Cancer. *Ann Surg Oncol* 2015;22(11):3618–3624.
 7. Yamaguchi K, Yoshida K, Tanahashi T, et al. The long-term survival of stage IV gastric cancer patients with conversion therapy. *Gastric Cancer Off J Int Gastric Cancer Assoc Jpn Gastric Cancer Assoc* 2018;21(2):315–323.
 8. Marte G, Tufo A, Steccanella F, et al. Efficacy of Surgery for the Treatment of Gastric Cancer Liver Metastases: A Systematic Review of the Literature and Meta-Analysis of Prognostic Factors. *J Clin Med* 2021;10(5):1141.
 9. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;9(3):215–221.
 10. Zhang X, Liang H, Li Z, et al. Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): an open-label, superiority and non-inferiority, phase 3 randomised controlled trial. *Lancet Oncol* 2021;22(8):1081–1092.
 11. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents. *Cancer Cell* 2015;28(6):690–714.
 12. Huang Y, Yuan J, Righi E, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumour microenvironment and enhance immunotherapy. *Proc Natl Acad Sci U S A* 2012;109(43):17561–17566.
 13. Jain RK. Normalizing tumour vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med* 2001;7(9):987–989.
 14. Li J, Qin S, Xu J, et al. Randomised, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastro-oesophageal Junction. *J Clin Oncol Off J Am Soc Clin Oncol* 2016;34(13):1448–1454.
 15. Fuchs CS, Doi T, Jang RW, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastro-oesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. *JAMA Oncol* 2018;4(5):e180013.
 16. Sun J-M, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet* 2021;398(10302):759–771.
 17. Janjigian YY, Shitara K, Moehler M, 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.
 18. Xu J, Jiang H, Pan Y, et al. Sintilimab Plus Chemotherapy for Unresectable Gastric or Gastro-oesophageal Junction Cancer: The ORIENT-16 Randomised Clinical Trial. *JAMA*

2023;330(21):2064–2074.

19. Kang Y-K, Chen L-T, Ryu M-H, 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):234–247.
20. Wang J, Zhou C, Yao W, et al. Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2022;23(6):739–747.
21. Peng Z, Wei J, Wang F, et al. Camrelizumab Combined with Chemotherapy Followed by Camrelizumab plus Apatinib as First-line Therapy for Advanced Gastric or Gastro-oesophageal Junction Adenocarcinoma. *Clin Cancer Res Off J Am Assoc Cancer Res* 2021;27(11):3069–3078.
22. Lin J-X, Tang Y-H, Zheng H-L, et al. Neoadjuvant camrelizumab and apatinib combined with chemotherapy versus chemotherapy alone for locally advanced gastric cancer: a multicentre randomised phase 2 trial. *Nat Commun* 2024;15(1):41.
23. Lorenzen S, Götze TO, Thuss-Patience P, et al. Perioperative Atezolizumab Plus Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel for Resectable Esophagogastric Cancer: Interim Results From the Randomised, Multicentre, Phase II/III DANTE/IKF-s633 Trial. *J Clin Oncol Off J Am Soc Clin Oncol* 2024;42(4):410–420.
24. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. *J Clin Invest* 2015;125(9):3384–3391.

Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

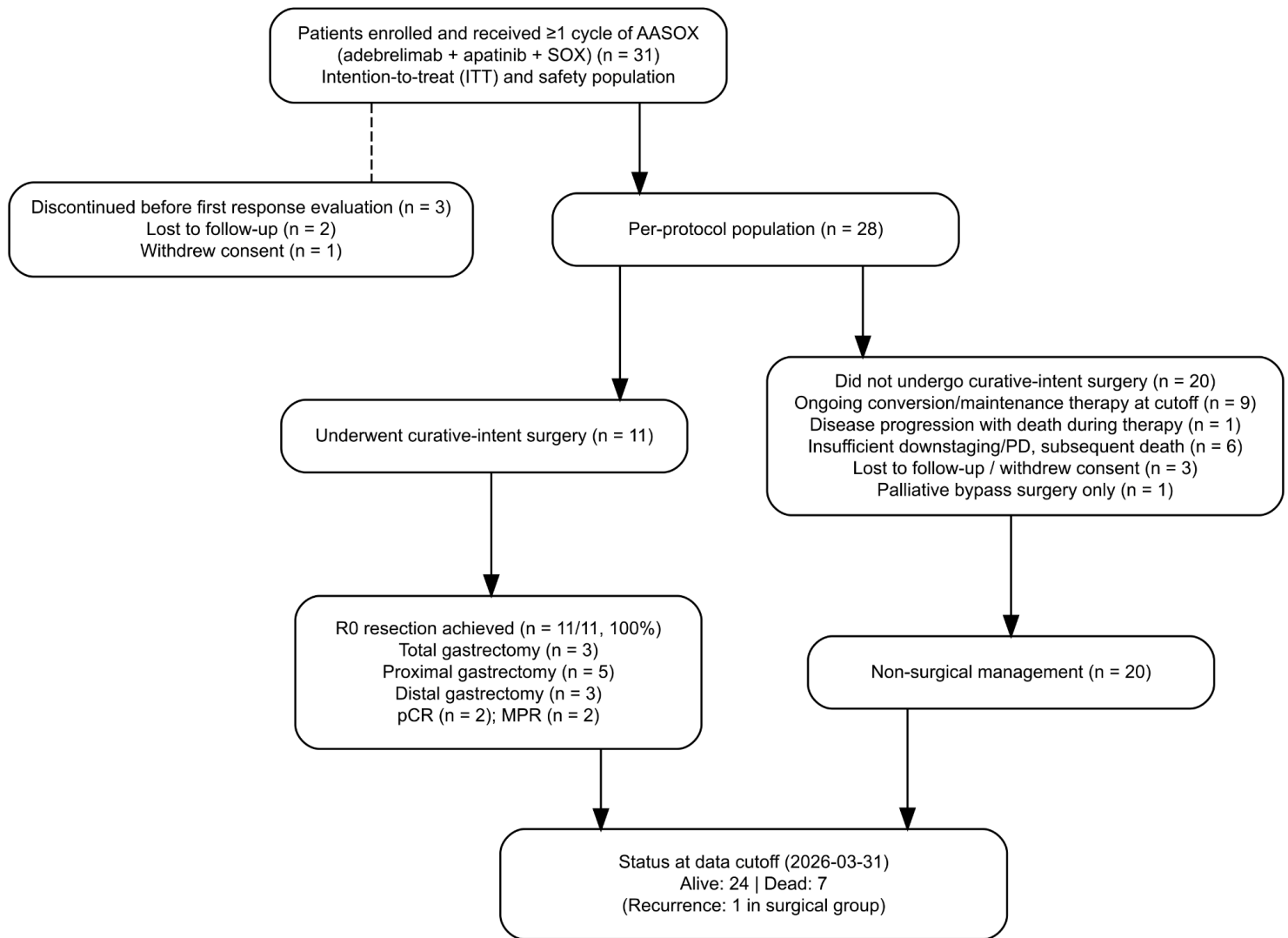


Figure 1

Study flow diagram.

Among 31 patients enrolled and treated with at least one cycle of adebrelimab plus apatinib and SOX (AASOX), 3 discontinued before the first post-baseline response assessment (2 lost to follow-up and 1 withdrew consent) and were excluded from the per-protocol (PP) population. Eleven patients underwent curative-intent surgery, and all achieved R0 resection (11/11, 100.0%), including 2 patients with pathological complete response (pCR) and major pathological response (MPR). Twenty patients did not undergo curative-intent surgery at data cutoff (March 31, 2026): 9 remained on systemic treatment with planned MDT reassessment, 1 died of progression during therapy, 6 had insufficient downstaging or progression and subsequently died without surgery, 3 were lost to follow-up or withdrew consent, and 1 underwent palliative bypass surgery only. At data cutoff, 24 patients were alive and 7 had died; 1 recurrence occurred in the surgical group.

Abbreviations: ITT, intention-to-treat; PP, per-protocol; pCR, pathological complete response; MPR, major pathological response; SOX, S-1 plus oxaliplatin.

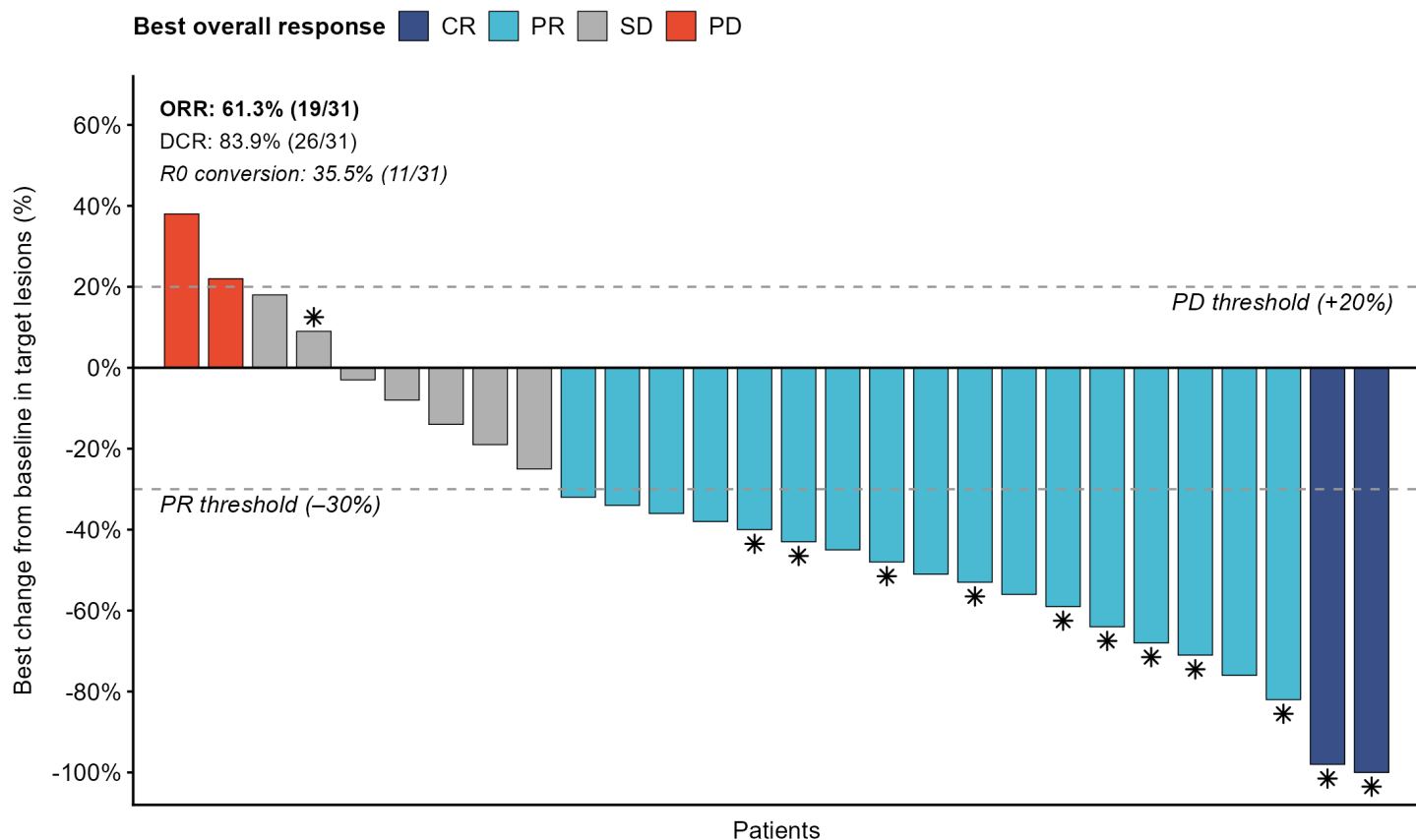


Figure 2

Waterfall plot of best percentage change in target lesions during preoperative AASOX therapy.

The plot shows the best percentage change from baseline in the sum of target lesion diameters for 28 patients with evaluable post-baseline imaging. Three patients discontinued before first response assessment and are not shown. Bars are color-coded by best overall response according to RECIST v1.1 (CR, PR, SD, PD). Dashed lines indicate RECIST thresholds for PR (-30%) and PD (+20%). Asterisks denote patients who underwent surgery (11 curative-intent resections and 1 palliative bypass procedure). ORR and DCR are reported using the ITT denominator (N = 31).

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; ITT, intention-to-treat.

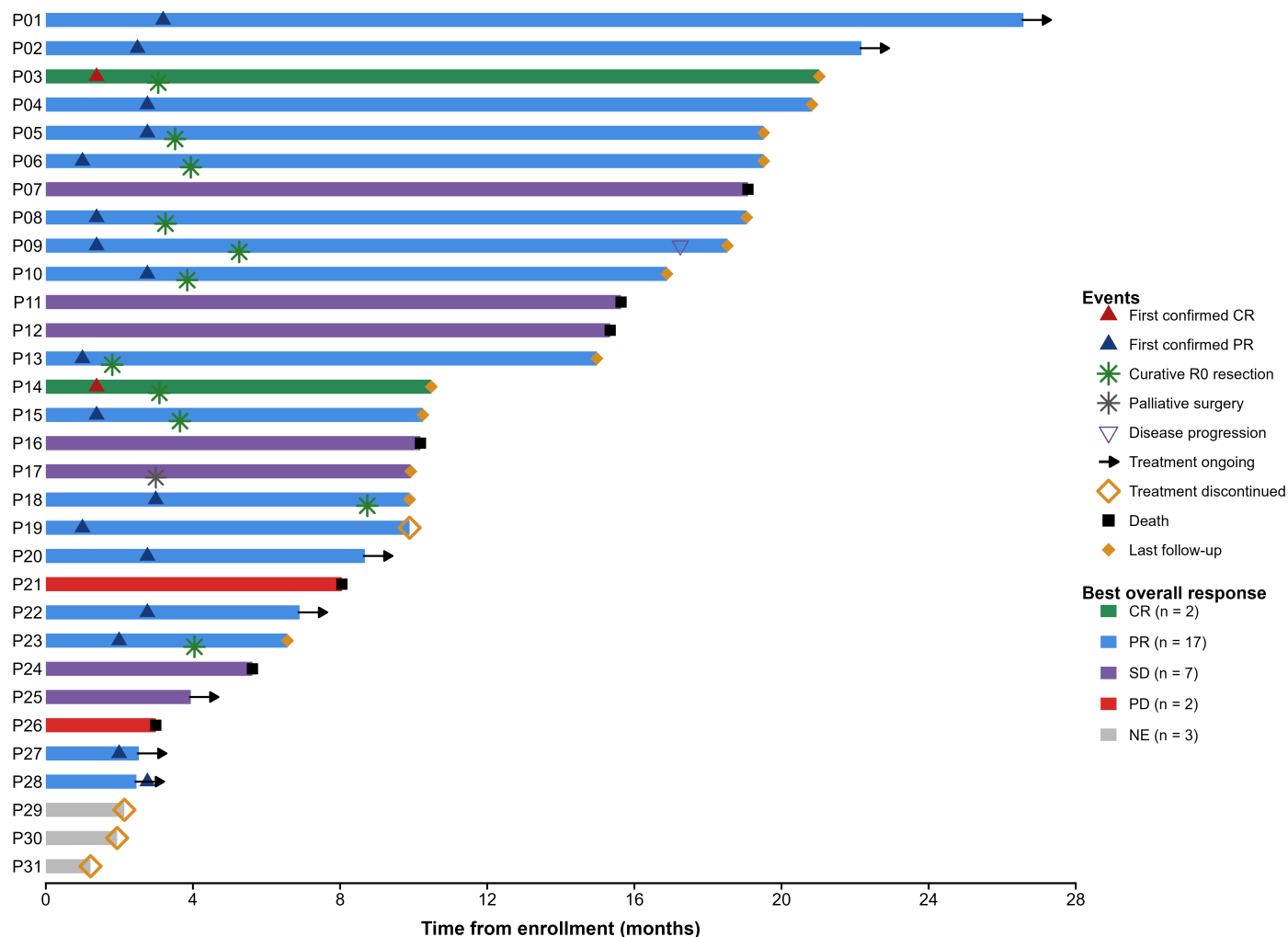


Figure 3

Swimmer plot of treatment exposure and clinical course (ITT population, N = 31).

Each horizontal bar represents one patient and is ordered by treatment duration. Symbols indicate timing of key events: first confirmed CR, first confirmed PR, curative R0 resection, palliative bypass surgery, progression/recurrence, treatment ongoing at data cutoff, treatment discontinuation (toxicity/loss to follow-up/withdrawal), death, and last follow-up without progression. Data cutoff was March 31, 2026. Abbreviations: BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, non-evaluable.

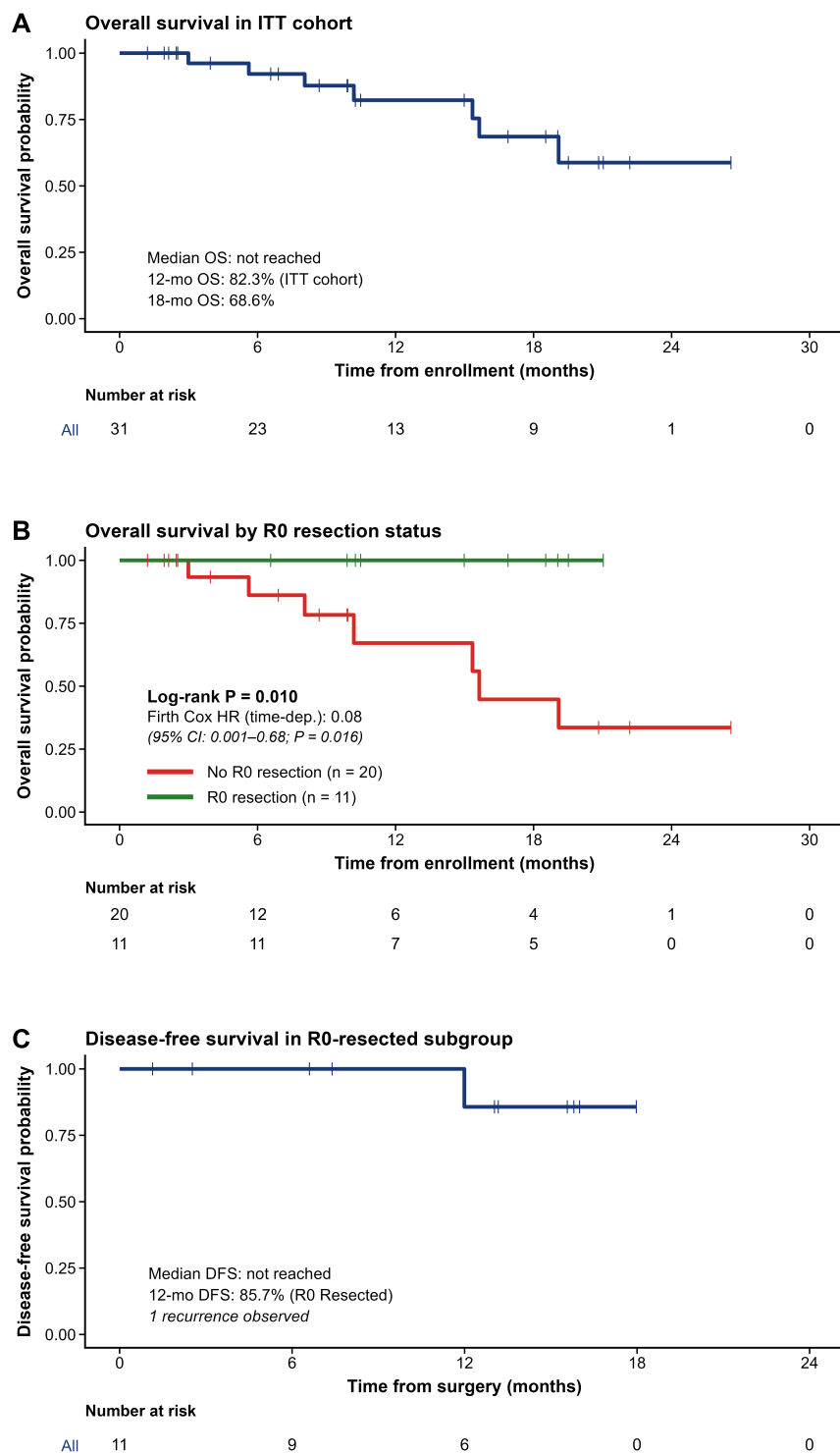


Figure 4

Kaplan–Meier survival analyses.

(A) Overall survival (OS) in the ITT population (N = 31). Median OS was not reached; 12-month OS was 82.3% (95% CI 58.9–93.1), and 18-month OS was 68.6% (95% CI 41.5–85.1).

(B) OS by R0 resection status. At data cutoff, the 7 observed deaths were all in the non-R0 subgroup. Median OS was not reached in the R0 subgroup and was 15.6 months (95% CI 8.1 to not reached) in the

non-R0 subgroup. Because R0 status is a post-baseline variable, log-rank comparison is descriptive only and subject to immortal time bias. A Firth-penalized Cox model with R0 resection as a time-dependent covariate yielded HR 0.08 (95% CI 0.001–0.68; P = 0.016). Given only 7 events, these estimates are unstable and should not be interpreted as evidence of a treatment or surgical effect on survival.

(C) Disease-free survival (DFS) among R0-resected patients (n = 11), with time origin at surgery. Median DFS was not reached; 12-month DFS was 85.7% (95% CI 33.4–98.0). One recurrence event was observed.

Tick marks indicate censored observations. Number-at-risk tables are shown below each panel. Data cutoff was March 31, 2026.

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; ITT, intention-to-treat; NR, not reached; OS, overall survival.

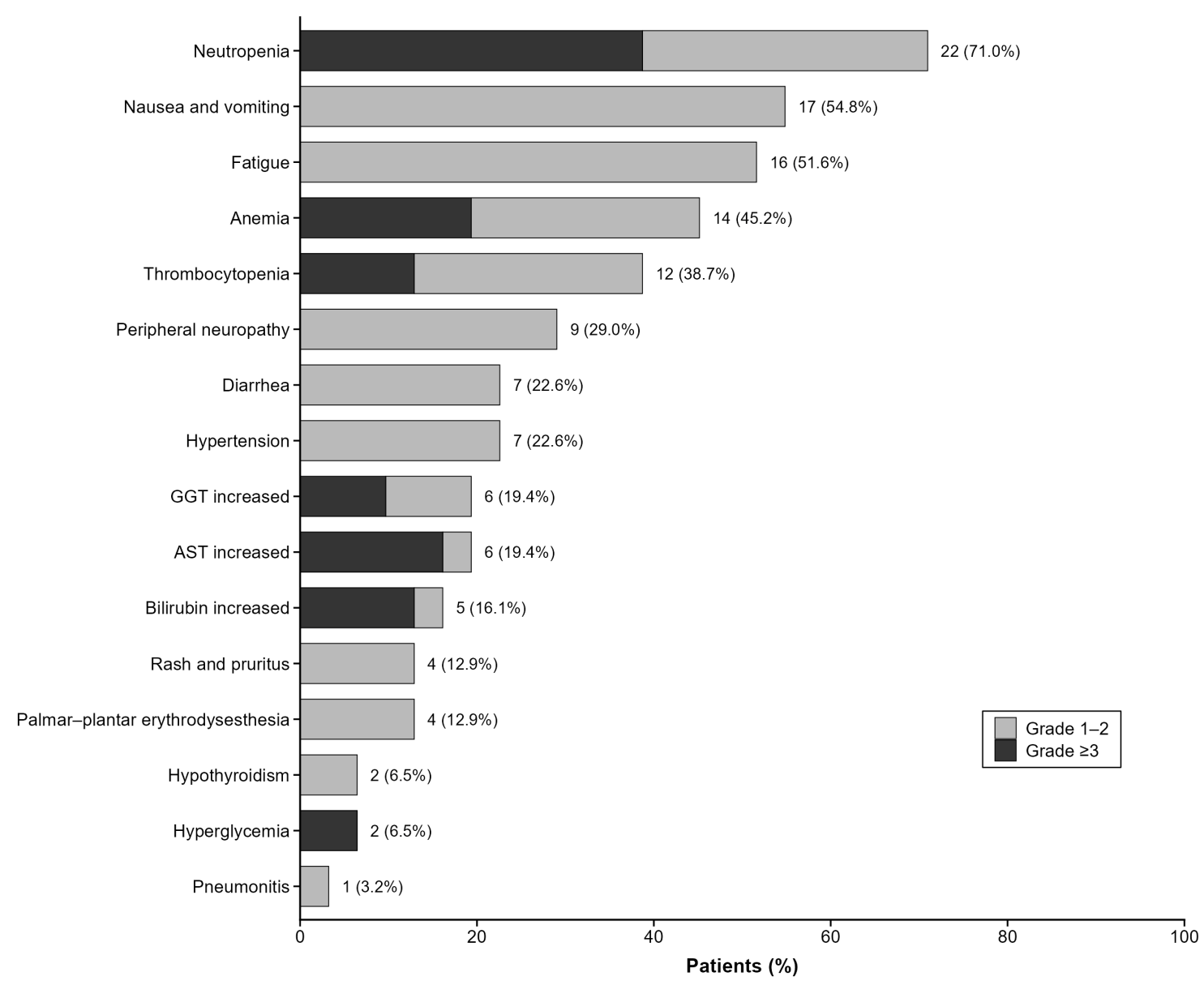


Figure 5

Treatment-related adverse events (TRAEs).

TRAEs occurring in $\geq 10\%$ of patients and all immune-related adverse events (irAEs) are shown for the safety population (N = 31), graded according to CTCAE v5.0. Bars display grade 1–2 and grade ≥ 3 events.

Abbreviations: AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; irAE, immune-related adverse event; TRAE, treatment-related adverse event.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryAppendix1.docx](#)
- [Table1AASOX.docx](#)
- [Table2AASOX.docx](#)
- [Table3AASOX.docx](#)