Zanzalintinib plus atezolizumab versus regorafenib in refractory colorectal cancer (STELLAR-303): a randomised, open-label, phase 3 trial

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The STELLAR-303 study investigators are listed in the appendix (pp 2–10)

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Summary

Background Zanzalintinib is a multitargeted tyrosine-kinase inhibitor that, when combined with atezolizumab, showed promising antitumour activity and manageable toxicity in a phase 1 study. We aimed to compare the efficacy and safety of zanzalintinib–atezolizumab versus regorafenib in patients with previously treated metastatic colorectal cancer.

Methods STELLAR-303 is a global, randomised, open-label, phase 3 trial done at 121 centres (including hospitals, academic medical centres, and specialised cancer research facilities) in 16 countries. Patients aged 18 years and older with confirmed metastatic adenocarcinoma of the colon or rectum, who had previously received standard-of-care therapy, and did not have microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours were randomly assigned (1:1) in blocks of four to oral zanzalintinib (100 mg daily) plus intravenous atezolizumab (1200 mg every 3 weeks) or oral regorafenib (160 mg daily on days 1–21 of each 28-day cycle) using an interactive response technology system, stratified by geographical region, *RAS* status, and presence of liver metastases. Dual primary endpoints were overall survival in the intention-to-treat (ITT) population and in the subset of patients without liver metastases. Safety was assessed in all patients who received at least one dose of study drug. This report is based on a planned overall survival analysis (data cutoff April 30, 2025); the trial is active but not recruiting, and continues to the final overall survival analysis in the subset of patients without liver metastases. This trial is registered with ClinicalTrials.gov (NCT05425940).

Findings 1325 patients were screened for eligibility; between Sept 7, 2022, and July 15, 2024, 901 patients were randomly assigned to zanzalintinib–atezolizumab (n=451) or regorafenib (n=450). 528 (59%) patients were male and 373 (41%) were female; 485 (54%) were White, 338 (38%) were Asian, 18 (2%) were Black, 24 (3%) were other races, and 36 (4%) had race not reported. At a median follow-up of 18·0 months (IQR 14·6–21·5), zanzalintinib–atezolizumab showed a significant overall survival benefit versus regorafenib in the ITT population (stratified hazard ratio [HR] 0·80 [95% CI 0·69–0·93]; p=0·0045) with a median overall survival of 10·9 months (95% CI 9·9–12·1) versus 9·4 months (8·5–10·2). At the interim analysis of overall survival in the subset of patients without liver metastases, the stratified HR for zanzalintinib–atezolizumab versus regorafenib was 0·79 (95% CI 0·61–1·03); p=0·087 (median overall survival 15·9 months [95% CI 13·5–17·6] *vs* 12·7 months [10·9–15·5]). Grade 3 or worse treatment-related adverse events occurred in 268 (60%) of 446 patients receiving zanzalintinib–atezolizumab and 161 (37%) of 434 patients receiving regorafenib. There were five (1%) treatment-related deaths in the zanzalintinib–atezolizumab group and one (<1%) in the regorafenib group.

Interpretation STELLAR-303 is the first phase 3 trial to show a significant improvement in overall survival with an immunotherapy-based regimen, zanzalintinib–atezolizumab, in patients with relapsed or refractory metastatic colorectal cancer that is not MSI-H or dMMR. This combination represents a chemotherapy-free treatment option with a novel mechanism of action for heavily pretreated patients in need of improved therapies.

Funding Exelixis.

Introduction

Outcomes for metastatic colorectal cancer remain poor, with a 5-year relative survival rate of approximately 15%.[1] Immune checkpoint inhibitors improve outcomes for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours and are standard of care in this setting;[2–6] however, only 5% of metastatic colorectal cancers are MSI-H or dMMR.[7] For the majority of patients with metastatic colorectal cancer, improved therapies in the salvage setting are needed. Although anti-VEGF agents and chemotherapy are integral to metastatic colorectal cancer treatment, overall survival with third-line monotherapy agents, including regorafenib, trifluridine–tipiracil, and

Research in context

Evidence before this study

We searched PubMed from Oct 1, 2014 to March 23, 2022, for clinical trials published in all languages that evaluated refractory metastatic colorectal cancer treatments using the search terms "colorectal cancer" AND ("metastatic" OR "advanced") AND ("refractory" OR "previously treated" OR "previously-treated") AND ("immunotherapy" OR "immune checkpoint inhibitor"). We also searched major oncology congress websites for relevant abstracts published between May 1, 2013, and March 23, 2022. From our searches, we found the phase 3 IMblaze370 trial, which evaluated atezolizumab with or without cobimetinib versus regorafenib and did not show an overall survival benefit in either atezolizumab group in patients with previously treated metastatic colorectal cancer that was not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), which represents 95% of patients with metastatic colorectal cancer. We also identified CAMILLA and other phase 1/2 trials of immune checkpoint inhibitor plus VEGF receptor tyrosine-kinase inhibitor combinations that showed higher response rates and overall survival outcomes than expected with either treatment alone in this population. During the conduct of the phase 3 STELLAR-303 study, data were presented from the phase 1 STELLAR-001 study showing that addition of atezolizumab to the multitargeted tyrosine-kinase inhibitor, zanzalintinib, improved overall survival, progression-free survival, and objective response rate compared with zanzalintinib alone with manageable toxicity. In addition, results from the phase 3 LEAP-017 trial were reported, showing that the immune checkpoint inhibitor plus VEGF receptor tyrosine-kinase inhibitor combination pembrolizumab–lenvatinib did not prolong survival versus regorafenib or trifluridine–tipiracil.

Added value of this study

To our knowledge, STELLAR-303 is the first phase 3 trial to show a significant improvement in overall survival with an immunotherapy-based regimen, zanzalintinib–atezolizumab, in patients with relapsed or refractory metastatic colorectal cancer that is not MSI-H or dMMR. A consistent overall survival benefit was observed across key subgroups, including liver involvement, *RAS* status, geographical region, and previous anti-VEGF therapy. The zanzalintinib–atezolizumab safety profile was generally consistent with that previously reported for this and similar immune checkpoint inhibitor plus tyrosine-kinase inhibitor combinations, although there was a higher rate of treatment-related deaths with the combination compared with regorafenib in the current trial.

Implications of all the available evidence

The results from STELLAR-303 show an overall survival benefit for zanzalintinib–atezolizumab compared with regorafenib in patients with previously treated metastatic colorectal cancer, regardless of liver metastasis status. These data, together with previous data from early phase trials, support that the zanzalintinib–atezolizumab combination represents a chemotherapy-free treatment option with a novel mechanism of action for heavily pretreated patients in need of improved therapies.

fruquintinib, is suboptimal, with median overall survival outcomes of less than 7·5 months in patients unselected for microsatellite instability status.[8–10]

The limited benefit from monotherapies prompted exploration of combination strategies. Adding bevacizumab to trifluridine–tipiracil prolonged survival over trifluridine–tipiracil monotherapy; however, the benefit was greater in bevacizumab-naive versus bevacizumab-pretreated patients.[11] In addition, immune checkpoint inhibitor-based combinations have been explored. The phase 3 IMblaze370 trial did not show an overall survival benefit of an immune checkpoint inhibitor and MEK inhibitor combination.[12] Conversely, CAMILLA and other phase 1/2 trials of immune checkpoint inhibitor plus VEGF receptor tyrosine-kinase inhibitor combinations showed higher response rates and overall survival outcomes than expected with either treatment alone, particularly in patients without active liver metastases.[13,14] However, to date, no phase 3 trial of an immune checkpoint inhibitor-based combination has shown improvement in overall survival in metastatic colorectal cancer that is not MSI-H or dMMR. The absence of benefit might be driven by several factors, including tumour location, vascular composition, and an immunosuppressive tumour microenvironment,[12,15–17] the latter prompting investigation into mechanisms to increase responsiveness to immune checkpoint inhibitors in this setting.

Zanzalintinib is a novel, small molecule inhibitor of multiple kinases, including the TAM kinases (TYRO3, AXL, and MER), MET, and VEGF receptors.[18] The TAM family receptors are negative immune regulators,[19] and the zanzalintinib kinase inhibition profile might help reprogramme the tumour microenvironment to support immune activation, thereby improving responsiveness to immune checkpoint inhibitors. Combining zanzalintinib with immune checkpoint inhibitors enhanced tumour growth inhibition in preclinical models[18] and, in the randomised metastatic colorectal cancer cohort of the phase 1 STELLAR-001 study, adding atezolizumab to zanzalintinib improved overall survival, progression-free survival, and objective response rate compared with zanzalintinib alone, with manageable toxicity.[20] Given the encouraging outcomes of early phase trials with immune checkpoint inhibitor plus VEGF receptor tyrosine-kinase inhibitor combinations as well as the zanzalintinib target profile, we aimed to evaluate the efficacy and safety of zanzalintinib–atezolizumab compared with regorafenib in patients with previously treated metastatic colorectal cancer.

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See Online for appendix

Methods

Study design and patients

STELLAR-303 is a global, randomised, open-label, phase 3 trial done at 121 centres (including hospitals, academic medical centres, and specialised cancer research facilities) in 16 countries (appendix pp 2–10). Eligible patients were aged 18 years or older with confirmed metastatic adenocarcinoma of the colon or rectum that radiographically progressed on or was refractory or intolerant to previous therapy with a fluoropyrimidine, irinotecan, and oxaliplatin, with or without an anti-VEGF monoclonal antibody; an anti-EGFR monoclonal antibody (if *RAS* wild-type); and a BRAF inhibitor (if known $BRAF^{V600E}$ [ie, Val600Glu] mutation). Eligibility also required that patients were documented not to have MSI-H or dMMR status. Measurable disease, determined by investigators using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, and an Eastern Cooperative Oncology Group performance status of 0–1 were required. Previous treatment with zanzalintinib, regorafenib, trifluridine–tipiracil, or PD-L1 and PD-1 targeting immune checkpoint inhibitors was not allowed. Documented *RAS* status and tumour tissue (archival or fresh biopsy) were required. Full eligibility criteria are provided in the trial protocol (appendix p 24).

This trial was approved by Advarra (Columbia, MD, USA) as well as the institutional review board or ethics committee at each site (appendix pp 2–10) and conducted in accordance with requirements of the regulatory authorities of each country and provisions of the Declaration of Helsinki and Good Clinical Practice guidelines of the International Council for Harmonisation. The trial investigators are listed in the appendix (pp 2–10). Independent patient representatives and advocacy groups were not involved in the design or conduct of the study or in writing the manuscript. Patients provided written informed consent. All unmasked efficacy and safety data were reviewed as planned by an independent data monitoring committee and according to charter.

This trial is registered with ClinicalTrials.gov (NCT05425940) and is active but not recruiting, and continues to the final overall survival analysis in the subset of randomly assigned patients without liver metastases (nlmITT population).

Randomisation and masking

Patients were randomly assigned (1:1) to zanzalintinib–atezolizumab or regorafenib monotherapy with stratification by geographical region (Asia *vs* rest of the world), *RAS* status (wild-type *vs* mutant), and presence of liver metastases (yes *vs* no).

Stratified permuted block randomisation (with block sizes of four) was performed centrally by an interactive response technology system. Although STELLAR-303 was an open-label study, unmasking of study treatment and sponsor review of aggregated data by treatment group was not permitted until after the primary analysis of overall survival, to maintain study data integrity and avoid bias during the conduct of the study.

Procedures

Zanzalintinib was administered at 100 mg orally (daily) and atezolizumab at 1200 mg intravenously every 3 weeks. Regorafenib was given at 160 mg orally (daily) on days 1–21 of each 28-day cycle. Patients continued study treatment in each group if they continued to have clinical benefit in the opinion of the investigator, or until unacceptable toxicity, the need for alternative anticancer treatment, or other reasons for treatment discontinuation. Treatment beyond radiographic progression was allowed per investigator discretion. Dose reductions were permitted for zanzalintinib and regorafenib, but not atezolizumab. Dose delays for adverse events were permitted for all agents. Either component of the combination could be continued if the other was discontinued. Tumour imaging was performed at baseline, then every 8 weeks through to week 49, and every 12 weeks thereafter, until disease progression. Tumour imaging consisted of CT of the chest, abdomen, and pelvis or CT of the chest and MRI of the abdomen and pelvis; MRI or CT of the brain was performed in patients with known or suspected brain metastasis at screening. The schedule of assessments is provided in the protocol (appendix p 24). Information on sex, race, and ethnicity was self-reported and entered into the case report form by study personnel.

Outcomes

The dual primary endpoints were overall survival among all randomly assigned patients (intention-to-treat [ITT] population) and in the nlmITT population. Secondary endpoints were progression-free survival (in the ITT, nlmITT, and the subset of patients with liver metastases [lmITT] populations), objective response rate, including sum of target lesion diameters and disease control rate (in the ITT and nlmITT populations), and duration of response (in the ITT and nlmITT populations) according to RECIST version 1.1 as well as overall survival in the lmITT population, plasma concentration of zanzalintinib, serum concentration of atezolizumab, and incidence of antidrug antibody response against atezolizumab. Overall survival was defined as the time from randomisation to death due to any cause. Progression-free survival was defined as the time from randomisation to either the date of radiographic progression or death (due to any cause), whichever was earlier. The best overall response was defined as the best tumour assessment category as determined by RECIST version 1.1. Duration of objective response was defined as the time from the first documentation of an objective response that was subsequently confirmed at a visit that was at least 28 days after the response was first observed to radiographic

disease progression or death due to any cause, whichever occurred first. Safety was assessed in patients who received at least one dose of any assigned treatment and included evaluation of laboratory parameters and vital signs as an exploratory endpoint. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Overall survival and progression-free survival outcomes were additionally evaluated in prespecified subgroups (sex, age group, race, ethnicity, geographical region, presence of liver metastases, *RAS* status, Eastern Cooperative Oncology Group performance status at baseline, location of primary tumour, location of colon tumour, single metastatic site *vs* multiple metastatic sites of disease, liver metastasis only *vs* liver metastasis plus at least one additional metastatic site of disease *vs* no liver metastatic site, peritoneal carcinomatosis, previous systemic therapy for metastatic colorectal cancer, time since diagnosis of metastatic colorectal cancer, previous anti-VEGF antibody treatment, previous anti-EGFR antibody treatment, and *BRAF* status).

The following secondary endpoints are not reported in this Article: progression-free survival in the lmITT population, objective response rate in the nlmITT population, duration of response in the ITT and nlmITT populations, overall survival in the lmITT population, pharmacokinetics, and immunogenicity. The following exploratory endpoints are not reported in this Article: patient-reported outcomes, health-care resource utilisation, biomarker analyses of tumour markers and circulating tumour DNA, and correlation of biomarker analyses with clinical outcomes in the ITT population. Analyses of these endpoints are in progress and will be considered for future publications.

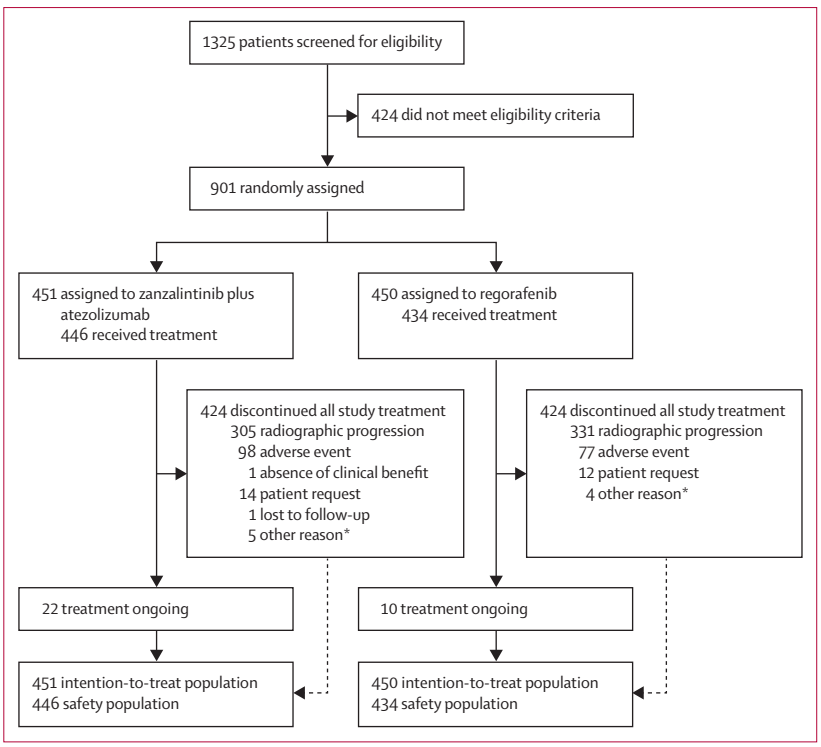


Figure 1: **Trial profile**
*Other reasons included investigator decision (n=1), clinical progression (n=3), and multiple reasons (clinical progression and patient decision, n=1) for the zanzalintinib–atezolizumab group and investigator decision (n=3) and clinical progression (n=1) for the regorafenib group.

Statistical analysis

The primary overall survival analysis in the ITT population was planned for when approximately 616 deaths had occurred to provide approximately 87% power to detect a hazard ratio (HR) of 0·75 using the log-rank test and a two-sided α of 0·015. For overall survival in the nlmITT population, it was estimated that 280 deaths would provide approximately 93% power to detect an HR of 0·65 at a two-sided α of 0·035, accounting for a prespecified interim analysis using Lan-DeMets O'Brien–Fleming α-spending function. One interim overall survival analysis in the nlmITT population was planned to coincide with the primary overall survival analysis in the ITT population. All secondary endpoints were analysed at the same timepoint as the primary overall survival analysis of the ITT population using a hierarchical approach; statistical significance of secondary endpoints cannot be claimed until superiority of overall survival in both the ITT and nlmITT populations has been shown in the final analysis.

The type I error rate associated with the dual primary and secondary endpoint analyses was controlled by a modified Bonferroni procedure and graphic approach.[21] The study-wise two-sided α of 0·05 was divided between the dual primary overall survival endpoints in the ITT population (0·015) and nlmITT population (0·035). The secondary endpoints of progression-free survival in both the ITT and nlmITT populations, overall survival in the lmITT population, and progression-free survival in the lmITT population were planned to be tested sequentially only after overall survival was significant in both the ITT and nlmITT populations.

Overall survival and progression-free survival were estimated using the Kaplan–Meier method and compared between treatment groups with the use of a two-sided log-rank test and stratification factors as collected at the time of randomisation. Estimates of the HR with corresponding two-sided 95% CIs were calculated using a stratified Cox proportional hazards model. Two-sided 95% exact CIs were used to describe objective response and disease control in each treatment group. Two-sided 95% CIs for between-group difference were calculated with the use of the normal approximation to the binomial distribution. Unstratified analysis results are reported for subgroup analyses of those endpoints.

This report is based on a planned overall survival analysis (data cutoff April 30, 2025). The trial continues

	Zanzalintinib–atezolizumab (n=451)	Regorafenib (n=450)
Median age, years	60 (53–68)	60 (51–67)
Age group, years		
<65	293 (65%)	300 (67%)
≥65	158 (35%)	150 (33%)
Sex		
Male	260 (58%)	268 (60%)
Female	191 (42%)	182 (40%)
Race		
White	248 (55%)	237 (53%)
Asian	163 (36%)	175 (39%)
Black	10 (2%)	8 (2%)
Other	15 (3%)	9 (2%)
Not reported	15 (3%)	21 (5%)
Eastern Cooperative Oncology Group performance status score		
0	210 (47%)	200 (44%)
1	239 (53%)	249 (55%)
Location of the primary tumour		
Rectum	167 (37%)	154 (34%)
Colon	284 (63%)	296 (66%)
Left side	184 (41%)	186 (41%)
Right side*	100 (22%)	110 (24%)
Number of metastatic sites		
Single site	88 (20%)	86 (19%)
Multiple sites	362 (80%)	363 (81%)
Presence of liver metastasis		
Yes	264 (59%)	254 (56%)
No	187 (41%)	196 (44%)
Non-MSI-high or non-dMMR†	451 (100%)	450 (100%)
BRAF and *RAS* mutation status		
BRAF mutant	15 (3%)	17 (4%)
RAS mutant	268 (59%)	268 (60%)
Previous systemic therapies for metastatic colorectal cancer		
Median previous systemic therapies	2 (2–3)	2 (2–3)
Previous fluoropyrimidine, irinotecan, and oxaliplatin	449 (>99%)‡	450 (100%)
Any previous anti-VEGF antibody	363 (80%)	375 (83%)
Any previous anti-EGFR antibody	184 (41%)	190 (42%)

Data are median (IQR) or n (%). dMMR=deficient mismatch repair. MSI=microsatellite instability. *Includes the transverse colon. †All patients were tested for MSI status, MMR status, or both. ‡Of the two patients who did not receive all three agents, one received a fluoropyrimidine, oxaliplatin, and bevacizumab without having received irinotecan and the other received two fluoropyrimidines, irinotecan, bevacizumab, and cetuximab without having received oxaliplatin.

Table 1: **Demographic and clinical characteristics of the intention-to-treat population at baseline**

to the final overall survival analysis in the nlmITT population. Statistical analyses were performed using SAS version 9.4. The statistical analysis plan can be found in the appendix (p 24).

Role of the funding source

The trial was designed by the sponsor in collaboration with the investigators with input from Roche, the atezolizumab manufacturer. The sponsor, in collaboration with the authors, was also involved in data analysis and data interpretation. The sponsor had no role in data collection. The authors vouch for the completeness and accuracy of the data and fidelity of the trial to the protocol. All authors, including those employed by the sponsor (CSH, GW, and RS), contributed to writing of the report and provided final approval of the manuscript. As part of the site agreement, investigators agreed to keep all aspects and outcomes of the trial confidential. Medical writers employed by the sponsor assisted with manuscript preparation.

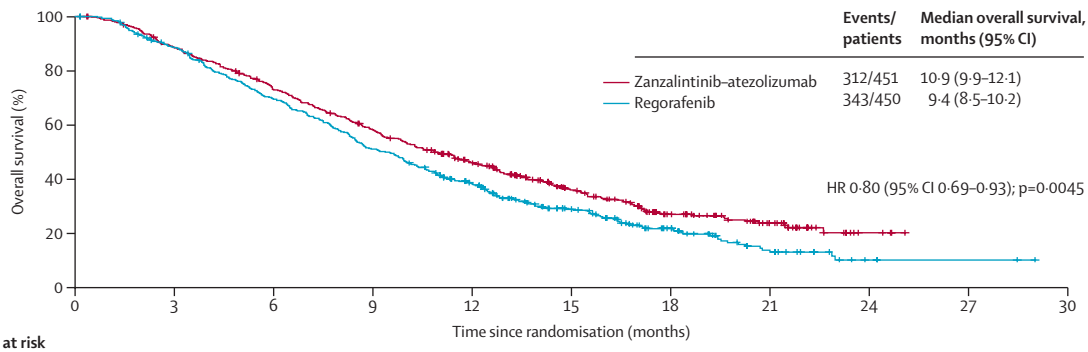
Results

1325 patients were screened for eligibility; between Sept 7, 2022, and July 15, 2024, 901 patients were randomly assigned to zanzalintinib–atezolizumab (n=451) or regorafenib (n=450; figure 1). The primary reason for discontinuing treatment was radiographic progression (305 [68%] of 451 patients in the zanzalintinib–atezolizumab group and 331 [74%] of 450 patients in the regorafenib group). Important protocol deviations are described in the appendix (p 11). Baseline characteristics were representative of patients with previously treated metastatic colorectal cancer and well balanced between the groups (table 1). 528 (59%) patients were male and 373 (41%) were female; 485 (54%) were White, 338 (38%) were Asian, 18 (2%) were Black, 24 (3%) were other races, and 36 (4%) had race not reported. 738 (82%) patients received a previous anti-VEGF antibody and 374 (42%) received a previous anti-EGFR antibody.

At a median follow-up of 18·0 months (IQR 14·6–21·5), zanzalintinib–atezolizumab showed a significant overall survival benefit over regorafenib in the ITT population (stratified HR 0·80 [95% CI 0·69–0·93]; p=0·0045; figure 2A). Median overall survival was 10·9 months (95% CI 9·9–12·1) with zanzalintinib–atezolizumab and 9·4 months (8·5–10·2) with regorafenib. Separation of the Kaplan–Meier curves occurred early and consistently favoured zanzalintinib–atezolizumab thereafter. The 12-month overall survival estimates were 46% (95% CI 41–51) for zanzalintinib–atezolizumab and 38% (34–43) for regorafenib; the 24-month overall survival estimates were 20% (15–26) for zanzalintinib–atezolizumab and 10% (6–16) for regorafenib.

At the interim analysis of overall survival in the nlmITT population, the stratified HR for zanzalintinib–atezolizumab versus regorafenib was 0·79 (95% CI 0·61–1·03); p=0·087 (median overall survival 15·9 months [95% CI 13·5–17·6] *vs* 12·7 months [10·9–15·5]). The overall survival benefit of zanzalintinib–atezolizumab over regorafenib was consistent across subgroups for the ITT population, including geographical region, *RAS* status, presence of liver metastases, and previous anti-VEGF antibody treatment (figure 2B).

A



Number at risk (censored)											
Zanzalintinib–atezolizumab	451 (0)	396 (4)	324 (7)	256 (10)	189 (24)	117 (58)	65 (83)	33 (109)	4 (135)	0 (139)	0 (139)
Regorafenib	450 (0)	392 (7)	307 (9)	225 (9)	156 (23)	90 (53)	47 (76)	19 (91)	4 (103)	2 (105)	0 (107)

B

	Zanzalintinib–atezolizumab		Regorafenib		HR (95% CI)
	Events/ patients	Median, months (95% CI)	Events/ patients	Median, months (95% CI)	
Sex					
Male	177/260	11·5 (9·8–12·8)	213/268	9·7 (8·3–10·4)	0·73 (0·60–0·90)
Female	135/191	10·3 (8·7–12·3)	130/182	9·2 (8·1–11·0)	0·91 (0·71–1·15)
Age, years					
<65	201/293	11·0 (9·9–12·5)	222/300	10·0 (8·8–10·9)	0·84 (0·69–1·01)
≥65	111/158	10·3 (8·4–13·4)	121/150	8·3 (7·7–9·9)	0·73 (0·56–0·94)
Geographical region					
Asia	103/158	11·5 (9·2–13·7)	120/159	8·8 (7·8–10·4)	0·77 (0·59–1·00)
Rest of the world	209/293	10·9 (9·3–12·3)	223/291	9·8 (8·3–10·9)	0·82 (0·68–0·99)
***RAS* status**					
Wild type	117/183	12·0 (10·1–14·6)	133/182	10·4 (8·7–12·3)	0·79 (0·61–1·01)
Mutant	195/268	10·3 (9·0–11·9)	210/268	8·7 (8·0–9·8)	0·80 (0·66–0·98)
Liver metastases					
Yes	214/264	8·9 (8·0–9·9)	224/254	7·7 (6·5–8·5)	0·78 (0·65–0·94)
No	98/187	15·9 (13·5–17·6)	119/196	12·7 (10·9–15·5)	0·77 (0·59–1·01)
ECOG performance status					
0	135/210	12·0 (10·8–14·4)	140/200	10·7 (9·2–12·7)	0·85 (0·67–1·07)
≥1	175/239	9·3 (8·3–11·6)	203/250	8·3 (7·4–9·6)	0·76 (0·62–0·93)
Primary tumour location					
Rectum	106/167	13·1 (10·6–15·5)	121/154	9·8 (8·5–10·6)	0·63 (0·48–0·82)
Colon	206/284	9·9 (8·7–11·3)	222/296	8·8 (8·0–10·6)	0·92 (0·76–1·11)
Time since diagnosis of mCRC					
<18 months	67/85	8·4 (5·9–10·0)	92/110	7·5 (5·3–8·5)	0·80 (0·58–1·09)
≥18 months	245/366	11·6 (10·3–13·2)	251/340	10·2 (8·9–11·1)	0·82 (0·69–0·98)
Previous anti-VEGF antibody					
Yes	252/363	10·5 (9·3–12·5)	285/375	8·8 (8·3–9·9)	0·80 (0·68–0·95)
No	60/88	11·5 (8·7–13·5)	58/75	11·1 (9·5–12·6)	0·80 (0·56–1·15)
Previous anti-EGFR antibody					
Yes	121/184	11·5 (9·3–14·4)	138/190	10·3 (8·5–12·3)	0·81 (0·64–1·04)
No	191/267	10·3 (9·1–12·1)	205/260	8·7 (8·0–9·8)	0·78 (0·64–0·95)
***BRAF* status**					
Wild type	236/338	10·9 (9·5–12·5)	276/349	8·9 (8·3–10·0)	0·75 (0·63–0·89)
Mutant	10/15	8·7 (4·0–NE)	12/17	11·3 (3·3–19·5)	0·96 (0·42–2·18)
Overall	**312/451**	**10·9 (9·9–12·1)**	**343/450**	**9·4 (8·5–10·2)**	**0·80 (0·69–0·93)**

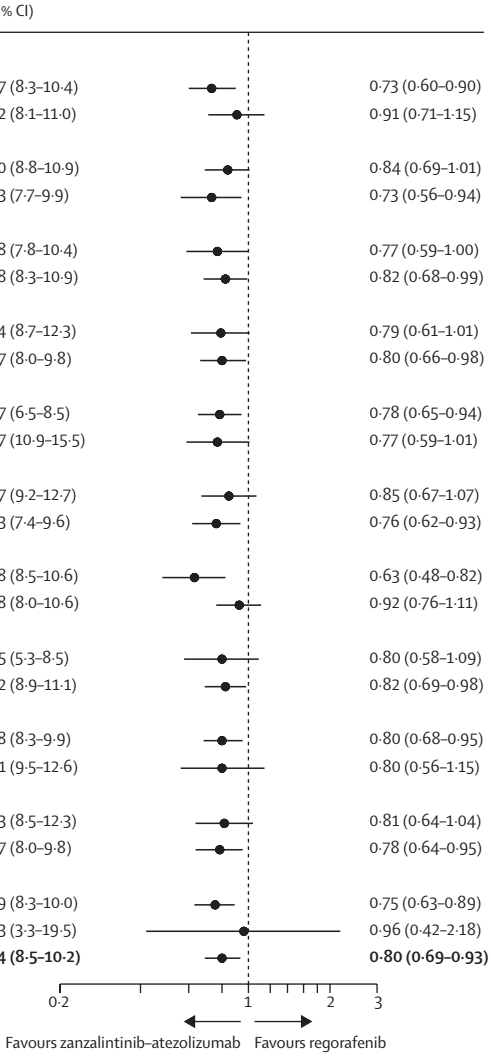
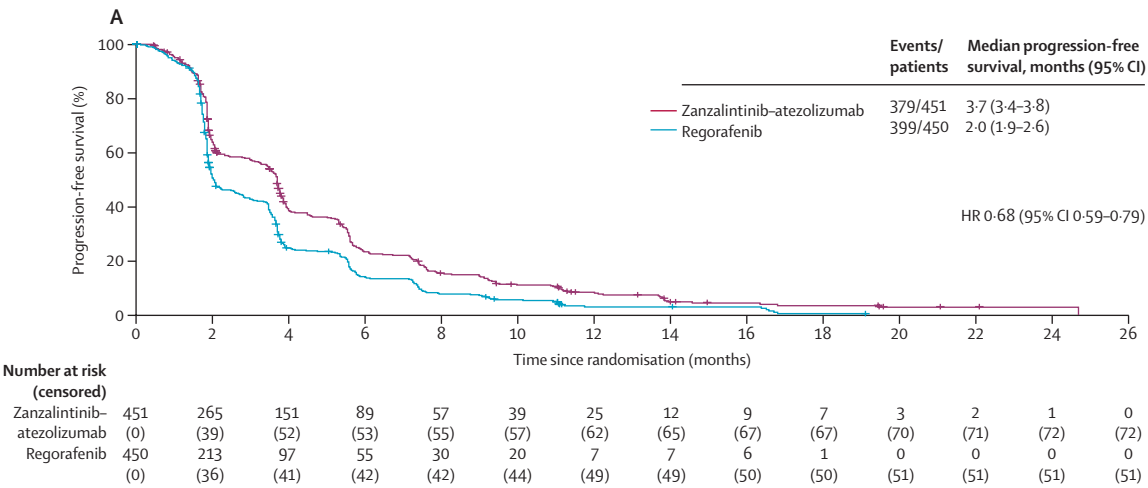


Figure 2: **Overall survival in the intention-to-treat population and according to subgroup**
(A) Overall survival in the intention-to-treat population. (B) Overall survival by stratification factors and clinical and molecular subgroups in the intention-to-treat population. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. mCRC=metastatic colorectal cancer. NE=not estimable.



B

	Zanzalintinib–atezolizumab		Regorafenib		HR (95% CI)
	Events/ patients	Median, months (95% CI)	Events/ patients	Median, months (95% CI)	
Sex					
Male	220/260	3·7 (3·5–3·9)	243/268	2·0 (1·9–2·6)	0·61 (0·51–0·74)
Female	159/191	3·6 (2·1–3·8)	156/182	2·2 (2·0–3·2)	0·86 (0·69–1·07)
Age, years					
<65	249/293	3·7 (3·4–3·8)	259/300	2·0 (1·9–2·7)	0·77 (0·65–0·91)
≥65	130/158	3·7 (2·1–4·2)	140/150	2·1 (1·9–3·1)	0·60 (0·47–0·77)
Geographical region					
Asia	132/158	3·7 (2·4–3·9)	141/159	2·8 (1·9–3·6)	0·86 (0·68–1·09)
Rest of the world	247/293	3·7 (3·3–3·8)	258/291	2·0 (1·9–2·2)	0·61 (0·51–0·73)
***RAS* status**					
Wild type	155/183	3·8 (3·7–3·9)	164/182	2·1 (1·9–3·5)	0·66 (0·53–0·82)
Mutant	224/268	3·5 (2·1–3·7)	235/268	2·0 (1·9–2·6)	0·73 (0·61–0·88)
Liver metastases					
Yes	235/264	2·1 (2·0–3·4)	238/254	1·9 (1·8–2·0)	0·69 (0·58–0·83)
No	144/187	5·3 (4·0–5·6)	161/196	3·7 (3·4–3·8)	0·67 (0·54–0·84)
ECOG performance status					
0	180/210	3·8 (3·7–3·9)	175/200	2·0 (1·9–2·6)	0·58 (0·47–0·72)
≥1	197/239	3·5 (2·1–3·7)	224/250	2·1 (1·9–3·4)	0·81 (0·67–0·98)
Primary tumour location					
Rectum	146/167	3·8 (3·4–4·0)	137/154	2·2 (2·0–3·5)	0·68 (0·54–0·87)
Colon	233/284	3·7 (2·9–3·7)	262/296	2·0 (1·9–2·6)	0·70 (0·59–0·84)
Time since diagnosis of mCRC					
<18 months	74/85	1·9 (1·9–2·1)	98/110	1·9 (1·8–2·0)	0·89 (0·66–1·19)
≥18 months	305/366	3·8 (3·7–4·0)	301/340	2·6 (2·0–3·4)	0·68 (0·58–0·80)
Previous anti-VEGF antibody					
Yes	300/363	3·7 (3·0–3·8)	333/375	2·0 (1·9–2·2)	0·69 (0·60–0·81)
No	79/88	3·8 (3·5–4·5)	66/75	3·6 (2·0–3·8)	0·68 (0·48–0·96)
Previous anti-EGFR antibody					
Yes	156/184	3·8 (3·6–3·9)	173/190	2·0 (1·9–3·0)	0·69 (0·56–0·85)
No	223/267	3·5 (2·3–3·8)	226/260	2·1 (1·9–2·8)	0·72 (0·60–0·86)
***BRAF* status**					
Wild type	287/338	3·7 (3·3–3·8)	313/349	2·0 (1·9–2·6)	0·70 (0·60–0·83)
Mutant	13/15	3·7 (1·7–4·2)	15/17	1·9 (1·6–3·6)	0·79 (0·38–1·64)
Overall	**379/451**	**3·7 (3·4–3·8)**	**399/450**	**2·0 (1·9–2·6)**	**0·68 (0·59–0·79)**

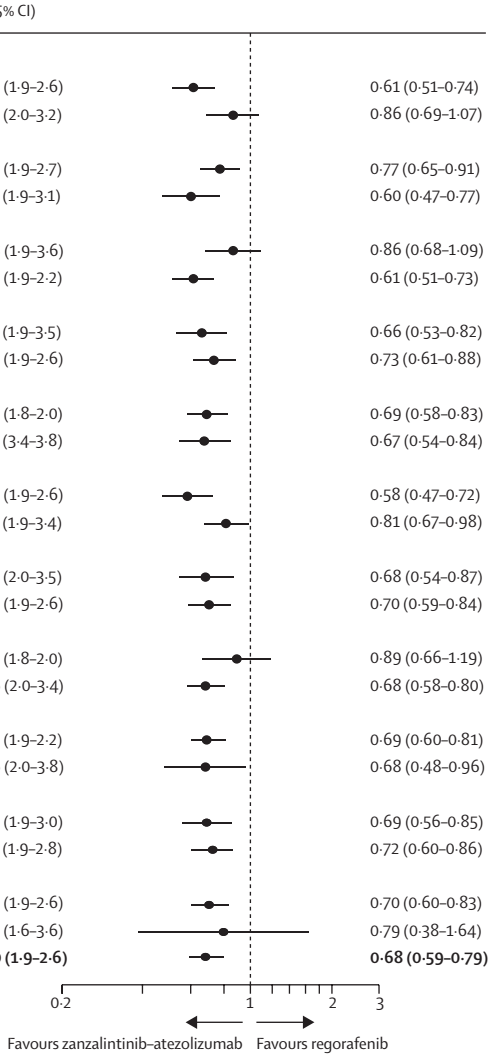


Figure 3: **Progression-free survival in the intention-to-treat population and according to subgroup**
(A) Progression-free survival in the intention-to-treat population. (B) Progression-free survival according to stratification factors and clinical and molecular subgroups in the intention-to-treat population. Progression-free survival assessed according to Response Evaluation Criteria in Solid Tumours version 1.1. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. mCRC=metastatic colorectal cancer.

For progression-free survival in the ITT population, the stratified HR for zanzalintinib–atezolizumab versus regorafenib was 0·68 (95% CI 0·59–0·79; median 3·7 months [95% CI 3·4–3·8] *vs* 2·0 months [1·9–2·6]; figure 3A); in the nlmITT population, the stratified HR was 0·66 (0·52–0·83; median 5·3 months [4·0–5·6] *vs* 3·7 months [3·4–3·8]). Statistical superiority for progression-free survival cannot be claimed at this time due to the prespecified hierarchical testing strategy. Progression-free survival was consistent across subgroups (figure 3B). Subsequent anticancer therapy was well balanced between the groups (appendix p 12).

In the ITT population, an objective response was observed in 16 (4% [95% CI 2–6]) of 451 patients in the zanzalintinib–atezolizumab group versus five (1% [0–3]) of 450 patients in the regorafenib group (appendix p 13). Any reduction in sum of target lesion diameters was observed in 168 (42%) of 401 evaluable patients in the zanzalintinib–atezolizumab group versus 102 (27%) of 382 evaluable patients in the regorafenib group; disease control was observed in 242 (54%) of 451 patients versus 183 (41%) of 450 patients.

446 patients in the zanzalintinib–atezolizumab group and 434 in the regorafenib group received at least one dose of assigned treatment and were included in the safety population. Exposure data are summarised in the appendix (p 11). Any-grade treatment-related adverse events occurred in 423 (95%) of 446 patients in the zanzalintinib–atezolizumab group and 399 (92%) of 434 patients in the regorafenib group. Grade 3 or worse treatment-related adverse events occurred in 268 (60%) of 446 patients receiving zanzalintinib–atezolizumab and 161 (37%) of 434 patients receiving regorafenib; grade 3 treatment-related adverse events occurred in 248 (56%) patients in the zanzalintinib–atezolizumab group and 143 (33%) patients in the regorafenib group and grade 4 treatment-related adverse events occurred in 15 (3%) patients in the zanzalintinib–atezolizumab group and 17 (4%) patients in the regorafenib group. The most common grade 3 or 4 treatment-related adverse events were hypertension (65 [15%] of 446 patients in the zanzalintinib–atezolizumab group *vs* 38 [9%] of 434 patients in the regorafenib group), proteinuria (26 [6%] *vs* seven [2%]), fatigue (25 [6%] *vs* eight [2%]), and diarrhoea (25 [6%] *vs* eight [2%]; table 2; appendix pp 14–22). A lower rate of treatment-related palmar–plantar erythrodysesthesia occurred in the zanzalintinib–atezolizumab group than in the regorafenib group (any grade, 71 [16%] of 446 patients *vs* 216 [50%] of 434 patients; grade 3, 12 [3%] *vs* 41 [9%]). Serious adverse events occurred in 255 (57%) of 446 patients in the zanzalintinib–atezolizumab group and 184 (42%) of 434 patients in the regorafenib group (appendix p 23); serious treatment-related adverse events occurred in 118 (26%) patients in the zanzalintinib–atezolizumab group and 45 (10%) in the regorafenib group.

	Zanzalintinib–atezolizumab (n=446)		Regorafenib (n=434)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
At least one adverse event	423 (95%)	268 (60%)	399 (92%)	161 (37%)
Serious adverse event	118 (26%)	96 (22%)	45 (10%)	41 (9%)
Event occurring in ≥10% of patients in either group				
Diarrhoea	221 (50%)	25 (6%)	104 (24%)	8 (2%)
Hypertension	153 (34%)	65 (15%)	114 (26%)	38 (9%)
Fatigue	146 (33%)	25 (6%)	88 (20%)	8 (2%)
Nausea	139 (31%)	12 (3%)	56 (13%)	4 (1%)
Decreased appetite	134 (30%)	10 (2%)	85 (20%)	6 (1%)
Vomiting	95 (21%)	10 (2%)	35 (8%)	1 (<1%)
Rash	84 (19%)	12 (3%)	27 (6%)	5 (1%)
Hypothyroidism	79 (18%)	0	11 (3%)	0
Aspartate aminotransferase increase	77 (17%)	11 (2%)	26 (6%)	9 (2%)
Proteinuria	75 (17%)	26 (6%)	29 (7%)	7 (2%)
Alanine aminotransferase increase	74 (17%)	10 (2%)	19 (4%)	4 (1%)
Palmar–plantar erythrodysesthesia syndrome	71 (16%)	12 (3%)	216 (50%)	41 (9%)
Stomatitis	68 (15%)	7 (2%)	46 (11%)	1 (<1%)
Platelet count decreased	65 (15%)	16 (4%)	16 (4%)	3 (1%)
Pyrexia	64 (14%)	4 (1%)	21 (5%)	0
Asthenia	62 (14%)	11 (2%)	68 (16%)	11 (3%)
Blood bilirubin increased	47 (11%)	10 (2%)	27 (6%)	4 (1%)
Thrombocytopenia	47 (11%)	12 (3%)	12 (3%)	0
Arthralgia	45 (10%)	4 (1%)	10 (2%)	0
Dysphonia	28 (6%)	0	54 (12%)	0

Data are n (%). Treatment-related adverse events that occurred in 10% or more of patients in either group are shown. The full list of treatment-related adverse events is in the appendix (pp 14–22). Preferred terms of disease progression under study in the adverse events database, as per medical review, are excluded. Events are listed by decreasing frequency in the any grade zanzalintinib–atezolizumab group. Adverse events are classified according to the Medical Dictionary for Regulatory Activities, version 28.0.

Table 2: **Treatment-related adverse events in the safety population**

Adverse events leading to discontinuation of the zanzalintinib–atezolizumab regimen occurred in 82 (18%) of 446 patients; 64 (15%) of 434 patients discontinued regorafenib due to adverse events. The most frequent adverse events leading to discontinuation of the zanzalintinib–atezolizumab regimen were abdominal pain, asthenia, and general physical health deterioration (four [1%] patients each of 446 patients).

Deaths considered related to treatment by investigators were due to intestinal perforation (n=2) for zanzalintinib, pneumonitis (n=1) and renal failure (n=1) for atezolizumab, altered state of consciousness (n=1) for zanzalintinib–atezolizumab, and jejunal perforation (n=1) for regorafenib.

Discussion

Zanzalintinib–atezolizumab significantly prolonged overall survival compared with regorafenib in patients with previously treated metastatic colorectal cancer. Robust and consistent survival benefits were observed across key subgroups, including liver involvement, *RAS* status, geographical region, and previous anti-VEGF

therapy, suggesting that the survival benefit in the ITT population was not driven by enrichment for a single subset of patients. The zanzalintinib–atezolizumab safety profile was generally consistent with that previously reported for this combination and other similar immune checkpoint inhibitor plus tyrosine-kinase inhibitor combinations,[20,22] although there was a higher rate of treatment-related deaths with the combination compared with regorafenib in the current trial.

To our knowledge, STELLAR-303 is the first phase 3 trial to show that an immunotherapy-containing regimen, zanzalintinib–atezolizumab, improved overall survival compared with standard of care in metastatic colorectal cancer that is not MSI-H or dMMR. In the phase 3 LEAP-017 trial,[22] lenvatinib–pembrolizumab did not prolong overall survival versus regorafenib or trifluridine–tipiracil. The differences between these trials might be explained by the variation in kinase inhibition profiles between lenvatinib and zanzalintinib—in addition to VEGF receptors, zanzalintinib targets the TAM kinases and MET.[18] TAM kinases contribute to tumour immune evasion by promoting an immunosuppressive macrophage phenotype and facilitating efferocytosis, thereby dampening proinflammatory responses.[19] Inhibiting these kinases with zanzalintinib might improve responsiveness to immune checkpoint inhibitors. Although the contribution of adding atezolizumab to zanzalintinib cannot be ascertained from this phase 3 trial, previous data from a randomised cohort in STELLAR-001 comparing zanzalintinib with zanzalintinib–atezolizumab in a similar population of patients with *RAS* wild-type metastatic colorectal cancer provide supportive evidence for the atezolizumab contribution across all key efficacy parameters tested in the ITT population.[20] The benefit of adding zanzalintinib to atezolizumab is supported by the phase 3 IMblaze370 trial,[12] in which atezolizumab monotherapy yielded an inferior overall survival outcome to regorafenib and did not improve progression-free survival or objective response rate. Collectively, these results suggest that targeting angiogenesis and immunosuppressive signalling, via multikinase inhibition, is needed for optimal outcomes with immune checkpoint inhibitor plus tyrosine-kinase inhibitor combinations in this setting.

In STELLAR-303 subgroup analyses, the overall survival benefit with zanzalintinib–atezolizumab was consistent in patients with liver metastases and without liver metastases. The nlmITT population results were from an interim analysis; patients will continue to be followed up to the planned final analysis. The activity in our patients with liver metastases is notable as LEAP-017 and early phase studies of immune checkpoint inhibitor plus VEGF receptor tyrosine-kinase inhibitor combinations showed a lack of benefit in this population.[22,23] The limited activity of immunotherapy combinations in these studies might be due to an immunosuppressive tumour microenvironment in the liver.[24–26] The benefit observed with zanzalintinib–atezolizumab in this population might result from immunostimulatory activity stemming from the different kinase inhibition profile with zanzalintinib.[18]

The overall survival HR of 0·80 in STELLAR-303 reflected the comparison with an active treatment. At the time this trial was initiated, guideline-directed, standard-of-care options in third-line or later-line metastatic colorectal cancer were regorafenib and trifluridine–tipiracil. Phase 3 trials with regorafenib and trifluridine–tipiracil were placebo-controlled, with overall survival HRs of 0·77 (95% CI 0·64–0·94) and 0·68 (0·58–0·81), respectively.[8,10] The median overall survival observed with these agents were similar at 6·4 months (IQR 3·6–11·8; regorafenib) and 7·1 months (95% CI 6·5–7·8; trifluridine–tipiracil).[8,10] In addition, regorafenib was associated with a lower grade 3 and 4 adverse event rate than trifluridine–tipiracil (270 [54%] of 500 *vs* 370 [69%] of 533, respectively). Given these data, regorafenib was selected as the control for STELLAR-303. In STELLAR-303, the median overall survival with regorafenib was 9·4 months, greater than the 6·4 months (IQR 3·6–11·8) observed in the phase 3 CORRECT trial[8] and the 8·8 months (95% CI 7·3–9·8) observed in the phase 3 Asian CONCUR trial.[27] Survival outcomes can differ in trials over time as a result of evolving patient management approaches, as well as differences in patient characteristics. Notably, the median progression-free survival associated with regorafenib in STELLAR-303 is consistent with that reported previously,[8] suggesting that progression-free survival outcomes with regorafenib have not substantially changed over time and access to additional life-prolonging therapies has affected overall survival. The median progression-free survival difference between groups in STELLAR-303 of 1·7 months is consistent with the median overall survival benefit of 1·5 months, suggesting that patients benefitted equally from subsequent anticancer therapies regardless of treatment assignment.

Additional standard-of-care regimens in refractory metastatic colorectal cancer include fruquintinib monotherapy and trifluridine–tipiracil–bevacizumab. Fruquintinib has shown a median overall survival of 7·4 months (95% CI 6·7–8·2), consistent with other single-agents and reflecting its selective inhibition of VEGF receptors.[9] In SUNLIGHT,[11] the median overall survival with trifluridine–tipiracil-bevacizumab was 10·8 months (95% CI 9·4–11·8) overall but was 9·0 months (8·3–10·8) among patients previously treated with bevacizumab, an established standard of care. Acknowledging the caveats associated with cross-trial comparisons and drawing conclusions from subgroup analyses, in STELLAR-303, the median overall survival with zanzalintinib–atezolizumab was 10·5 months among patients who received previous anti-VEGF antibody treatment. These findings suggest a potential survival

benefit in a heavily pretreated population, including those previously exposed to bevacizumab. Importantly, this combination offers a non-chemotherapy-based regimen and was associated with a lower incidence of haematological adverse events than the chemotherapy-based SUNLIGHT regimen.

The objective response rate of 4% observed in our trial is consistent with that observed in other trials in the salvage metastatic colorectal cancer setting, despite improvements in overall survival.[9,11] These data suggest that a benefit of agents in this setting might instead be manifested through measures of disease control.

Adverse events were consistent with known class effects and no new safety signals emerged. Most adverse events were grade 1–3. The most common any-grade and grade 3 or worse adverse events (eg, diarrhoea, hypertension, and fatigue) were more frequent with zanzalintinib–atezolizumab than with regorafenib. In the case of palmar–plantar erythrodysesthesia, the rate with zanzalintinib–atezolizumab (16% any grade, 3% grade 3 or worse) was lower than that with regorafenib (50% any grade, 9% grade 3 or worse) despite the longer treatment duration with the combination. No serious adverse events occurred in more than 5% of patients in either group. The safety profile of zanzalintinib–atezolizumab was consistent with that previously reported for this regimen and similar combinations in metastatic colorectal cancer[20,22] as well as other immune checkpoint inhibitor plus tyrosine-kinase inhibitor regimens in different tumour types.[28–30] The adverse events observed with zanzalintinib–atezolizumab are well known and manageable by dose reductions or supportive care treatment strategies familiar to oncologists. A higher rate of treatment-related deaths was observed with the combination compared with regorafenib in the current trial. Ultimately, the safety profile must be balanced with the efficacy outcomes observed in this advanced setting.

Strengths of this trial include its size and the stratification by liver metastasis status, permitting hypothesis testing in these relevant subgroups, and its international scope and active-controlled design. A limitation was the open-label design, which might have influenced patient management at the investigator level. In addition, since the study was initiated, the trifluridine–tipiracil–bevacizumab regimen has become a standard-of-care treatment in refractory metastatic colorectal cancer. A randomised clinical trial comparing that regimen with zanzalintinib–atezolizumab is an unmet need in the metastatic colorectal cancer treatment landscape at this time.

In summary, STELLAR-303 is the first phase 3 trial to show a significant improvement in overall survival with an immunotherapy-based regimen, zanzalintinib–atezolizumab, in patients with relapsed or refractory metastatic colorectal cancer that is not MSI-H or dMMR. This combination represents a chemotherapy-free treatment option with a novel mechanism of action for heavily pretreated patients in need of improved therapies.

Contributors
All authors participated in drafting and critically revising the manuscript. The study sponsor along with ASa, JRH, YSP, JT, and CE were responsible for the conceptualisation and design of the study. JRH, YSP, M-AL, SL, ACV, MVdE, EF, MF, GA, JS, ASt, OD, LB, CE, and ASa participated in enrolling patients, supervising the trial, and collecting data. CSH, GW, and RS were involved in data analysis, and all authors were involved in data interpretation. ASa, JRH, and CSH accessed and verified the raw data. All authors had full access to the study data, vouch for the completeness and accuracy of the data and for the fidelity of the trial, and had final responsibility for the decision to submit for publication.

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Data sharing

Individual patient data will not be shared. The study protocol is available online as part of the appendix (p 24).

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