research

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ORIGINAL RESEARCH RATIONALE-305 randomised, double blind, phase 3 trial

Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma

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Study question How efficacious and safe is tislelizumab added to chemotherapy as first line (primary) treatment for locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma compared with placebo plus chemotherapy?

Methods This global, randomised, double blind, placebo controlled, phase 3 study enrolled patients with human epidermal growth factor receptor 2 negative locally advanced gastric or gastro-oesophageal junction adenocarcinoma, regardless of programmed death-ligand 1 (PD-L1) expression status, who had not received systemic anticancer therapy for advanced disease. Patients were randomly (1:1) assigned to receive either tislelizumab 200 mg or placebo intravenously every three weeks, in combination with chemotherapy (investigator's choice of oxaliplatin and capecitabine, or cisplatin and 5-fluorouracil) and stratified by region, PD-L1 expression, presence or absence of peritoneal metastases, and investigator's choice of chemotherapy. The primary endpoint was overall survival, defined as the time from randomisation to death due to any cause, assessed in patients with a PD-L1 TAP score of ≥5% and in all randomised patients (intention-to-treat population). The TAP score was defined as the total percentage of tumour area (tumour and any desmoplastic stroma) covered by tumour cells with PD-L1 membrane staining (any intensity), and tumour associated immune cells with PD-L1 staining (any intensity), visually estimated by pathologists using an investigational use only version of the Ventana PD-L1 (SP263) assay (Roche Diagnostics). Safety was assessed in all those who received at least one dose of study treatment.

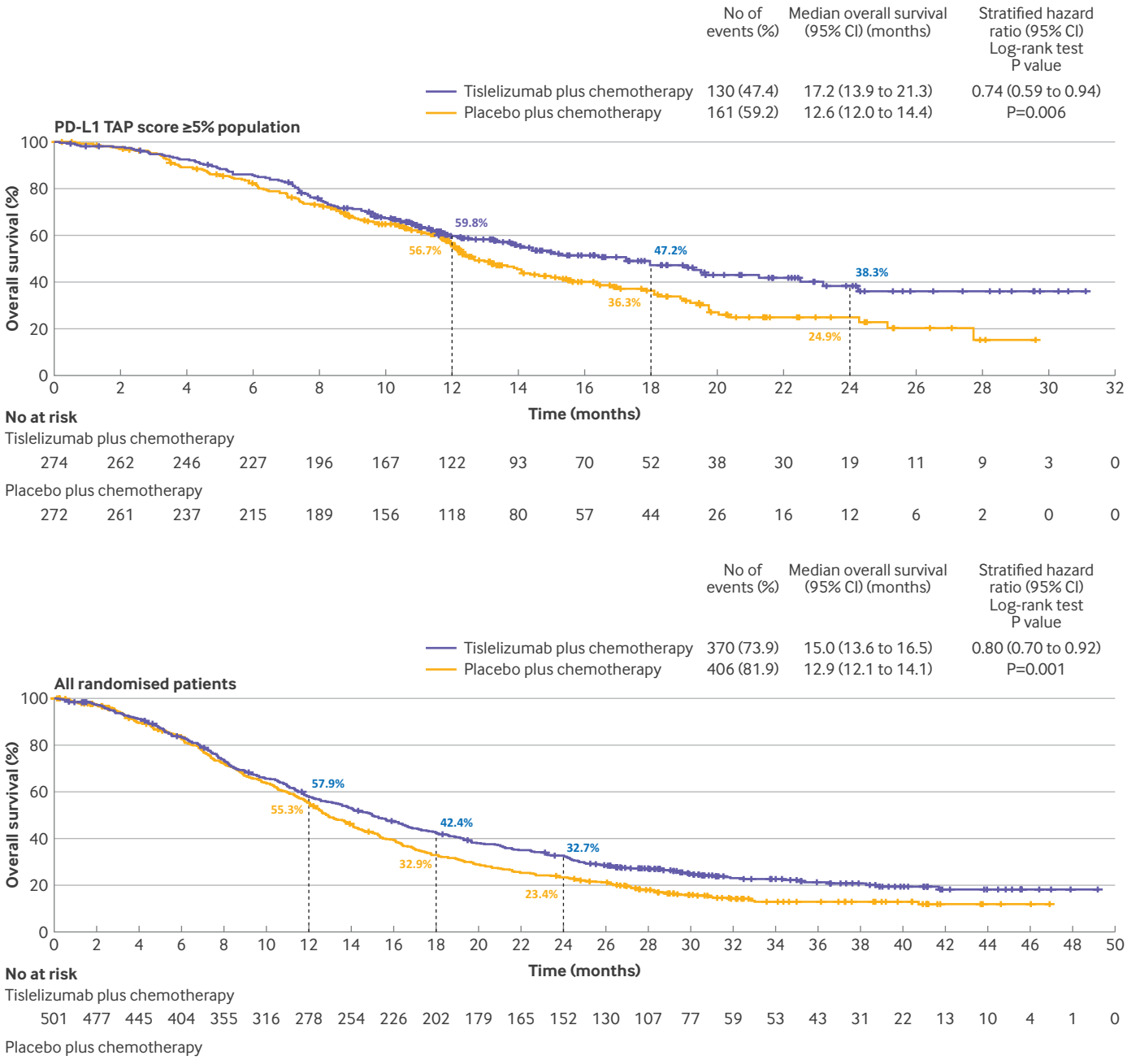
Study answer and limitations 997 patients were randomly assigned to receive either tislelizumab plus chemotherapy (n=501) or placebo plus chemotherapy (n=496). Tislelizumab plus chemotherapy showed statistically significant improvements in overall survival versus placebo plus chemotherapy in patients

with a PD-L1 TAP score of ≥5% (hazard ratio 0.74 (95% confidence interval 0.59 to 0.94); P=0.006 (interim analysis)) and in all randomised patients (0.80 (0.70 to 0.92); P=0.001 (final analysis)). Grade 3 or worse treatment related adverse events were observed in 54% (268/498) of patients in the tislelizumab plus chemotherapy arm versus 50% (246/494) in the placebo plus chemotherapy arm. The most common grade 3 or worse treatment related adverse events were decreased neutrophil count, decreased platelet count, neutropenia, and anaemia. A potential limitation of the study was the lack of independent review committee assessment of tumour responses, although the double blind design of the study minimised the potential for bias in investigator assessed responses.

What this study adds The addition of tislelizumab to chemotherapy provided significant survival benefit with a manageable safety profile versus placebo plus chemotherapy in patients with previously untreated advanced gastric or gastro-oesophageal junction adenocarcinoma and a PD-L1 TAP score of ≥5%, and in all randomised patients. This combination may represent a new primary treatment option for this patient population.

Funding, competing interests, and data sharing
Funded by BeiGene. See full paper on bmj.com for competing interests. Data sharing will be considered on request.

Study registration ClinicalTrials.gov NCT03777657.



Kaplan-Meier plots of overall survival in population with PD-L1 TAP scores of ≥5% (interim analysis) and in all randomised patients (final analysis). Log-rank and Cox regression models were stratified by region (Asia *v* Europe/North America), PD-L1 expression (all randomised patients), and presence of peritoneal metastasis. P values are one sided and based on the stratified log-rank test. CI=confidence interval; PD-L1=programmed death-ligand 1; TAP=tumour area positivity

Prioritising patient outcomes over in vitro resistance

ORIGINAL RESEARCH Pragmatic, factorial randomised controlled trial

Mailed feedback to primary care physicians on antibiotic prescribing for patients aged 65 years and older

Schwartz KL, Shuldiner J, Langford BJ, et al

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Study question Are antibiotic prescriptions reduced by providing family physicians with feedback on their antibiotic prescribing behaviour compared with that of their peers?

Methods In this pragmatic randomised controlled trial in Ontario, Canada, an audit and feedback letter was sent to family physicians and compared with physicians who were not sent a letter (4:1 physician allocation). Letters were mailed in January 2022 to physicians who prescribed antibiotics to patients aged 65 years or older. The control group did not receive a letter. The intervention group was further randomly assigned in a 2×2 factorial trial to assess the effects of providing case mix adjusted feedback data that accounted for patient and practice differences, and of antibiotic harms messaging on antibiotic prescribing. The primary outcome was the antibiotic prescribing rate per 1000 patient visits six months after the intervention, analysed using Poisson regression in the modified intention-to-treat population.

Study answer and limitations 5046 physicians were included and analysed: 1005 in the control group and 4041 in the intervention group. At six months, the antibiotic prescribing rate was significantly lower in the intervention group (mean antibiotic prescribing rate of 56.0 (standard deviation 39.2)) compared with the control group of 59.4 (42.0), with a relative reduction of 5% (relative rate 0.95 (95% confidence interval 0.94 to 0.96)). No significant effect was seen for including emphasis on harms messaging. A 1% relative increase in antibiotic prescribing was observed with case mix adjusted reports. The study was limited by the data, which were only for patients aged 65 years and older, possible contamination between groups in the factorial trial, and the study not being powered for the factorial trial component.

What this study adds Peer comparison audit and feedback letters significantly reduced overall antibiotic prescribing with no benefit of case mix adjustment or harms messaging. Antibiotic prescribing audit and feedback is a scalable and effective intervention and should be a routine quality improvement initiative in primary care.

Funding, competing interests, and data sharing Funded by the Canadian Institutes of Health Research. See full paper on bmj.com for competing interests. Data are not publicly available.

Trial registration ClinicalTrials.gov NCT04594200.

CORDELIA MOLLOY/SPL

Comparison of outcomes of antibiotic prescribing rates at six months for the primary analysis and factorial trial. Values are mean (SD) unless stated otherwise

	Prescribing rate per 1000 visits			
	Antibiotics overall	Unnecessary Antibiotics	Long duration (>7 days) antibiotics	Broad spectrum antibiotics
Control *v* intervention				
Pre-intervention:				
Control	55.2 (35.2)	5.5 (5.8)	15.7 (14.4)	25.1 (19.5)
Intervention	54.1 (33.1)	5.4 (5.9)	15.2 (14.3)	24.3 (17.7)
Six months post-intervention:				
Control	59.4 (42.0)	8.6 (9.9)	16.5 (16.1)	28.4 (25.1)
Intervention	56.0 (39.2)	7.5 (9.2)	13.7 (15.5)	26.0 (21.7)
Relative rate* (95% CI)	0.95 (0.94 to 0.96)	0.89 (0.86 to 0.92)	0.85 (0.83 to 0.87)	0.94 (0.92 to 0.95)
Case-mix adjusted *v* standard feedback				
Pre-intervention:				
Standard	54.4 (33.1)	5.3 (5.7)	14.9 (13.3)	24.3 (17.5)
Case-mix adjusted	53.9 (33.1)	5.4 (6.1)	15.5 (15.3)	24.2 (17.9)
Six months post intervention:				
Standard	56.0 (36.9)	7.4 (9.0)	13.2 (14.3)	25.9 (20.4)
Case-mix adjusted	55.9 (41.3)	7.6 (9.5)	14.1 (16.3)	26.2 (23.0)
Relative rate* (95% CI)	1.01 (1.00 to 1.03)	1.01 (0.98 to 1.04)	1.03 (1.01 to 1.06)	1.02 (1.01 to 1.04)
Harms *v* no harms messaging				
Pre-intervention:				
No harms	53.6 (32.4)	5.4 (5.7)	15.1 (14.0)	24.1 (17.7)
Harms	54.7 (33.8)	5.4 (6.1)	15.4 (14.7)	24.4 (17.8)
Six months post intervention:				
No harms	55.7 (39.1)	7.6 (8.9)	13.6 (15.0)	25.8 (21.7)
Harms	56.3 (39.2)	7.4 (9.6)	13.7 (15.8)	26.2 (21.8)
Relative rate* (95% CI)	1.00 (0.99 to 1.01)	0.99 (0.96 to 1.02)	1.00 (0.98 to 1.02)	1.01 (0.99 to 1.03)

CI=confidence interval; SD=standard deviation.
*Models adjusted for baseline prescribing rates, stratification variable from previous feedback trial, physician's sex, and physician years in practice.

The goal of prescribing medical interventions is to improve patient outcomes. Yet, research shows that a third of antibiotic prescriptions in the US are unnecessary, and this figure is up to seven in 10 prescriptions in other countries.[1 2]

In their paper, Schwartz and colleagues contribute to the literature on stewardship.[4] Their randomised trial included >5000 physicians in Ontario, Canada who had not opted into a previous programme, evaluating prescriptions to adults older than age 65. The intervention was a letter providing information on prescribing compared with peers, with further interventions of information on case mix adjustments and general information on harms of antimicrobials. The primary outcome measure was the average antimicrobial prescription rate per 1000 patient visits at six months. The results showed that prescribing was decreasing before the intervention then increased after randomisation in the intervention and control groups.

Several limitations pose threats to the internal validity and generalisability of the study findings, many of which the authors outline in their discussion. These include focusing on physicians while excluding other prescribers, evaluating prescriptions only to patients older than 65 years, pre-randomisation exclusion of physicians who previously opted into a programme of prescribing feedback, and post-randomisation exclusion of prescribing outliers. These factors affect trial pragmatism because they might affect real world intervention effectiveness when applied to broader populations of physicians and patients.

The main limitation of this study was the primary outcome measure. Antimicrobial prescribing rate is not a direct measure of patients' health status and, therefore, whether the intervention improves patient outcomes is unknown.

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JIM VARNEY/SPL

The priority for appropriate prescribing should be direct patient outcomes

Lower prescribing does not necessarily mean better prescribing. Patients routinely do not take drugs as prescribed. They may not take them at all or may discontinue drugs once they feel better—the reason for recent studies on shortening durations of treatment.[5]

Measuring health status

Additionally, the antimicrobial prescription rate is not a direct measure of patients' health status. As one study pointed out, "The ideal amount of antibiotic use is an elusive benchmark because it can be variable by setting and patient and is, to some degree, subjective."[6] Antimicrobial prescription rate is a surrogate endpoint, but a surrogate for what? The authors claim antimicrobial prescription rate is "known to drive antimicrobial resistance."[4] However, antimicrobial resistance is also not a direct patient outcome; it is a measure of the interaction of organisms with drugs in vitro, where the host's immune system is absent.

The primary reason for appropriate prescribing is not solely to prevent antimicrobial resistance but to improve patient outcomes. While resistance is associated with worse patient outcomes, recent research shows 17 of 18 deaths associated with bloodstream infections are from bacteria susceptible to currently available drugs.[7] Schwartz and colleagues reference a 2014 document predicting more deaths from antimicrobial resistance than cancer in 2050.[8] This prediction was based on modelling that thankfully has not come to pass a decade later. More recent research shows decreasing antimicrobial resistance in the US and internationally.[9-12] Only one in four deaths with a resistant organism are attributable to resistance.[13] Furthermore, all resistance is not equal. In vitro resistance to one or more classes of drugs is less accurate at predicting patient outcomes than the more clinically relevant measure of resistance to all available first line drugs (ie, difficult-to-treat resistance).[14 15] Difficult-to-treat resistance is thankfully uncommon in the US and has remained stable or decreased over time; perhaps inferring the benefits of antimicrobial stewardship on patient outcomes.

Adverse effects

Yet, if antimicrobial resistance did not exist, the need for appropriate prescribing would not be obviated. The more common and more proximal harm to patients is from direct adverse effects of antimicrobials. The authors note up to 30% of patients may experience direct adverse effects.[16] These adverse effects are the most common cause of drug related admissions for children to emergency departments.[17] Studies raise the possibility that the antimicrobial effects on the host microbiome may decrease the efficacy of immunotherapies for cancer.[18]

The priority for appropriate prescribing and the outcomes measured in future stewardship studies should be direct patient outcomes. Showing direct benefits for patients would justify the cost and implementation of such programmes before they are routinely recommended.

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