Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial

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Summary

Background Microsatellite-stable metastatic colorectal cancer is typically unresponsive to immunotherapy. This phase 3 study was designed to assess atezolizumab plus cobimetinib in metastatic colorectal cancer. Here, we report the comparison of atezolizumab plus cobimetinib or atezolizumab monotherapy versus regorafenib in the third-line setting.

Methods IMblaze 370 is a multicentre, open-label, phase 3, randomised, controlled trial, done at 73 academic medical centres and community oncology practices in 11 countries. Patients aged at least 18 years with unresectable locally advanced or metastatic colorectal cancer, baseline Eastern Cooperative Oncology Group performance status of 0–1, and disease progression on or intolerance to at least two previous systemic chemotherapy regimens were enrolled. We used permuted-block randomisation (block size four) to assign patients (2:1:1) via an interactive voice and web response system to atezolizumab (840 mg intravenously every 2 weeks) plus cobimetinib (60 mg orally once daily for days 1–21 of a 28-day cycle), atezolizumab monotherapy (1200 mg intravenously every 3 weeks), or regorafenib (160 mg orally once daily for days 1–21 of a 28-day cycle). Stratification factors were extended *RAS* status (wild-type *vs* mutant) and time since diagnosis of first metastasis (<18 months *vs* ≥18 months). Recruitment of patients with high microsatellite instability was capped at 5%. The primary endpoint was overall survival in the intention-to-treat population. Safety was assessed in the population of patients who received at least one dose of their assigned treatment. IMblaze370 is ongoing and is registered with ClinicalTrials.gov, number NCT02788279.

Findings Between July 27, 2016, and Jan 19, 2017, 363 patients were enrolled (183 patients in the atezolizumab plus cobimetinib group, 90 in the atezolizumab group, and 90 in the regorafenib group). At data cutoff (March 9, 2018), median follow-up was 7·3 months (IQR 3·7–13·6). Median overall survival was 8·87 months (95% CI 7·00–10·61) with atezolizumab plus cobimetinib, 7·10 months (6·05–10·05) with atezolizumab, and 8·51 months (6·41–10·71) with regorafenib; the hazard ratio was 1·00 (95% CI 0·73–1·38; p=0·99) for the combination versus regorafenib and 1·19 (0·83–1·71; p=0·34) for atezolizumab versus regorafenib. Grade 3–4 adverse events were reported in 109 (61%) of 179 patients in the atezolizumab plus cobimetinib group, 28 (31%) of 90 in the atezolizumab group, and 46 (58%) of 80 in the regorafenib group. The most common all-cause grade 3–4 adverse events in the combination group were diarrhoea (20 [11%] of 179), anaemia (ten [6%]), increased blood creatine phosphokinase (12 [7%]), and fatigue (eight [4%]). Serious adverse events were reported in 71 (40%) of 179 patients in the combination group, 15 (17%) of 90 in the atezolizumab group, and 18 (23%) of 80 in the regorafenib group. Two treatment-related deaths occurred in the combination group (sepsis) and one in the regorafenib group (intestinal perforation).

Interpretation IMblaze370 did not meet its primary endpoint of improved overall survival with atezolizumab plus cobimetinib or atezolizumab versus regorafenib. The safety of atezolizumab plus cobimetinib was consistent with those of the individual drugs. These results underscore the challenge of expanding the benefit of immunotherapy to patients whose tumours have lower baseline levels of immune inflammation, such as those with microsatellite-stable metastatic colorectal cancer.

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See **Comment** page 752

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Introduction

Metastatic colorectal cancer is associated with a poor prognosis and low 5-year overall survival (5–8%).[1] The standard of care for patients with chemorefractory metastatic colorectal cancer in the third-line setting and beyond is regorafenib (a small-molecule multikinase inhibitor) or TAS-102 (a cytotoxic combination of trifluridine and tipiracil).[2] Patients with chemorefractory metastatic colorectal cancer treated with regorafenib have a median progression-free survival of 1·9 months

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed and international congress presentations pertaining to studies on metastatic colorectal cancer before study initiation and then again during manuscript preparation. We searched with medical subject heading search terms "metastatic" AND "colon cancer", "colorectal carcinoma", "programmed cell death 1", "PD-1", "programmed cell death ligand 1", or "PD-L1" for articles published between June 1, 2011, and June 1, 2016, in English. We found that despite improvements in treatment, the prognosis for heavily pretreated patients with metastatic colorectal cancer remains poor, with a median overall survival of about 6 months. Additionally, therapies are associated with substantial toxicity. Therefore, more efficacious and tolerable treatments are needed for patients with metastatic colorectal cancer.

Added value of this study

The IMblaze370 trial tested innovative and important hypotheses in the field of metastatic colorectal cancer and cancer immunotherapy. Although not superior to standard of care, treatment with the combination of atezolizumab and cobimetinib resulted in equivalent survival without the introduction of any new safety signals compared with the safety profile of the individual drugs. These results contribute to our ongoing understanding of metastatic colorectal cancer and cancer immunotherapy. Despite the importance of both the MEK and PD-L1 pathways in metastatic colorectal cancer pathogenesis, dual inhibition of the PD-L1 immune checkpoint and MAPK-mediated immune suppression did not improve overall survival in patients with difficult-to-treat chemorefractory metastatic colorectal cancer compared with the standard of care drug, regorafenib.

Implications of all the available evidence

These results from IMblaze370 highlight the biological differences between metastatic colorectal cancer that is microsatellite stable and that which has high microsatellite instability, underscoring the divergent treatment needs of patients with these two disease types. Although atezolizumab plus cobimetinib will not be a treatment option for microsatellite-stable patients, given the activity of these drugs, they will continue to be explored in patients with other tumour types as well as in different treatment combinations.

(IQR 1·6–3·9) and median overall survival of 6·4 months (3·6–11·8), with an objective response achieved by only about 1% of patients.[3] Patients treated with TAS-102 have a median progression-free survival of 2·0 months (95% CI 1·9–2·1) and median overall survival of 7·1 months (6·5–7·8), with an objective response achieved by only 1·6% of patients.[2,4] Accordingly, these drugs have a small survival benefit and substantial potential toxicity issues,[1,3–6] demonstrating the remaining unmet need for more efficacious treatment options for most patients with chemorefractory metastatic colorectal cancer.

Immune checkpoint inhibitors targeting the programmed cell death ligand 1 (PD-L1) and programmed cell death-1 (PD-1) pathway have shown durable responses and disease control in patients with metastatic colorectal cancer with high microsatellite instability, a population that constitutes 3–5% of patients with metastatic colorectal cancer.[7–11] By contrast, immune checkpoint inhibitors have little clinical benefit in patients with microsatellite-stable tumour types,[7] a population that comprises most patients with metastatic colorectal cancer. Although most microsatellite-stable tumours do not have T-cell infiltration and are considered immune excluded, the mechanism underlying immune resistance in such tumours remains poorly understood. Preclinical data have suggested that MAPK signalling might affect mechanisms of immune escape, including downregulation of major histocompatibility complex class 1 expression and upregulation of multiple immunosuppressive cytokines and cell surface molecules.[12–14] Preclinical models have also shown that MAPK pathway inhibition with MEK inhibitors might increase T-cell infiltration into tumours and augment the anti-tumour activity of PD-1 inhibitors by increasing MHC-1 and PD-L1 expression.[12,13] Cobimetinib is a MEK1 and MEK2 inhibitor that blocks the MAP kinase pathway, which is integral in cell cycle regulation and affects the immune contexture in the tumour microenvironment. Cobimetinib has been shown in colorectal cancer preclinical models to increase major histocompatibility complex class 1 expression on tumours, increase effector $CD8^+$ cell infiltration into tumours, downregulate multiple immunosuppressive cytokines and receptors, and lead to durable anti-tumour immunity when combined with a PD-L1 inhibitor.[13] MEK inhibitors have been previously assessed in the treatment of metastatic colorectal cancer; however, cobimetinib monotherapy produced no response in 41 patients with colorectal cancer, 28 of whom had a *KRAS* mutation.[15]

Atezolizumab is a humanised IgG1 monoclonal antibody that selectively targets PD-L1 and blocks its interactions with PD-1 and B7.1 protein receptors, thereby reinvigorating the antitumour T-cell response.[16–18] In a phase 1b clinical trial of 23 patients,[19] the drug combination of atezolizumab plus cobimetinib resulted in 17% of patients achieving an objective response. Results from an expanded update after initiation of our phase 3 trial showed the combination to be tolerable, with an objective response in 8% of patients, median overall survival of 10·0 months (95% CI 6·2–14·1), and 46% of patients were alive at 12 months,[20] which compares favourably to the results with regorafenib.[3] Additionally, partial responses were achieved by patients with both *KRAS* mutations and wild-type tumours.[20]

Preclinical results, supported by early-phase studies, provided an impetus to assess the combination of atezolizumab plus cobimetinib in a phase 3 trial (IMblaze370) in patients with predominantly microsatellite-stable metastatic colorectal cancer who had progressed or were intolerant of 5-fluoropyrimidine, oxaliplatin, and irinotecan. Here, we report the efficacy and safety results from the primary analysis of IMblaze370.

Methods

Study design and participants

We did this multicentre, open-label, phase 3, randomised, controlled trial at 73 academic medical centres and community oncology practices in 11 countries (appendix pp 3–4). Eligible patients were aged 18 years or older with unresectable locally advanced or metastatic colorectal cancer, with a baseline Eastern Cooperative Oncology Group performance status of 0–1, a life expectancy of at least 3 months, adequate haematological and end organ function, and disease progression or intolerance of at least two previous systemic chemotherapy regimens (containing fluorouracil, oxaliplatin, and irinotecan) in the metastatic setting. Patients who had received previous antiangiogenic or anti-epidermal growth factor receptor (EGFR) therapy were eligible; however, those who had received previous treatment with any cancer immunotherapy (including CD137 agonists, anti-PD-L1, anti-PD-1, or anti-CTLA4 agents), MEK or ERK inhibitors, or regorafenib were excluded. Patients who had received major surgery or radiotherapy within 21 days before the start of treatment were excluded, as were those who had received treatment with any anticancer drug within 14 days before treatment initiation. Enrolment of patients with tumours with high microsatellite instability was capped at about 5%. Enrolment of patients with *RAS* wild-type tumours was capped at 50%. Comorbidities that were not permitted include active malignancy (other than colorectal cancer), active or untreated CNS metastases, uncontrolled infections, history of clinically significant cardiovascular disease, evidence or risk of retinal vein occlusion or central serous retinopathy, and autoimmune disease. Full inclusion and exclusion criteria are in the protocol (appendix pp 47–50).

The study protocol was approved by the institutional review board or independent ethics committee of each study site and was done in accordance with the Guideline for Good Clinical Practice and Declaration of Helsinki. All patients gave written informed consent.

Randomisation and masking

Patients were randomly assigned (2:1:1) to receive atezolizumab plus cobimetinib (group A), atezolizumab monotherapy (group B), or regorafenib (group C) via an interactive voice and web response system. A permuted-block randomisation (block size of four) was applied to obtain balanced assignment in each treatment group with respect to the stratification factors: extended *RAS* mutation status (wild-type *vs* mutant) and time since diagnosis of first metastasis (<18 months *vs* ≥18 months). The trial centres enrolled the patients. The study was open label and investigators and participants were not masked to treatment allocation.

Procedures

Atezolizumab was given intravenously at 840 mg every 2 weeks to patients in group A and at 1200 mg every 3 weeks to patients in group B. Atezolizumab dose modification was not permitted. Cobimetinib 60 mg (group A) or regorafenib 160 mg (group C) was given orally once daily on days 1–21 of a 28-day cycle. Atezolizumab, cobimetinib, and regorafenib were provided by the funder. Cobimetinib dose modification was permitted and dose reduction for adverse events was allowed in 20 mg increments (appendix p 109). Regorafenib was also prescribed through pharmacy as standard of care and dose modifications were allowed on the basis of local prescribing guidelines. Treatment was continued until loss of clinical benefit, as assessed by the investigator, or unacceptable toxicity. Because this patient population has few treatment options, patients could continue treatment despite radiographic progression, as approved by the funder, as long as requirements regarding patient safety were met. No crossover was allowed per protocol. Disease progression will be established on the basis of investigator assessment with use of RECIST, version 1.1. Efficacy outcomes were assessed in prespecified patient subgroups defined by centrally confirmed extended *RAS* mutation and microsatellite instability status, as well as key baseline clinical characteristics.

All tumour assessments were done according to Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1. Baseline assessments were done within 35 days before cycle 1 day 1, whereas on-treatment response assessments were done every 8 weeks (or within 1 week either side of this timepoint) until investigator-established progressive disease, loss of clinical benefit, withdrawal of consent, or death, whichever occurred first. Patients who discontinued treatment for any reason other than disease progression had additional tumour assessments every 8 weeks (or within 1 week either side of this timepoint) until disease progression. Patients in all groups who continued study treatment beyond disease progression (defined per RECIST version 1.1) had additional tumour assessments every 8 weeks (or within 1 week either side of this timepoint). The National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, was used to characterise the toxicity profile, including the incidence, nature, and severity of adverse events. Extended *RAS* mutation and microsatellite instability status were established by next-generation sequencing with the FMOne test (Foundation Medicines Inc;

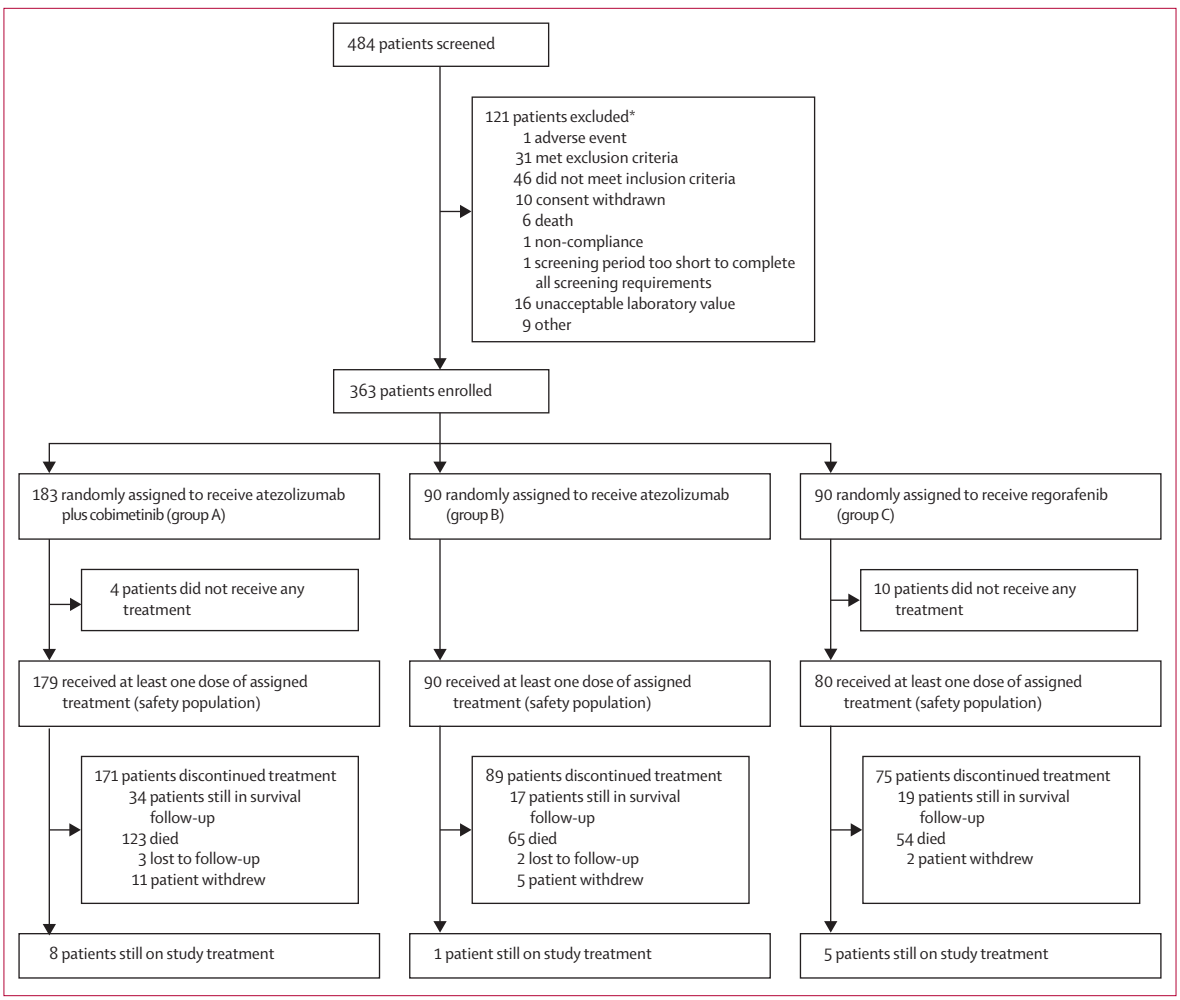


Figure 1: **Trial profile**
*Includes five patients who were excluded, were rescreened, and then were able to enrol in the study.

Cambridge, MA, USA). Microsatellite instability status was established by examination of indel characteristics at 114 homopolymer repeat loci in or near the targeted gene regions of the FMOne gene panel. The 114 loci were selected from a set of 1897 microsatellites that have the best coverage. PD-L1 protein expression levels in infiltrating immune cells were established by immunohistochemistry (Ventana SP142 assay; Tucson, AZ, USA). Tumour samples were archival tissues from primary or metastatic lesions collected less than 5 years previously.

Outcomes

The primary endpoint was overall survival with atezolizumab plus cobimetinib versus regorafenib and overall survival with atezolizumab monotherapy versus regorafenib. The key secondary efficacy endpoints were investigator-assessed objective response, duration of response, and progression-free survival per RECIST, version 1.1, with atezolizumab plus cobimetinib versus regorafenib and with atezolizumab monotherapy versus regorafenib. Other secondary endpoints were impact on functioning and health-related quality of life, assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire, and are not reported here. Overall survival was defined as the time from randomisation to death from any cause. Progression-free survival was defined as the time from randomisation to documented disease progression or death, whichever occurred first. Objective response was defined as the proportion of patients who had a confirmed objective response of complete or partial response, assessed by the investigator. Duration of response was measured in all patients who had an objective response during the study and was defined as the time from the first occurrence of a complete or partial response (whichever is recorded first) until the first date of documented disease progression or death.

Pharmacokinetic exploratory biomarker studies and patient-reported outcome assessments were also done but are not presented here.

	Atezolizumab plus cobimetinib group (n=183)	Atezolizumab group (n=90)	Regorafenib group (n=90)
Age, years	58 (51–67)	56 (51–64)	59 (52–66)
Sex			
Women	76 (42%)	31 (34%)	39 (43%)
Men	107 (58%)	59 (66%)	51 (57%)
Race			
White	152 (83%)	73 (81%)	71 (79%)
Non-white	27 (15%)	14 (16%)	12 (13%)
Unknown	4 (2%)	3 (3%)	7 (8%)
Region			
North America	68 (37%)	33 (37%)	31 (34%)
Europe	87 (48%)	39 (43%)	44 (49%)
Asia or Australia	28 (15%)	18 (20%)	15 (17%)
ECOG performance status			
1	95 (52%)	48 (53%)	45 (50%)
0	88 (48%)	42 (47%)	45 (50%)
Time since diagnosis of first metastasis			
Less than 18 months	56 (31%)	28 (31%)	27 (30%)
18 months or more	127 (69%)	62 (69%)	63 (70%)
Liver metastases			
Yes	121 (66%)	57 (63%)	59 (66%)
No	62 (34%)	33 (37%)	31 (34%)
More than three lines of previous treatment in metastatic setting			
Yes	49 (27%)	26 (29%)	21 (23%)
No	134 (73%)	64 (71%)	69 (77%)
Previous targeted treatment			
None	25 (14%)	13 (14%)	8 (9%)
Any (anti-VEGF, anti-EGFR, or both)	158 (86%)	77 (86%)	82 (91%)
Anti-VEGF (but not anti-EGFR)	89 (49%)	43 (48%)	48 (53%)
Anti-EGFR (but not anti-VEGF)	18 (10%)	4 (4%)	5 (6%)
Both (anti-VEGF and anti-EGFR)	51 (28%)	30 (33%)	29 (32%)
Site of primary tumour			
Right	45 (25%)	21 (23%)	27 (30%)
Left	104 (57%)	48 (53%)	44 (49%)
Transverse	10 (5%)	2 (2%)	4 (4%)
Unknown	24 (13%)	19 (21%)	14 (16%)
Extended *RAS* mutation status			
Wild-type	84 (46%)	41 (46%)	41 (46%)
Mutant	99 (54%)	49 (54%)	49 (54%)
BRAF mutation status			
Wild-type	174 (95%)	87 (97%)	90 (100%)
Mutant	9 (5%)	3 (3%)	0
Microsatellite instability status			
High	3 (2%)	3 (3%)	0
Stable or low	170 (93%)	83 (92%)	80 (89%)
Missing	10 (5%)	4 (4%)	10 (11%)
PD-L1 status in tumour-infiltrating immune cells			
High PD-L1 expression (≥1%)	79 (43%)	35 (39%)	31 (34%)
Low PD-L1 expression (<1%)	84 (46%)	42 (47%)	40 (44%)
Missing	20 (11%)	13 (14%)	19 (21%)

(Table 1 continues in next column)

(Continued from previous column)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. EGFR=epidermal growth factor receptor. PD-L1=programmed death-ligand 1. VEGF=vascular endothelial growth factor.

Table 1: **Demographic and baseline characteristics**

Statistical analysis

IMblaze370 was designed to have 87% power to detect an overall survival hazard ratio (HR) of 0·61 (an increase in the median overall survival from 6·4 to 10·5 months) in favour of atezolizumab plus cobimetinib (group A) versus regorafenib (group C), and 80% power to detect an overall survival HR of 0·61 in favour of atezolizumab monotherapy (group B) versus regorafenib (group C), both with a two-sided type I error rate of 0·05 controlled by a hierarchical statistical testing procedure (testing atezolizumab monotherapy *vs* regorafenib only if atezolizumab plus cobimetinib *vs* regorafenib was positive). These HRs represent clinically meaningful differences that were potentially achievable based on the phase 1b study results.[19] The overall survival final analysis was triggered when there were about 235 deaths across all three groups (specifically, around 178 deaths for the comparison of group A *vs* group C and around 127 deaths for the comparison of group B *vs* group C). No interim overall survival analyses were planned.

Overall survival and radiologically confirmed progression-free survival and duration of response were analysed using the stratified log-rank test. HRs for overall survival and progression-free survival were estimated using a stratified Cox regression model. The Kaplan-Meier method was used to estimate median survival and duration of response, whereas the Brookmeyer-Crowley method was used to calculate 95% CIs for the medians. The objective response and corresponding 95% CIs for each treatment group were calculated using the Clopper-Pearson method. The efficacy analysis of overall survival, progression-free survival, and objective response was done in all enrolled patients (intention-to-treat [ITT] population). Duration of response was assessed in patients who achieved an objective response. Safety, including summary of adverse events, was assessed in all enrolled patients who received at least one dose of study treatment (safety population).

Statistical analyses were done using SAS, version 9.4. Full details of the statistical analysis plan are in the appendix (p 128).

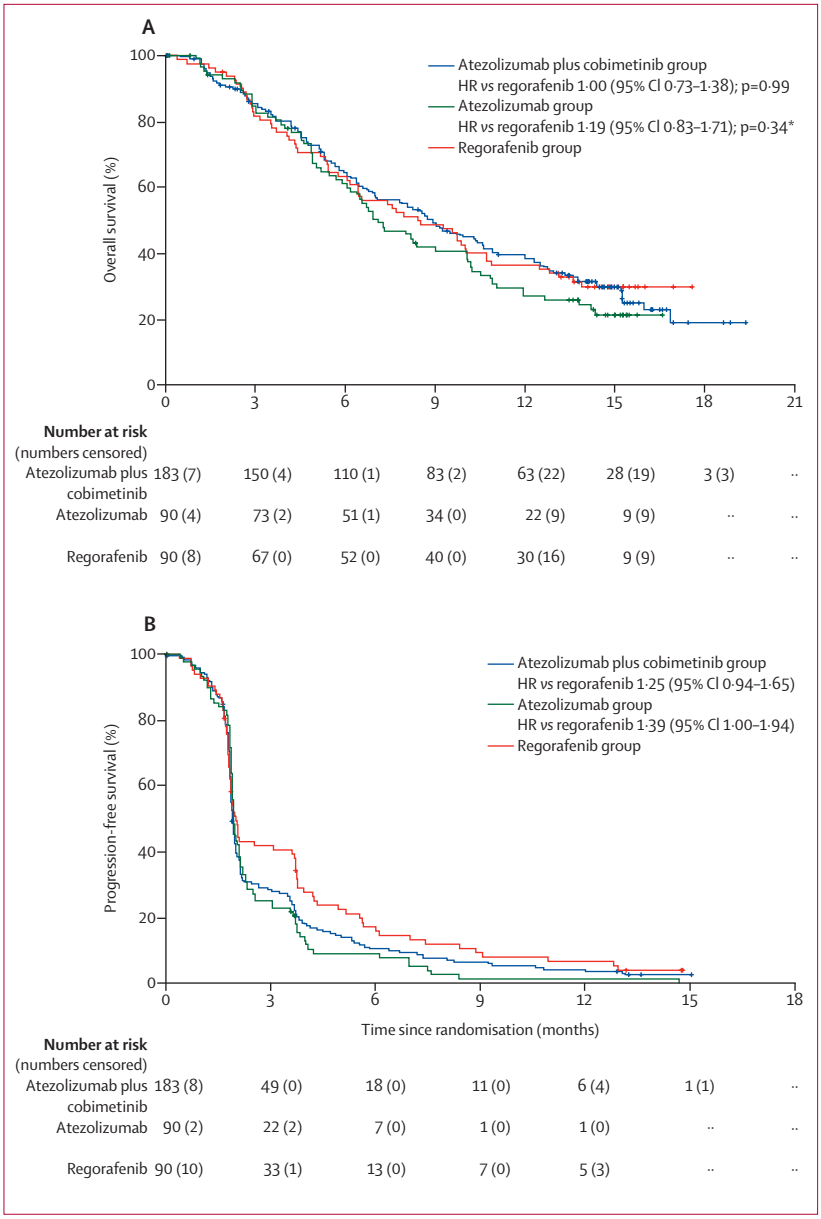


Figure 2: **Efficacy in the intention-to-treat population**
Kaplan-Meier analysis of overall survival (A) and progression-free survival (B) in the intention-to-treat population. HRs are from stratified log-rank tests. HR=hazard ratio. *The p value for the overall survival comparison between atezolizumab versus regorafenib is for descriptive purposes only. No p values are provided for progression-free survival because of the hierarchical testing sequence used and the non-significant overall survival endpoint.

This trial is registered with ClinicalTrials.gov, number NCT02788279.

Role of the funding source

The funder collaborated with the authors on the study design, data collection, data analysis, and data interpretation, and was involved in the writing of the report. YY, IC, AU, and LR had access to the raw data and all authors had final responsibility for the decision to submit for publication.

Results

Between July 27, 2016, and Jan 19, 2017, 484 patients were screened, of whom 121 were excluded because they did not meet inclusion criteria; 363 patients were enrolled (figure 1). 183 patients were randomly assigned to receive atezolizumab plus cobimetinib, 90 to receive atezolizumab monotherapy, and 90 to receive regorafenib. 349 patients received at least one dose of their assigned treatment and were included in the safety population (179 in the atezolizumab plus cobimetinib group, 90 in the atezolizumab group, and 80 in the regorafenib group. Demographic and baseline clinical characteristics were well balanced between study groups (table 1). Numbers of patients with microsatellite-stable or microsatellite-low disease versus those with high microsatellite instability were 170 (93%) of 183 versus three (2%) of 183 in the atezolizumab plus cobimetinib group, 83 (92%) of 90 versus three (3%) of 90 in the atezolizumab monotherapy group, and 80 (89%) of 90 versus none in the regorafenib group. The prevalence of patients with *RAS*-mutant tumours was balanced across the three groups. At least 86% of patients in all three groups had received previous anti-EGFR or anti-VEGF treatment. Similar proportions of patients received subsequent systemic therapies across the three groups, with about 25% of all patients receiving at least one subsequent treatment after study treatment, and eight (2%) of all 363 patients receiving anti-PD-1 or anti-PD-L1 in later lines (appendix p 11).

At data cutoff (March 9, 2018; median follow-up 7·3 months [IQR 3·7–13·6]), 14 months after the last patient was enrolled, 247 patients had died (event-to-patient ratio of 68%); 125 (68%) in the atezolizumab plus cobimetinib group, 65 (72%) in the atezolizumab group, and 57 (63%) in the regorafenib group. The study did not meet its primary endpoint of overall survival, since overall survival did not differ significantly between any of the treatment groups. Median overall survival was 8·87 months (95% CI 7·00–10·61) with atezolizumab plus cobimetinib, 7·10 months (6·05–10·05) with atezolizumab, and 8·51 months (6·41–10·71) with regorafenib (figure 2A), with a stratified HR of 1·00 (95% CI 0·73–1·38; p=0·99) for atezolizumab plus cobimetinib versus regorafenib and 1·19 (0·83–1·71; p=0·34 [p value for descriptive purposes only]) for atezolizumab monotherapy versus regorafenib (figure 2A). Overall survival in the ITT population was 64·7% (57·6–71·8) at 6 months and 38·5% (31·2–45·8) at 12 months with atezolizumab plus cobimetinib, 61·3% (50·9–71·6) and 27·2% (17·6–37·8) with atezolizumab, and 63·5% (53·0–73·9) and 36·6% (26·2–47·0) with regorafenib.

Median progression-free survival was 1·91 months (95% CI 1·87–1·97) in the combination group, 1·94 months (1·91–2·10) in the atezolizumab group, and 2·00 months (1·87–3·61) in the regorafenib group (figure 2B). Similar proportions of patients in the three treatment groups achieved an objective response;

no complete responses were recorded in any of the groups (table 2). Duration of response was also similar between the groups.

Post-hoc exploratory analyses were done to compare survival between the atezolizumab plus cobimetinib group and the atezolizumab group. Both median progression-free survival and median overall survival were similar in both groups (figure 2). 125 (68%) of 183 patients died and 111 (61%) had progression in the combination group, whereas 65 (72%) of 90 patients died and 61 (68%) had progresion in the atezolizumab monotherapy group (table 2).

Subgroup analyses of overall and progression-free survival showed similar results to the primary analyses (figure 3; appendix pp 5–10). Subgroup analyses of secondary efficacy endpoints showed similar proportions of patients with *RAS*-mutated tumours achieving an objective response between the treatment groups (table 2). Partial responses were achieved by two (67%) of three patients with high microsatellite instability in the atezolizumab plus cobimetinib group (duration of response 9·1 months for one patient and 11·8 months for the other) and by one (33%) of three patients with high microsatellite instability in the atezolizumab monotherapy group (duration of response 5·8 months). In a post-hoc subgroup analysis of patients with high PD-L1 expression, the proportion of patients achieving an objective response in this subgroup was higher in both atezolizumab-containing groups than in the control regorafenib monotherapy group (table 2).

Patients had a median treatment duration of 59·0 days (IQR 42·0–112·0) for cobimetinib and 1·9 months (1·4–3·7) for atezolizumab in the combination group, 1·4 months (1·0–3·5) for atezolizumab in the monotherapy group, and 51·5 days (42·5–161·5) for regorafenib. Key safety outcomes and reasons for treatment discontinuation are in the appendix (pp 12–13).

All-cause adverse events were reported in 178 (99%) of 179 patients who received atezolizumab plus cobimetinib, 83 (92%) of 90 who received atezolizumab, and 78 (98%) of 80 treated with regorafenib (table 3); grade 3–4 adverse events were reported in 109 (61%) patients, 28 (31%) patients, and 46 (58%) patients in the three groups, respectively. The most common all-cause grade 3–4 adverse events in the combination group were diarrhoea (20 [11%] of 179), anaemia (ten [6%]), increased blood creatine phosphokinase (12 [7%]), and fatigue (eight [4%]). Serious adverse events were reported in 71 (40%) of 179 patients in the combination group, 15 (17%) of 90 in the atezolizumab group, and 18 (23%) of 80 in the regorafenib group (appendix pp 14–16). Incidence, grade, and nature of adverse events of special interest are in appendix (pp 17–18). 37 (21%) of 179 patients discontinued atezolizumab plus cobimetinib, four (4%) of 90 discontinued atezolizumab monotherapy, and seven (9%) of 80 discontinued regorafenib because of adverse events (appendix pp 12–13). Five (3%) of 179 patients treated with atezolizumab plus cobimetinib had adverse events resulting in death, including two treatment-related sepsis events (table 3), whereas two (3%) of 80 patients had adverse events resulting in death in the regorafenib group, one of which was treatment related (intestinal perforation). No fatal adverse events occurred in the atezolizumab monotherapy group.

	Atezolizumab plus cobimetinib group (n=183)	Atezolizumab group (n=90)	Regorafenib group (n=90)
Intention-to-treat population			
Objective response	5 (3%; 0·9–6·3)	2 (2%; 0·3–7·8)	2 (2%; 0·3–7·8)
Complete response	0	0	0
Partial response	5 (3%)	2 (2%)	2 (2%)
Stable disease	43 (23%)	17 (19%)	29 (32%)
Progressive disease	111 (61%)	61 (68%)	44 (49%)
Missing or non-evaluable	24 (13%)	10 (11%)	15 (17%)
Disease control	48 (26%)	19 (21%)	31 (34%)
Duration of response, months	11·4 (2·7–NE)	4·8 (3·8–5·8)	9·2 (NE–NE)
Ongoing response	2 (1%)	0	1 (1%)
Objective response in subgroups			
RAS mutant	1/99 (1%)	1/49 (2%)	1/49 (2%)
Microsatellite instability high	2/3 (67%)	1/3 (33%)	..
High PD-L1 (≥1% in tumour-infiltrating immune cells)	3/79 (4%)	1/35 (3%)	0/31

Data are n (%), n (%; 95% CI), median (95% CI), or n/N (%). Disease control is defined as partial response and stable disease for at least 6 weeks. PD-L1=programmed cell death ligand 1. NE=not estimable.

Table 2: **Confirmed best overall response and disease control**

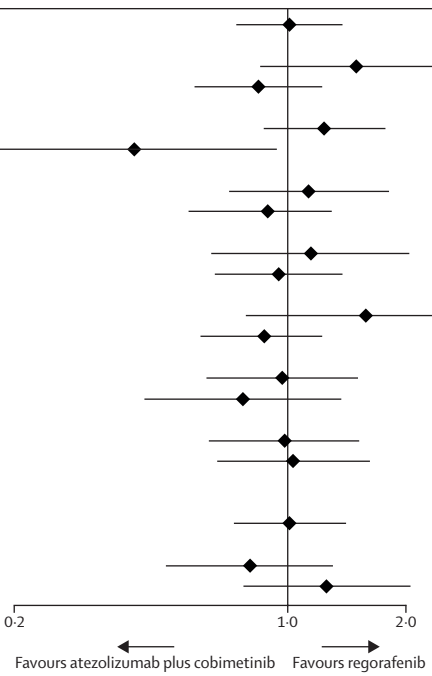
Discussion

The IMblaze370 phase 3 study did not meet its primary endpoint of improvement in overall survival with atezolizumab plus cobimetinib or atezolizumab monotherapy versus regorafenib. The combination also did not improve overall survival compared with regorafenib or atezolizumab alone. Secondary endpoints of progression-free survival, objective response, and duration of response also showed no significant difference across all three groups. Regorafenib, which was chosen as the standard of care because it is approved globally for all patients with metastatic colorectal cancer who have previously received fluorouracil, oxaliplatin, irinotecan, an anti-VEGF therapy, and—if the patient has wildtype *RAS* status—an anti-EGFR therapy. Notably, in this randomised trial, patients in the regorafenib group survived longer than the protocol assumption of 6·4 months, based on the CORRECT study.[3]

Although many patients with metastatic colorectal cancer who have tumours with high microsatellite instability benefit from clinical improvement after immune checkpoint inhibitor therapy, patients with microsatellite-stable tumours do not. This difference in drug sensitivity might be attributed to the unique microenvironments of these tumour types. Tumours with high microsatellite instability exhibit a more active

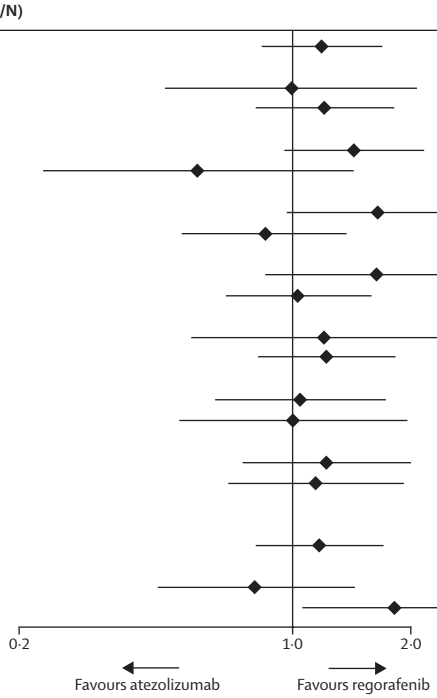
A

	Combination group (n/N)	Regorafenib group (n/N)	Unstratified hazard ratio (95% CI)
Intention-to-treat population	183/273	90/273	1·01 (0·74–1·38)
Age, years			
≥65	58/86	28/86	1·50 (0·85–2·64)
<65	125/187	62/187	0·84 (0·58–1·23)
Race			
White	152/223	71/223	1·24 (0·87–1·78)
Non-white	27/39	12/39	0·40 (0·17–0·94)
ECOG performance status			
0	88/133	45/133	1·13 (0·71–1·82)
1	95/140	45/140	0·85 (0·56–1·30)
Time since diagnosis of first metastasis, months			
<18	56/83	27/83	1·15 (0·64–2·05)
≥18	127/190	63/190	0·94 (0·65–1·38)
Number of previous treatments			
>3	49/70	21/70	1·58 (0·78–3·19)
≤3	134/203	69/203	0·86 (0·60–1·23)
Position of tumour			
Left	104/148	44/148	0·97 (0·62–1·51)
Right	45/72	27/72	0·77 (0·43–1·37)
RAS mutation status			
Mutant	99/148	49/148	0·98 (0·63–1·52)
Wild type	84/125	41/125	1·03 (0·66–1·62)
Microsatellite instability status			
High instability	3/3	0/3	Not evaluable
Low instability or stable	170/250	80/250	1·01 (0·73–1·41)
PD-L1 expression			
High	79/110	31/110	0·80 (0·49–1·31)
Low	84/124	40/124	1·26 (0·77–2·06)



B

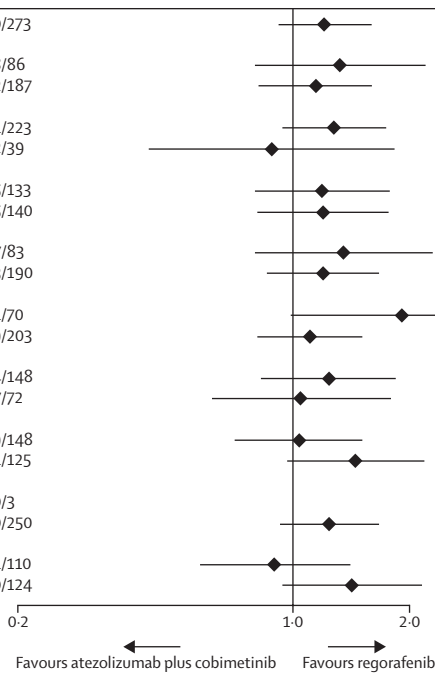
	Atezolizumab group (n/N)	Regorafenib group (n/N)	Unstratified hazard ratio (95% CI)
Intention-to-treat population	90/180	90/180	1·18 (0·83–1·69)
Age, years			
≥65	22/50	28/50	0·99 (0·47–2·07)
<65	68/130	62/130	1·20 (0·80–1·81)
Race			
White	73/144	71/144	1·43 (0·95–2·15)
Non-white	14/26	12/26	0·57 (0·23–1·42)
ECOG performance status			
0	42/87	45/87	1·65 (0·96–2·81)
1	48/93	45/93	0·85 (0·52–1·37)
Time since diagnosis of first metastasis, months			
<18	28/55	27/55	1·63 (0·85–3·15)
≥18	62/125	63/125	1·03 (0·67–1·58)
Number of previous treatments			
>3	26/47	21/47	1·20 (0·55–2·63)
≤3	64/133	69/133	1·22 (0·81–1·82)
Position of tumour			
Left	48/92	44/92	1·04 (0·63–1·72)
Right	21/48	27/48	1·00 (0·51–1·96)
RAS mutation status			
Mutant	49/98	49/98	0·22 (0·74–1·99)
Wild type	41/82	41/82	1·14 (0·68–1·91)
Microsatellite instability status			
High instability	3/3	0/3	Not evaluable
Low instability or stable	83/163	80/163	1·17 (0·80–1·70)
PD-L1 expression			
High	35/66	31/66	0·80 (0·45–1·43)
Low	42/82	40/82	1·81 (1·05–3·13)



(Figure 3 continues on next page)

C

	Combination group (n/N)	Regorafenib group (n/N)	Unstratified hazard ratio (95% CI)
Intention-to-treat population	183/273	90/273	1·21 (0·92–1·60)
Age, years			
≥65	58/86	28/86	1·32 (0·80–2·18)
<65	125/187	62/187	1·15 (0·82–1·60)
Race			
White	152/223	71/223	1·28 (0·94–1·74)
Non-white	27/39	12/39	0·89 (0·43–1·82)
ECOG performance status			
0	88/133	45/133	1·19 (0·80–1·77)
1	95/140	45/140	1·20 (0·81–1·76)
Time since diagnosis of first metastasis, months			
<18	56/83	27/83	1·35 (0·80–2·28)
≥18	127/190	63/190	1·20 (0·86–1·66)
Number of previous treatments			
>3	49/70	21/70	1·91 (0·99–3·68)
≤3	134/203	69/203	1·11 (0·81–1·51)
Position of tumour			
Left	104/148	44/148	1·24 (0·83–1·83)
Right	45/72	27/72	1·05 (0·62–1·79)
RAS mutation status			
Mutant	99/148	49/148	1·04 (0·71–1·51)
Wild type	84/125	41/125	1·45 (0·97–2·17)
Microsatellite instability status			
High instability	3/3	0/3	Not evaluable
Low instability or stable	170/250	80/250	1·24 (0·93–1·66)
PD-L1 expression			
High	79/110	31/110	0·90 (0·58–1·41)
Low	84/124	40/124	1·42 (0·94–2·14)



D

	Atezolizumab group (n/N)	Regorafenib group (n/N)	Unstratified hazard ratio (95% CI)
Intention-to-treat population	90/180	90/180	1·39 (1·00–1·91)
Age, years			
≥65	22/50	28/50	1·12 (0·60–2·11)
<65	68/130	62/130	1·45 (1·00–2·12)
Race			
White	73/144	71/144	1·50 (1·03–2·18)
Non-white	14/26	12/26	1·30 (0·58–2·92)
ECOG performance status			
0	42/87	45/87	2·36 (1·40–3·97)
1	48/93	45/93	0·95 (0·61–1·47)
Time since diagnosis of first metastasis, months			
<18	28/55	27/55	1·87 (1·01–3·47)
≥18	62/125	63/125	1·22 (0·84–1·79)
Number of previous treatments			
>3	26/47	21/47	1·50 (0·75–2·98)
≤3	64/133	69/133	1·36 (0·94–1·97)
Position of tumour			
Left	48/92	44/92	1·50 (0·94–2·39)
Right	21/48	27/48	1·01 (0·54–1·89)
RAS mutation status			
Mutant	49/98	49/98	1·41 (0·89–2·25)
Wild type	41/82	41/82	1·35 (0·85–2·15)
Microsatellite instability status			
High instability	3/3	0/3	Not evaluable
Low instability or stable	83/163	80/163	1·41 (1·00–1·97)
PD-L1 expression			
High	35/66	31/66	0·71 (0·42–1·21)
Low	42/82	40/82	2·17 (1·31–3·59)

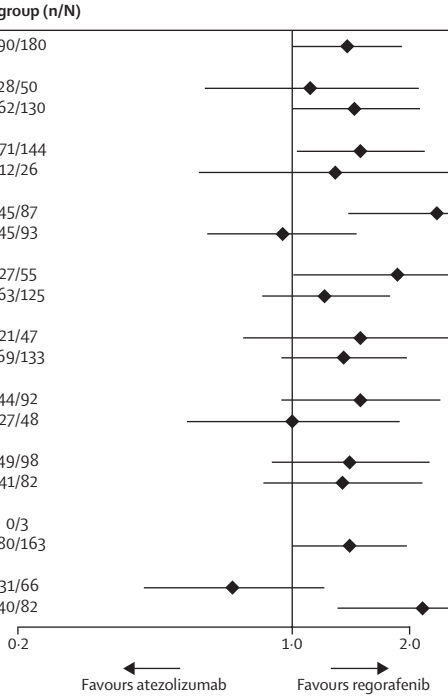


Figure 3: **Efficacy in subgroups**
Subgroup analysis of overall survival in the combination group versus the regorafenib group (A) and the atezolizumab monotherapy group versus the regorafenib group (B). Subgroup analysis of progression-free survival in the combination group versus the regorafenib group (C) and the atezolizumab monotherapy group versus the regorafenib group (D). ECOG=Eastern Cooperative Oncology Group. MET=metastatic. MSI=microsatellite instability. NE=not evaluable. PD-L1=programmed cell death ligand 1.

	Atezolizumab plus cobimetinib group (n=179)			Atezolizumab group (n=90)			Regorafenib group (n=80)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
Any event	64 (36%)	92 (51%)	17 (9%)	55 (61%)	25 (28%)	3 (3%)	30 (38%)	39 (49%)	7 (9%)
Diarrhoea	97 (54%)	20 (11%)	0	16 (18%)	1 (1%)	0	25 (31%)	5 (6%)	0
Rash	76 (42%)	7 (4%)	0	7 (8%)	1 (1%)	0	17 (21%)	2 (3%)	0
Nausea	64 (36%)	2 (1%)	0	19 (21%)	0	0	11 (14%)	0	0
Fatigue	56 (31%)	8 (4%)	0	18 (20%)	5 (6%)	0	30 (38%)	7 (9%)	0
Pyrexia	52 (29%)	7 (4%)	0	14 (16%)	0	0	20 (25%)	0	0
Vomiting	50 (28%)	1 (1%)	0	13 (14%)	0	0	8 (10%)	0	0
Decreased appetite	46 (26%)	2 (1%)	0	22 (24%)	0	0	31 (39%)	2 (3%)	0
Dermatitis acneiform	44 (25%)	2 (1%)	0	2 (2%)	0	0	2 (3%)	0	0
Asthenia	30 (17%)	7 (4%)	0	10 (11%)	2 (2%)	0	16 (20%)	1 (1%)	0
Constipation	32 (18%)	1 (1%)	0	11 (12%)	0	0	17 (21%)	0	0
Dyspnoea	31 (17%)	2 (1%)	0	12 (13%)	0	0	12 (15%)	1 (1%)	0
Cough	29 (16%)	0	0	12 (13%)	0	0	7 (9%)	0	0
Abdominal pain	26 (15%)	2 (1%)	0	10 (11%)	4 (4%)	0	21 (26%)	3 (4%)	0
Anaemia	18 (10%)	9 (5%)	1 (1%)	5 (6%)	0	0	6 (8%)	2 (3%)	0
Oedema peripheral	25 (14%)	2 (1%)	0	8 (9%)	0	0	3 (4%)	0	0
Blood creatine phosphokinase increased	11 (6%)	6 (3%)	6 (3%)	0	0	0	1 (1%)	0	1 (1%)
Pruritus	22 (12%)	0	0	3 (3%)	0	0	2 (3%)	0	0
Stomatitis	18 (10%)	0	0	0	0	0	13 (16%)	0	0
Back pain	15 (8%)	0	0	11 (12%)	3 (3%)	0	8 (10%)	0	0
Headache	14 (8%)	1 (1%)	0	11 (12%)	0	0	10 (13%)	0	0
Blood alkaline phosphatase increased	8 (4%)	5 (3%)	0	6 (7%)	2 (2%)	0	1 (1%)	0	0
Hypokalaemia	11 (6%)	1 (1%)	0	0	1 (1%)	0	1 (1%)	2 (3%)	0
Hypophosphataemia	4 (2%)	6 (3%)	0	1 (1%)	1 (1%)	1 (1%)	3 (4%)	3 (4%)	1 (1%)
Hypertension	7 (4%)	2 (1%)	0	1 (1%)	3 (3%)	0	15 (19%)	10 (13%)	0
Weight decreased	8 (4%)	0	0	7 (8%)	0	0	17 (21%)	0	0
Hypocalcaemia	7 (4%)	0	0	0	2 (2%)	0	5 (6%)	0	0
Sepsis	1 (1%)	0	2 (1%)	0	0	0	0	0	2 (3%)
Palmar–plantar erythrodysaesthesia syndrome	3 (2%)	0	0	1 (1%)	0	0	33 (41%)	9 (11%)	0
Blood bilirubin increased	1 (1%)	2 (1%)	0	0	2 (2%)	0	2 (3%)	1 (1%)	1 (1%)
Hyperglycaemia	1 (1%)	0	0	0	0	0	1 (1%)	2 (3%)	0
Dysphonia	0	0	0	1 (1%)	0	0	19 (24%)	0	0
Autoimmune hepatitis	0	0	0	0	2 (2%)	0	0	0	0

Data are n (%). The table lists grade 1–2 events that occurred in ≥10% of patients in any treatment group and grade 3 and 4 events that occurred in ≥2% of patients in any treatment group. All grade 3 and 4 events are listed in the appendix pp 19–22. Five grade 5 events were reported in the atezolizumab plus cobimetinib group (two sepsis, one general physical health deterioration, one acute kidney injury, and one cerebrovascular accident). No grade 5 events were reported in the atezolizumab group. Two grade 5 events were reported in the regorafenib group (one intestinal perforation and one unattributed to a cause).

Table 3: **Patients with all-cause adverse events**

immune microenvironment than microsatellite-stable tumours because of neoantigens arising from the hypermutated state of the tumour cells.[7,21–23] By contrast, microsatellite-stable tumours have little to no response to immunotherapy, in part because of reduced expression of checkpoint proteins, including PD-L1, which provide a target for cancer immunotherapy.[21,24] In patients with metastatic colorectal cancer being treated in the third-line setting, where overall survival is less than 6 months, combination treatment might be a strategy to overcome this treatment resistance regardless of microsatellite instability status.

Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, have shown clinical benefit in

metastatic colorectal cancer with high microsatellite instability in both a monotherapy and combination setting with ipilimumab, but not in microsatellite-stable cohorts, including those with high PD-L1 expression.[7,8,25,26] In a pivotal phase 2 study,[7] the importance of mismatch repair status for prediction of clinical benefit from immune checkpoint blockade with pembrolizumab was reported. In patients with colorectal cancer without mismatch repair, 40% achieved an objective response and 78% were alive without disease progression at 20 weeks compared with those with proficient mismatch repair, of whom none achieved an objective response and 11% achieved progression-free survival at 20 weeks.[7] Results from the CheckMate-142 study[26] reported that 55% of patients with metastatic colorectal cancer with high microsatellite instability who were treated with the combination of nivolumab plus ipilimumab achieved an objective response.[26] By contrast, 4% of patients with PD-L1-positive metastatic colorectal cancer had an objective response (one of 23 patients, and that patient had high microsatellite instability), with a median progression-free survival of 1·8 months (95% CI 1·4–1·9) and median overall survival of 5·3 months (2·2–11·0).[27] Because of the better efficacy seen in patients with metastatic colorectal cancer with high microsatellite instability and absence of efficacy seen in PD-L1-positive patients, the IMblaze370 study capped patients with high microsatellite instability at 5%, which is the prevalence in this patient population, and did not enrich enrolment for PD-L1-positive patients.

Beneficial immunomodulatory effects due to MEK inhibition have been shown in models of colorectal cancer, melanoma, and breast cancer. In preclinical models, MEK inhibitors combined with anti-PD-1 or anti-CTLA4 antibodies provide additional activity over each individual drug.[12,28] In mouse models, treatment with cobimetinib impedes tumour growth while promoting the effector phenotype and longevity of tumour-infiltrating CD8+ T cells. Treatment with the combination of a MEK inhibitor and anti-PD-L1 drug resulted in synergistic inhibition of tumour growth, including durable responses and, in some instances, complete regression.[13] A phase 1b–2 study was initiated to assess the combination of cobimetinib and atezolizumab in metastatic colorectal cancer and had promising results,[19,20] and thus this phase 3 trial was initiated.

Despite hypotheses supported by preclinical and clinical data, in IMblaze370 we did not observe clinically meaningful differences in progression-free survival and overall survival in patients with microsatellite-stable metastatic colorectal cancer by clinical or biomarker subgroup between the three treatment groups, including patients with extended *RAS* mutation or high PD-L1 expression. The immunomodulatory effects of the addition of a MEK inhibitor to an anti-PD-L1 might have not been adequate to overcome the immune resistance in microsatellite-stable metastatic colorectal cancer, a tumour type known for its non-inflamed, non-immunogenic phenotype. Although too few patients with high microsatellite instability were included to draw firm conclusions, some clinical activity with the combination treatment was observed in this subgroup. Responses to atezolizumab monotherapy seem to be consistent with published data for other PD-L1 or PD-1 inhibitors in microsatellite-stable disease.[7,25,26] Safety in the atezolizumab plus cobimetinib group was consistent with the known safety profiles of the individual drugs, with no new signals reported.

Metastatic colorectal cancer has a heterogenous genomic landscape, characterised by multiple genetic alterations and diverse molecular phenotypes. Patients having third-line treatment are those in whom multiple therapeutic regimens have failed or become non-viable because of intolerance.

Despite the rationale supported by preclinical data, our results suggest that dual inhibition of the PD-L1 immune checkpoint and MAPK-mediated immune suppression is insufficient to generate antitumour immune responses in immune-excluded tumours, such as microsatellite-stable metastatic colorectal cancer. This failure to generate a response could be because of alternative mechanisms to bypass the inhibition of the MAPK pathway by a MEK inhibitor in microsatellite-stable metastatic colorectal cancer. The combination of a selective *BRAF* inhibitor (dabrafenib) and a selective MEK inhibitor (trametinib) did not result in the same extent of MAPK signalling inhibition in tumour samples from patients with metastatic colorectal cancer with $BRAF^{V600}$ mutations as it did for patients with this same mutation in melanoma.[29] Overall, the limitations of the IMblaze370 trial were as follows: this study was not designed to assess the combination in different biomarker subsets, which might have been more sensitive to this combination; and the study population of patients with chemorefractory metastatic colorectal cancer is a very difficult-to-treat population.

The overall safety of the atezolizumab plus cobimetinib combination is consistent with the toxicity profile of the two single drugs, and no unexpected new safety signals or increased frequency of the known safety signals of the single drugs were detected. The two drugs have very distinct adverse event profiles, and overlapping adverse events such as diarrhoea or colitis do not seem to be increased in frequency or severity by the combination. The atezolizumab plus cobimetinib combination did have more treatment-related adverse events, including grade 3 or worse and serious adverse events, than atezolizumab monotherapy, but were consistent with those seen with the vemurafenib plus cobimetinib combination in *BRAF*-mutant melanoma, the setting in which cobimetinib is approved.[30]

Overall, in this trial, no improvement was observed in patients with microsatellite-stable metastatic colorectal cancer receiving atezolizumab plus cobimetinib over

those treated with regorafenib. These results highlight the strong biological differences between microsatellite-stable tumours and those with high microsatellite instability, underscoring the divergent treatment needs between these two disease types. Other immunotherapy combinations are worth exploring in patients with metastatic colorectal cancer, despite the negative results of the IMblaze370 study, because a high unmet need remains for patients with chemorefractory metastatic colorectal cancer and the potential of immunotherapy has not been demonstrated with single drugs.

Contributors

CE, NHS, IC, AU, and FC contributed to the design of the study. MDB and AF contributed to data collection. CE, TWK, JB, GA, NCT, MK, NHS, YY, IC, AU, LR, and FC contributed to data collection, data analysis, and interpretation. IC contributed to statistical analysis. All authors contributed to the writing of the manuscript, approved the final version, and are accountable for all aspects of the report. All authors verify that this study was conducted per protocol and vouch for data accuracy and completeness.

Declaration of interests

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Data sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform and further details on Roche's criteria for eligible studies are available. Further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents are also available online.

For the **data request platform** and details on **Roche's criteria** see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx

For **Roche's Global Policy on the Sharing of Clinical Information** see http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm

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References

1 Goel G. Evolution of regorafenib from bench to bedside in colorectal cancer: is it an attractive option or merely a "me too" drug? *Cancer Manag Res* 2018; **10:** 425–37.
2 Vogel A, Hofheinz RD, Kubicka S, Arnold D. Treatment decisions in metastatic colorectal cancer—beyond first and second line combination therapies. *Cancer Treat Rev* 2017; **59:** 54–60.
3 Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381:** 303–12.
4 Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015; **372:** 1909–19.
5 Giampieri R, Prete MD, Prochilo T, et al. Off-target effects and clinical outcome in metastatic colorectal cancer patients receiving regorafenib: the TRIBUTE analysis. *Sci Rep* 2017; **7:** 45703.
6 Weinberg BA, Marshall JL, Salem ME. Trifluridine/tipiracil and regorafenib: new weapons in the war against metastatic colorectal cancer. *Clin Adv Hematol Oncol* 2016; **14:** 630–38.
7 Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015; **372:** 2509–20.
8 Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol* 2017; **18:** 1182–91.
9 Koopman M, Kortman GA, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. *Br J Cancer* 2009; **100:** 266–73.
10 Gelsomino F, Barbolini M, Spallanzani A, Pugliese G, Cascinu S. The evolving role of microsatellite instability in colorectal cancer: a review. *Cancer Treat Rev* 2016; **51:** 19–26.
11 Fujiyoshi K, Yamaguchi T, Kakuta M, et al. Predictive model for high-frequency microsatellite instability in colorectal cancer patients over 50 years of age. *Cancer Med* 2017; **6:** 1255–63.
12 Liu L, Mayes PA, Eastman S, et al. The BRAF and MEK inhibitors dabrafenib and trametinib: effects on immune function and in combination with immunomodulatory antibodies targeting PD-1, PD-L1, and CTLA-4. *Clin Cancer Res* 2015; **21:** 1639–51.
13 Ebert PJR, Cheung J, Yang Y, et al. MAP kinase inhibition promotes T cell and anti-tumor activity in combination with PD-L1 checkpoint blockade. *Immunity* 2016; **44:** 609–21.
14 Inoue M, Mimura K, Izawa S, et al. Expression of MHC class I on breast cancer cells correlates inversely with HER2 expression. *Oncoimmunology* 2012; **1:** 1104–10.
15 Rosen LS, LoRusso P, Ma WW, et al. A first-in-human phase I study to evaluate the MEK1/2 inhibitor, cobimetinib, administered daily in patients with advanced solid tumors. *Invest New Drugs* 2016; **34:** 604–13.
16 Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res* 2012; **18:** 6580–87.
17 Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013; **39:** 1–10.
18 Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014; **515:** 563–67.
19 Bendell J, Kim T, Goh B, et al. Clinical activity and safety of cobimetinib (cobi) and atezolizumab in colorectal cancer (CRC). *Proc Am Soc Clin Oncol* 2016; **34** (suppl): 3502 (abstr).
20 Bendell J, Bang YJ, Chee CE, et al. A phase Ib study of safety and clinical activity of atezolizumab (A) and cobimetinib (C) in patients (pts) with metastatic colorectal cancer (mCRC). 2018 Gastrointestinal Cancer Symposium; San Francisco, CA; Jan 18–20, 2018. 560 (abstr).

21 Llosa NJ, Cruise M, Tam A, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. *Cancer Discov* 2015; **5:** 43–51.

22 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366:** 2443–54.

23 Yamamoto H, Imai K. Microsatellite instability: an update. *Arch Toxicol* 2015; **89:** 899–921.

24 Gatalica Z, Snyder C, Maney T, et al. Programmed cell death 1 (PD-1) and its ligand (PD-L1) in common cancers and their correlation with molecular cancer type. *Cancer Epidemiol Biomarkers Prev* 2014; **23:** 2965–70.

25 Le DT, Durham JN, Smith KN, et al. Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357:** 409–13.

26 Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol* 2018; **36:** 773–79.

27 O'Neil BH, Wallmark JM, Lorente D, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma. *PLoS One* 2017; **12:** e0189848.

28 Loi S, Dushyanthen S, Beavis PA, et al. RAS/MAPK activation is associated with reduced tumor-infiltrating lymphocytes in triple-negative breast cancer: therapeutic cooperation between MEK and PD-1/PD-L1 immune checkpoint inhibitors. *Clin Cancer Res* 2016; **22:** 1499–509.

29 Corcoran RB, Atreya CE, Falchook GS, et al. Combined BRAF and MEK inhibition with dabrafenib and trametinib in BRAF V600-mutant colorectal cancer. *J Clin Oncol* 2015; **33:** 4023–31.

30 Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma, *N Engl J Med* 2014; **271:** 1867–76.