Overall survival with first-line atezolizumab in combination with vemurafenib and cobimetinib in *BRAF*^{V600} mutation-positive advanced melanoma (IMspire150): second interim analysis of a multicentre, randomised, phase 3 study

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Summary

Background Primary analysis of the phase 3 IMspire150 study showed improved investigator-assessed progression-free survival with first-line atezolizumab, vemurafenib, and cobimetinib (atezolizumab group) versus placebo, vemurafenib, and cobimetinib (control group) in patients with *BRAF*^{V600} mutation-positive melanoma. With a median follow-up of 18·9 months (IQR 10·4–23·8) at the primary analysis, overall survival data were immature. Here, we report the results from the second, prespecified, interim overall survival analysis.

Methods The multicentre, double-blind, placebo-controlled, randomised, phase 3 IMspire150 study was done at 108 academic and community hospitals in 20 countries. Patients aged 18 years or older with previously untreated unresectable stage IIIc or stage IV melanoma and an Eastern Cooperative Oncology Group performance status of 0 or 1 were eligible for inclusion. Patients were randomly assigned (1:1) to receive either atezolizumab (840 mg intravenously on day 1 and 15) or placebo plus vemurafenib (960 mg or 720 mg twice daily orally) and cobimetinib (60 mg once daily orally; 21 days on and 7 days off) in 28-day cycles. Atezolizumab and placebo were added to treatment regimens from cycle two onwards. Randomisation was done centrally (Durham, NC, USA) based on a permuted block randomisation scheme (block size of 4) using an interactive web-based response system and was stratified by geographical region and baseline lactate dehydrogenase concentration. Overall survival was analysed in the intention-to-treat population and safety was analysed in all patients who received at least one dose of study drug according to actual treatment received. The primary endpoint was investigator-assessed progression-free survival, which was previously reported. Here, we report the second, prespecified, interim overall survival analysis, which was planned after about 270 overall survival events had occurred. The trial is ongoing, but is no longer enrolling patients, and it is registered with ClinicalTrials.gov, NCT02908672.

Findings Between Jan 13, 2017, and April 26, 2018, 514 patients (median age 54 years [IQR 43–63]; 299 [58%] men and 215 [42%] women) were enrolled in the trial and randomly assigned to the atezolizumab group (256 [50%] patients) or the control group (258 [50%] patients). At the data cutoff (Sept 8, 2021), 273 patients had died (126 in the atezolizumab group and 147 in the control group). Median follow-up was 29·1 months (IQR 10·1–45·4) for the atezolizumab group versus 22·8 months (10·6–44·1) for the control group. Median overall survival was 39·0 months (95% CI 29·9–not estimable) in the atezolizumab group versus 25·8 months (22·0–34·6) in the control group (HR 0·84 [95% CI 0·66–1·06]; p=0·14). The most common adverse events of any grade in the atezolizumab group were blood creatine phosphokinase increased (123 [53%] of 231 patients), diarrhoea (116 [50%]), and pyrexia (115 [50%]). The most common adverse events of any grade in the control group were diarrhoea (157 [56%] of 280 patients), blood creatine phosphokinase increased (135 [48%]), and rash (119 [43%]). The most common grade 3–4 adverse events were increased lipase (54 [23%] of 231 patients in the atezolizumab group *vs* 62 [22%] of 280 patients in the control group), increased blood creatine phosphokinase (51 [22%] *vs* 50 [18%]), and increased alanine aminotransferase (32 [14%] *vs* 26 [9%]). Serious adverse events were reported in 112 (48%) patients in the atezolizumab group and 117 (42%) patients in the control group. Grade 5 adverse events were reported in eight (3%) patients in the atezolizumab group versus six (2%) patients in the control group. Two grade 5 adverse events (hepatitis fulminant and hepatic failure) in the atezolizumab group were considered to be associated with the triplet combination, and one event in the control group (pulmonary haemorrhage) was considered to be associated with cobimetinib.

Interpretation Additional follow-up of the IMspire150 trial showed that overall survival was not significantly improved with atezolizumab, vemurafenib, and cobimetinib compared with placebo, vemurafenib, and cobimetinib in patients with *BRAF*^{V600} mutation-positive advanced melanoma. Results of the final analysis are awaited to establish whether a significant improvement in overall survival can be achieved with long-term treatment with this triplet combination versus vemurafenib plus cobimetinib.

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Introduction

Several immunotherapies and targeted therapies, including cytotoxic T-lymphocyte antigen 4 inhibitors, PD-1 inhibitors, BRAF inhibitors, and MEK inhibitors, have been approved for the management of patients with *BRAF* mutation-positive metastatic melanoma.[1] Although targeted therapies have led to high response rates, duration of response is short; by contrast, immunotherapies have led to relatively low response rates, but these responses were more durable.[2] Triplet combination with immunotherapy plus a BRAF inhibitor and a MEK inhibitor has the potential to deliver high response rates induced by combined BRAF and MEK inhibition[3] along with longer durability of response provided by immune checkpoint inhibition.[4] These complementary response kinetics suggest that combining immunotherapy with targeted therapy might improve the duration of response and extend overall survival.[5,6] Preclinical and translational data have shown immunological changes in the tumour microenvironment with BRAF and MEK inhibition that might sensitise tumours to immune checkpoint inhibition, including upregulation of antigen expression, upregulation of PD-L1 expression, and increased tumour T-cell infiltration.[5,7,8] Results from early-phase studies have also shown clinical activity and a manageable safety profile with immunotherapy plus targeted therapy combinations.[9–12]

Atezolizumab is a PD-L1 inhibitor with activity in advanced melanoma.[13] Combination treatment with vemurafenib, a BRAF inhibitor, and cobimetinib, a MEK inhibitor, is approved for the treatment of patients with unresectable or metastatic melanoma with *BRAF* Val600Glu or Val600Lys ($BRAF^{V600}$) mutations based on the outcomes of the phase 3 coBRIM trial.[14–16] The randomised, multicentre, phase 3 IMspire150 study compared the efficacy and safety of a triplet combination of atezolizumab, vemurafenib, and cobimetinib versus placebo, vemurafenib, and cobimetinib in patients with previously untreated $BRAF^{V600}$ mutation-positive advanced or metastatic melanoma.[17] Primary analysis of the IMspire150 trial showed significantly improved investigator-assessed progression-free survival in the atezolizumab, vemurafenib, and cobimetinib group versus the placebo, vemurafenib, and cobimetinib group (hazard ratio [HR] 0·78 [95% CI 0·63–0·97]; p=0·025).[17] These results led to approval of this triplet combination for treatment of patients with $BRAF^{V600}$ mutation-positive advanced melanoma in the USA,[8] Russia, and Israel, and for patients with $BRAF^{V600E}$ mutation-positive advanced melanoma in Switzerland.

With a median follow-up of 18·9 months (IQR 10·4–23·8) at primary analysis, overall survival data were immature; interim overall survival analysis at the time of

Research in context

Evidence before this study

We searched PubMed from inception of the database to July 4, 2022, for clinical trials using the search terms "melanoma" AND "immune checkpoint inhibitors" AND "MEK inhibitors OR BRAF inhibitors" with no language restrictions. Two trials were identified that studied triplet combination with BRAF and MEK inhibitors plus immune checkpoint inhibitors. The randomised, double-blind, phase 2 KEYNOTE-022 study assessed the safety and efficacy of pembrolizumab, dabrafenib, and trametinib in patients with previously untreated $BRAF^{V600E/K}$-mutated advanced melanoma, while the randomised, multicentre, phase 3 COMBI-i trial evaluated the safety and efficacy of spartalizumab plus dabrafenib and trametinib versus dabrafenib and trametinib in patients with previously untreated unresectable or metastatic $BRAF^{V600}$ mutation-positive melanoma. Neither study showed significantly longer overall survival in the immune checkpoint inhibitor groups. The IMspire150 trial aimed to establish the safety and efficacy of atezolizumab, vemurafenib, and cobimetinib versus placebo, vemurafenib, and cobimetinib in patients with previously untreated $BRAF^{V600}$ mutation-positive advanced or metastatic melanoma.

Added value of this study

The results of this second interim analysis of IMspire150 showed that although overall survival was numerically longer in patients treated with the triplet combination versus vemurafenib plus cobimetinib, no significant difference in overall survival was observed between the two treatment groups. Improvements in progression-free survival and duration of response were maintained with additional follow-up, and no new safety signals were identified.

Implications of all the available evidence

These results suggest that patients with previously untreated $BRAF^{V600}$ mutation-positive advanced melanoma might achieve durable clinical benefit with atezolizumab, vemurafenib, and cobimetinib. The triplet combination has the potential to overcome the limitations of up-front treatment with targeted therapy or immune checkpoint inhibition alone, delivering high response rates induced by targeted therapy along with durability of clinical benefit provided by the addition of immune checkpoint inhibition. Evidence from the KEYNOTE-022 trial suggests that long-term follow-up is needed to establish whether a significant improvement in overall survival can be achieved with this triplet combination therapy versus a BRAF inhibitor plus MEK inhibitor doublet.

the primary analysis showed a numerically but not statistically significantly longer overall survival in the atezolizumab group (estimated 2-year overall survival rate 60%) compared with the control group (53%).[17] We present results from the second prespecified interim overall survival analysis of the IMspire150 trial.

Methods

Study design and participants

The IMspire150 trial is an ongoing, multicentre, double-blind, placebo-controlled, randomised, phase 3 study done in 108 academic and community hospitals in 20 countries (appendix pp 2–3). Detailed methods of IMspire150 have been previously reported[17] and the protocol is available in the appendix. Briefly, eligible patients were aged 18 years or older who had previously untreated, histologically confirmed stage IV or unresectable stage IIIc melanoma, as defined by the American Joint Committee on Cancer (7th revised edition),[18] had *BRAF*^{V600} mutation-positive tumours by a locally approved test, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, had measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria, and had a life expectancy of 18 weeks or more. The study excluded patients with other active malignancies, untreated or actively progressing brain metastases, or a history of serious autoimmune disease. Eligibility was assessed using adequate haematological and end-organ function tests (absolute neutrophil count ≥1·5×10^9/L, white blood cell count ≥2·5×10^9/L, lymphocyte count ≥0·5×10^9/L, platelet count ≥100×10^9/L, haemoglobin concentration ≥90 g/L, serum albumin concentration ≥25 g/L, total bilirubin concentration ≤1·5 times the upper limit of normal [ULN], alanine aminotransferase and aspartate aminotransferase concentrations ≤2·0 times the ULN, amylase and lipase concentrations ≤1·5 times the ULN, alkaline phosphatase concentration ≤2·5 times the ULN [≤5·0 times the ULN for patients with liver or bone metastases], serum creatinine concentration ≤1·5 times the ULN or creatinine clearance ≥40 mL/min, and international normalised ratio or activated partial thromboplastin time ≤1·5 times the ULN [patients not receiving anticoagulation] or stable during 28 days before initiation of study treatment in patients receiving stable anticoagulation). Patients were permitted to use oral contraceptives, hormone replacement therapy, prophylactic or therapeutic anticoagulation therapy, inactivated influenza vaccinations, megestrol administered as an appetite stimulant, inhaled corticosteroids, mineralocorticoids, low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency and pain medications per standard practice. Prohibited therapies included concomitant use of approved or experimental cancer treatment, investigational therapy, prophylactic antiemetics, antidiarrhoea medication, haematopoietic growth factors, antiarrhythmic drugs, medications with a risk of torsades de pointes, and acetaminophen. Additional details on permitted and prohibited therapies during the study are in the protocol (appendix).

The study protocol was approved by an independent ethics committee at each study site. The study was done in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. All amendments to the study protocol affecting trial recruitment or conduct were approved by the institutional review board or independent ethics committee before implementation. All patients provided written, informed consent before participation. Safety data reported during the study were continuously monitored by an independent data and safety monitoring committee.

See Online for appendix

Randomisation and masking

Patients were randomly assigned (1:1) to receive atezolizumab, vemurafenib, and cobimetinib (atezolizumab group) or placebo, vemurafenib, and cobimetinib (control group) in 28-day cycles based on a permuted block randomisation scheme (block size of 4). Randomisation was done centrally using an interactive web-based response system, which assigned patients to treatment groups on the basis of the allocation sequence, generated by Parexel (Durham, NC, USA). Participants were enrolled by the study investigators. Randomisation was stratified by geographical region (Europe *vs* North America *vs* other) and baseline lactate dehydrogenase concentration (more than the ULN *vs* equal to or less than the ULN). Investigators, patients, and the sponsor were masked to treatment assignment. Blinding was ensured from cycle one onwards by using four vemurafenib 240 mg tablets in the control group and three vemurafenib 240 mg tablets and one placebo tablet in the atezolizumab group.

Procedures

As previously described,[17] in cycle one, all patients received oral cobimetinib 60 mg once daily plus oral vemurafenib 960 mg twice daily for 21 days then vemurafenib 720 mg twice daily (atezolizumab group) or 960 mg twice daily (control group) for 7 days. Atezolizumab or placebo was added from cycle 2 onwards. Patients in the atezolizumab group received intravenous atezolizumab 840 mg (day 1 and 15), once-daily cobimetinib 60 mg (21 days on and 7 days off), and twice-daily vemurafenib 720 mg; patients in the control group received intravenous placebo (day 1 and 15), once-daily cobimetinib 60 mg (21 days on and 7 days off), and twice-daily vemurafenib 960 mg. The main criteria for patient discontinuation included withdrawal of consent by the patient, patient non-compliance (not complying with protocol requirements as determined by the investigator or sponsor), study termination or site closure, and development of a contraindication to atezolizumab therapy during cycle 1 that was not present at randomisation. Patients with

contraindication to atezolizumab during cycle 1 were allowed to continue cobimetinib and vemurafenib (960 mg twice daily) and were eligible to receive atezolizumab if their condition resolved or improved at a later date. Dose reductions or interruptions were allowed for cobimetinib and vemurafenib for the management of adverse events as outlined in the protocol; only treatment interruptions were allowed for atezolizumab.

Tumour assessments (contrast-enhanced CT or MRI scans) were done every 7–9 weeks for the first 24 months and every 11–13 weeks thereafter until investigator-determined disease progression or death, whichever occurred first. Adverse events were monitored from initiation of study treatment until 30 days after the last dose (90 days for serious adverse events) or until initiation of subsequent anticancer treatment, whichever occurred first, and were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Haematology was assessed at screening, day 1 of cycle 1 and each subsequent treatment cycle, and at treatment discontinuation; serum or plasma chemistry was assessed at screening, day 1 and 15 of cycle 1, days 1, 8, 15, and 22 of subsequent treatment cycles, and treatment discontinuation; thyroid function tests were assessed at screening, day 1 of each treatment cycle, and at treatment discontinuation. Additional details on laboratory monitoring are available in the protocol.

Outcomes

The primary outcome was investigator-assessed progression-free survival, defined as time from randomisation until first occurrence of disease progression according to RECIST version 1.1, or death from any cause. Secondary outcomes were overall survival, objective response rate, duration of response, independent review committee-assessed progression-free survival, safety, and time to deterioration in global health status and physical functioning as determined by the European Organization for the Research and Treatment of Cancer Quality of Life 30 item-questionnaire (EORTC QLQ-C30). All patients were closely monitored for safety and tolerability throughout the study. Independent review committee-assessed progression-free survival, and time to deterioration in global health status and physical functioning as determined by EORTC QLQ-C30 are not reported in this Article. Progression-free survival by independent review committee assessment was done for the primary analysis only and was previously reported;[17] time to deterioration in global health status and physical functioning will be reported in a separate quality-of-life-focused manuscript.

Overall survival was defined as time from randomisation until death from any cause. Objective response rate was defined as complete response or partial response confirmed on two consecutive occasions at least 4 weeks apart, as determined by the investigator according to RECIST version 1.1. Duration of response was defined as time from first occurrence of documented objective response until disease progression, as determined by the investigator according to RECIST version 1.1, or death from any cause.

Statistical analysis

The study sample size was calculated based on the primary endpoint of progression-free survival as described previously.[17] The second interim overall survival analysis was planned after approximately 270 overall survival events were recorded, which was projected to have a minimally detectable difference of a HR of 0·74 with a p value boundary of 0·014. The type I error for the overall survival analysis was 0·05 (two-sided).

Overall survival was analysed in the intention-to-treat population, which included all patients randomly assigned to study treatment. Objective response was analysed in all evaluable patients; patients were classified as not evaluable for objective response rate if all post-baseline overall response assessments were reported as not evaluable, or if stable disease, non-complete response, or non-progressive disease assessment was reported within 42 days of baseline. Safety was analysed in the safety population, which included all randomly assigned patients who received at least one dose of study drug grouped by actual treatment received.

Progression-free survival and overall survival were estimated using the Kaplan-Meier method. Prespecified landmark overall survival rates at 24 months and post-hoc landmark overall survival rates at 12 months and progression-free survival rates at 6, 12, and 18 months were descriptive and estimated using the Kaplan-Meier approach, with 95% CIs calculated using the standard error derived from Greenwood's formula. Patients without disease progression or death were censored at the last tumour assessment date. HRs for progression-free survival and overall survival were estimated using a stratified Cox model and reported with two-sided 95% CIs. The proportional hazards assumption was assessed with Schoenfeld residuals. Post-hoc exploratory analyses were done to evaluate overall survival across different patient subgroups. Objective response rates were calculated as the proportion of patients with complete or partial response with 95% Clopper-Pearson CIs. Duration of response was estimated using the Kaplan-Meier method. Safety was summarised descriptively.

All analyses were done using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT02908672.

Role of the funding source

The study was sponsored by F Hoffmann-La Roche and was designed by the sponsor in collaboration with members of the steering committee (PAA, CR, KL, GAM, and RG). The sponsor had no role in data collection; data were collected by investigators and their research teams.

The sponsor confirmed accuracy of the data, compiled them for analysis, and was involved in data analysis and interpretation and writing and review of the report.

Results

Between Jan 13, 2017, and April 26, 2018, 514 patients (median age 54 years [IQR 43–64]; 299 [58%] men and 215 [42%] women) were enrolled and randomly assigned (256 [50%] to the atezolizumab group and 258 [50%] to the control group). Baseline characteristics have been reported previously.[18] Overall, 442 (86%) of 514 patients had sufficient tumour sample available for central confirmation of *BRAF* mutation genotype, and 379 (86%) of 442 patients with a sufficient sample had $BRAF^{V600E}$ mutations (197 of 228 [86%] patients in the atezolizumab group and 182 of 214 [85%] patients in the control group).

At the time of analysis, 37 (14%) patients in the atezolizumab group and 37 (14%) in the control group were continuing treatment (figure 1). The median follow-up duration was 29·1 months (IQR 10·1–45·4) for the atezolizumab group and 22·8 months (10·6–44·1) for the control group. Overall, 199 (78%) patients in the atezolizumab group discontinued atezolizumab and 202 (78%) patients in the control group discontinued placebo. The most common reason for discontinuation study regimens was progressive disease (102 [40%] in the atezolizumab group and 146 [57%] patients in the control group). The incidence of major protocol deviations was similar between the two treatment groups (appendix p 4).

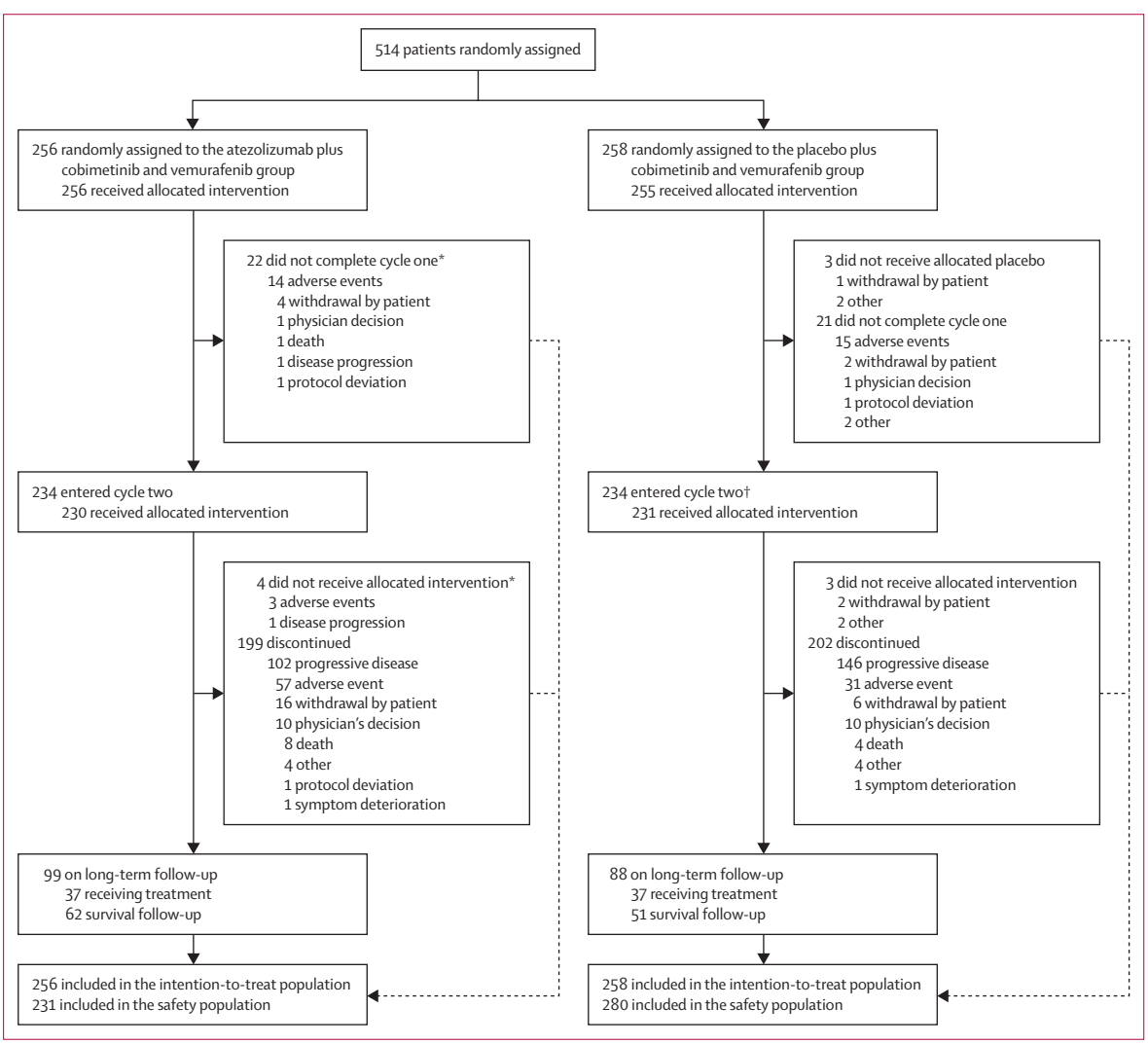


Figure 1: **Trial profile**

*26 patients did not receive any dose of atezolizumab and were included in the safety population for the control group. †One patient received atezolizumab and was included in the safety population for the atezolizumab group. The safety population for the atezolizumab group comprised 230 patients randomly allocated to the atezolizumab group who received atezolizumab in the triplet combination phase as allocated, plus one patient randomly allocated to the control group who received atezolizumab. The safety population for the control group comprised 255 patients randomly allocated to the control group who received intervention as allocated minus one patient who received atezolizumab, plus 26 patients randomly allocated to the atezolizumab group who did not receive any dose of atezolizumab.

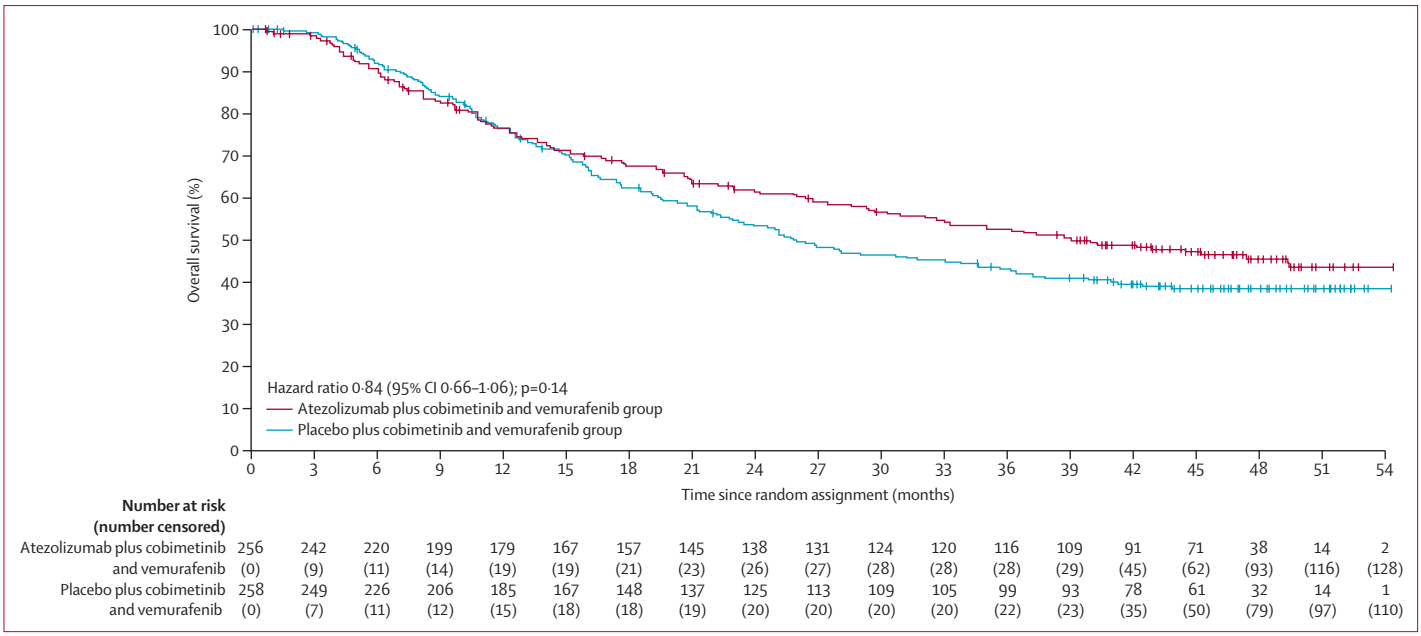


Figure 2: **Overall survival**
Vertical dashes denote censored patients.

A summary of subsequent anticancer therapy is presented in appendix (p 7).

At the data cutoff (Sept 8, 2021), 273 patients had died (126 in the atezolizumab group and 147 in the control group). The secondary efficacy endpoint of overall survival was not met. Median overall survival was 39·0 months (95% CI 29·9–not estimable) in the atezolizumab group and 25·8 months (22·0–34·6) in the control group (HR 0·84 [95% CI 0·66–1·06], p=0·14; figure 2). A late separation of overall survival curves was observed (figure 2). Post-hoc landmark 12-month overall survival was 76% (95% CI 71–81) in the atezolizumab group compared with 76% (71–82) in the control group and prespecified landmark overall survival at 24 months was 62% (55–68) in the atezolizumab group compared with 53% (47–60) in the control group. The plot of scaled Schoenfeld residual for the treatment group did not show a strong trend along the original time variable, and there was no compelling evidence of gross violation of the proportional hazard assumption (appendix p 5). The primary cause of death was most commonly progressive disease (appendix p 6). A post-hoc subgroup analysis of overall survival by baseline risk factors is shown in figure 3.

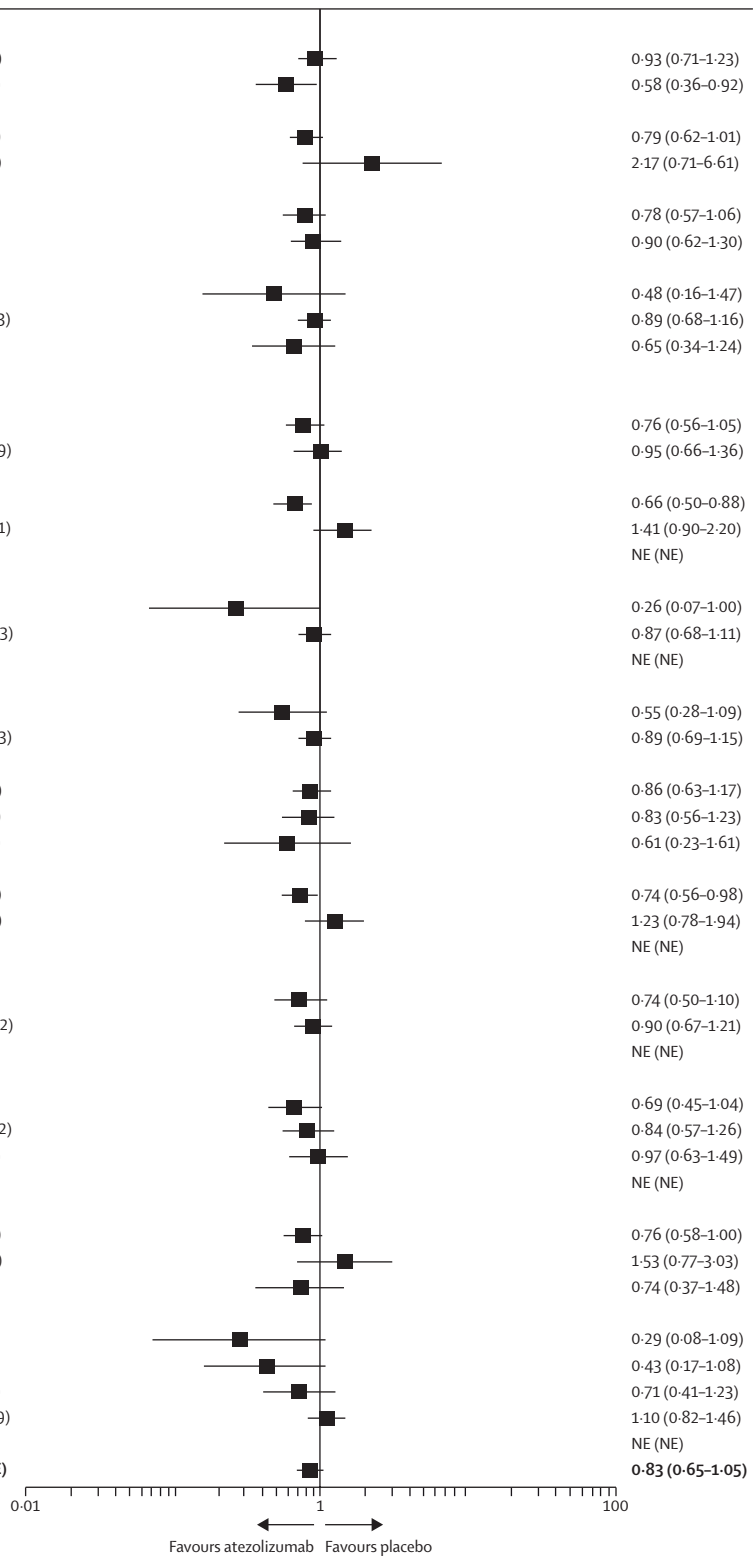
With additional follow-up, the atezolizumab group continued to show a benefit over the control group in terms of investigator-assessed progression-free survival (HR 0·79 [95% CI 0·64–0·97], p=0·022; figure 4). 168 progression-free survival events were reported in the atezolizumab group versus 198 events in the control group. Median progression-free survival was 15·1 months (95% CI 11·4–18·4) in the atezolizumab group and 10·6 months (9·3–12·7) in the control group. Post-hoc landmark progression-free survival for the atezolizumab group versus the control group was 73% (95% CI 67–78) versus 74% (69–80) at 6 months; 54% (48–60) versus 46% (39–52) at 12 months; and 44% (37–50) versus 32% (26–38) at 18 months.

The objective response rate and median duration of response for the atezolizumab group versus the control group remained consistent with those reported at primary analysis (table 1). Objective responses were achieved in 170 (67%; 95% CI 61–72] of 255 evaluable patients in the atezolizumab group versus 160 (65%; 59–71) of 246 patients in the control group, and median duration of response was 21·0 months (95% CI 16·6–32·2) in the atezolizumab group and 12·6 months (10·5–16·7) in the control group.

The safety analysis included 511 patients (231 from the atezolizumab group and 280 from the control group). One patient randomly assigned to the control group received atezolizumab and was included in the atezolizumab group; 26 patients randomly assigned to the atezolizumab group never received atezolizumab and were included in the control group. Median duration of treatment was 9·2 months (IQR 3·3–23·0) in the atezolizumab group and 8·9 months (4·2–18·8) in the control group. The safety profile for atezolizumab group was similar to that observed during the primary analysis, with no new safety signals observed with additional follow-up. Adverse events led to discontinuation of any

Figure 3: **Subgroup analysis of overall survival**
Forest plot of unstratified hazard ratios for overall survival across patient subgroups. NE=not estimable. ULN=upper limit of normal. *Missing central testing data.

	Placebo plus cobimetinib and vemurafenib group (n=258)		Atezolizumab plus cobimetinib and vemurafenib group (n=256)		Hazard ratio (95% CI)
	Events/patients	Median overall survival (95% CI)	Events/patients	Median overall survival (95% CI)	
Age group, years					
<65	104/199	31·1 (23·4–NE)	96/195	39·9 (29·3–NE)	0·93 (0·71–1·23)
≥65	43/59	19·5 (14·6–26·9)	30/61	38·7 (26·3–NE)	0·58 (0·36–0·92)
Race					
White	142/246	25·6 (21·2–33·7)	117/243	42·2 (32·8–NE)	0·79 (0·62–1·01)
Non–White	5/12	NE (15·9–NE)	9/13	22·9 (16·8–NE)	2·17 (0·71–6·61)
Sex					
Male	87/149	27·9 (22·7–36·4)	74/150	40·2 (31·7–NE)	0·78 (0·57–1·06)
Female	60/109	23·4 (17·3–NE)	52/106	32·9 (20·7–NE)	0·90 (0·62–1·30)
Geographic region					
North America	8/14	23·9 (10·3–NE)	5/13	NE (24·1–NE)	0·48 (0·16–1·47)
Europe	116/203	25·6 (20·7–34·6)	106/203	36·3 (27·4–47·3)	0·89 (0·68–1·16)
Australia, New Zealand, or other	23/41	33·0 (17·5–NE)	15/40	NE (25·9–NE)	0·65 (0·34–1·24)
Serum lactate dehydrogenase concentration at baseline					
≤ULN	86/173	36·1 (26·9–NE)	70/172	NE (44·4–NE)	0·76 (0·56–1·05)
>ULN	61/85	15·2 (11·5–19·4)	56/84	15·6 (10·9–25·9)	0·95 (0·66–1·36)
Eastern Cooperative Oncology Group performance status					
0	113/198	27·7 (22·9–36·4)	80/194	NE (40·2–NE)	0·66 (0·50–0·88)
1	34/56	18·6 (11·6–43·9)	46/62	15·6 (10·9–24·1)	1·41 (0·90–2·20)
Unknown	0/4	NE (NE–NE)			NE (NE)
Melanoma staging					
IIIc	9/16	26·7 (19·5–NE)	3/14	NE (NE–NE)	0·26 (0·07–1·00)
IV	138/240	25·8 (21·8–34·6)	123/242	36·7 (28·4–49·3)	0·87 (0·68–1·11)
Unknown	0/2	NE (NE–NE)			NE (NE)
Previous adjuvant therapy					
Yes	17/30	19·0 (13·3–NE)	16/41	NE (29·6–NE)	0·55 (0·28–1·09)
No	130/228	26·4 (22·7–35·6)	110/215	36·7 (26·7–49·3)	0·89 (0·69–1·15)
PD-L1 expression					
IC 1/2/3	84/158	25·9 (22·7–43·9)	74/160	45·2 (29·6–NE)	0·86 (0·63–1·17)
IC 0	53/86	26·4 (15·1–37·2)	45/85	36·7 (25·9–NE)	0·83 (0·56–1·23)
Unknown	10/14	17·5 (9·7–34·6)	7/11	30·4 (17·6–NE)	0·61 (0·23–1·61)
Organ involvement					
<3	109/197	30·6 (23·1–41·3)	89/205	49·3 (38·7–NE)	0·74 (0·56–0·98)
≥3	38/57	16·1 (13·1–25·6)	37/51	11·7 (9·4–25·9)	1·23 (0·78–1·94)
Unknown	0/4	NE (NE–NE)			NE (NE)
Sum of the longest diameter, mm					
<44	52/99	39·8 (24·5–NE)	45/109	NE (39·9–NE)	0·74 (0·50–1·10)
≥44	95/155	22·3 (17·3–28·9)	81/147	26·8 (20·4–42·2)	0·90 (0·67–1·21)
Unknown	0/4	NE (NE–NE)			NE (NE)
Histological subtype					
Superficial spreading	51/83	25·8 (17·5–40·8)	39/85	NE (33·2–NE)	0·69 (0·45–1·04)
Nodular	51/80	20·7 (16·1–34·6)	47/84	28·4 (19·2–45·2)	0·84 (0·57–1·26)
Other	45/93	31·1 (23·1–NE)	39/86	47·3 (22·9–NE)	0·97 (0·63–1·49)
Unknown	0/2	NE (NE–NE)	1/1	10·9 (NE–NE)	NE (NE)
***BRAF* mutation subtype**					
V600E	106/182	25·1 (19·3–31·6)	97/197	42·2 (30·4–NE)	0·76 (0·58–1·00)
V600K/D/R	16/32	42·4 (25·8–NE)	17/31	28·8 (10·9–NE)	1·53 (0·77–3·03)
Missing*	25/44	28·9 (15·1–NE)	12/28	32·8 (17·6–NE)	0·74 (0·37–1·48)
Distant metastasis stage					
M0	9/16	26·7 (19·5–NE)	3/13	NE (42·9–NE)	0·29 (0·08–1·09)
M1A	13/35	NE (21·2–NE)	7/41	NE (NE–NE)	0·43 (0·17–1·08)
M1B	25/42	31·1 (22·3–NE)	27/57	44·4 (31·7–NE)	0·71 (0·41–1·23)
M1C	100/163	23·9 (17·3–30·6)	89/144	20·7 (15·7–29·9)	1·10 (0·82–1·46)
Unknown	0/2	NE (NE–NE)	0/1	NE (NE–NE)	NE (NE)
Overall	**147/258**	**25·8 (22·0–34·6)**	**126/256**	**39·0 (29·9–NE)**	**0·83 (0·65–1·05)**



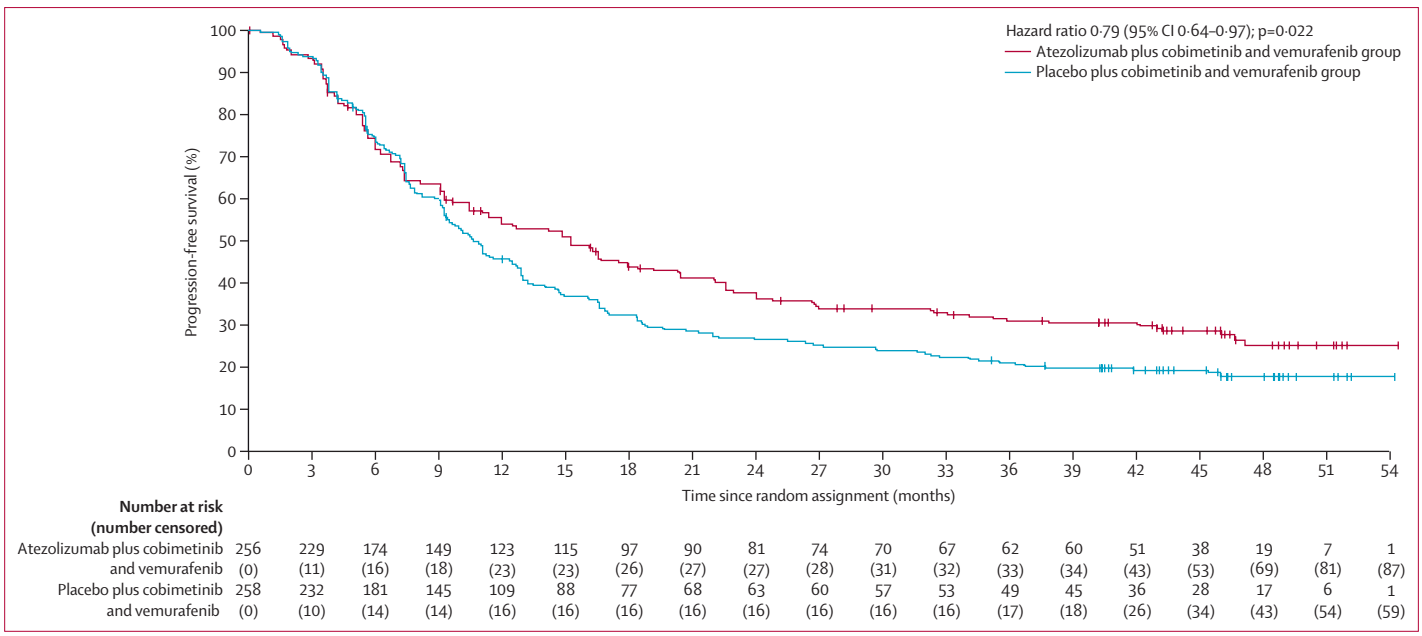


Figure 4: **Investigator-assessed progression-free survival**
Vertical dashes denote censored patients.

	Placebo plus cobimetinib and vemurafenib (n=246)	Atezolizumab plus cobimetinib and vemurafenib (n=255)
Objective response rate	160 (65%; 59–71)	170 (67%; 61–72)
Response		
Complete response	47 (19%)	45 (18%)
Partial response	113 (46%)	125 (49%)
Stable disease	56 (23%)	57 (22%)
Progressive disease	16 (7%)	14 (5%)
Not evaluable	1 (<1%)	1 (<1%)
Missing	13 (5%)	13 (5%)
Duration of response, months	12·6 (10·5–16·7)	21·0 (16·6–32·2)

Data are n (%; 95% CI), n (%), or median (95% CI).

Table 1: **Investigator-assessed objective response rate and duration of response in patients with measurable disease at baseline**

study treatment in 88 (38%) of 231 patients in the atezolizumab group versus 90 (32%) of 280 patients in the control group (appendix pp 8–9). Adverse events led to discontinuation of all study treatments in 34 (15%) of 231 patients in the atezolizumab group versus 45 (16%) of 280 patients in the control group (appendix pp 8–9). Adverse events led to any treatment dose modification or interruption in 207 (90%) of 231 patients in the atezolizumab group versus 223 (80%) of 280 patients in the control group. Adverse events led to dose reduction of vemurafenib in 204 (89%) of 230 patients in the atezolizumab group and 226 (81%) of 281 patients in the control group. Adverse events led to cobimetinib dose reduction in 180 (78%) of 230 patients in the atezolizumab group and 198 (70%) of 281 patients in the control group.

The most common adverse events of any grade were diarrhoea (116 [50%] of 231 patients in the atezolizumab group *vs* 157 [56%] of 280 patients in the control group), increased blood creatine phosphokinase (123 [53%] *vs* 135 [48%]), rash (105 [46%] *vs* 119 [43%]), pyrexia (115 [50%] *vs* 97 [35%]), arthralgia (103 [45%] *vs* 98 [35%]), increased lipase (83 [36%] *vs* 86 [31%]), nausea (71 [31%] *vs* 91 [33%]), fatigue (70 [30%] *vs* 86 [31%]), increased alanine aminotransferase (83 [36%] *vs* 69 [25%]), and increased aspartate aminotransferase (74 [32%] *vs* 59 [21%]; table 2; appendix pp 10–16).

The most common grade 3–4 adverse events were increased lipase (54 [23%] in the atezolizumab group *vs* 62 [22%] in the control group), increased blood creatine phosphokinase (51 [22%] *vs* 50 [18%]), and increased alanine aminotransferase (32 [14%] *vs* 26 [9%]). A higher proportion of patients in the atezolizumab group compared with the control group (difference of ≥2%) had grade 3–4 blood creatine phosphokinase increased, alanine aminotransferase increased, maculopapular rash, increased amylase, hypertension, aspartate aminotransferase increased, arthralgia, photosensitivity reaction, lymphopenia, acute kidney injury, and infusion-related reaction (appendix p 17).

Serious adverse events were reported in 112 (48%) of 231 patients in the atezolizumab group and 117 (42%) of 280 patients in the control group (appendix p 18). 57 (25%) patients had atezolizumab-associated serious adverse events, and 35 (13%) patients had placebo-associated serious adverse events. Cobimetinib-associated serious adverse events were reported in 53 (23%) patients in the atezolizumab group and 61 (22%) patients in the control group. Vemurafenib-related serious adverse events

were reported in 58 (25%) patients in the atezolizumab group and 71 (25%) patients in the control group. Grade 5 adverse events were reported in eight (3%) patients in the atezolizumab group (cardiac arrest, pneumonia, septic shock, hepatic failure, hepatitis fulminant, and dyspnoea, one each; two due to sepsis) and six (2%) of 280 patients in the control group (cardiac arrest, cardiac failure, left ventricular failure, cerebrovascular accident, hydrocephalus, and pulmonary haemorrhage, one each; appendix pp 10–16). Two grade 5 adverse events in the atezolizumab group (hepatitis fulminant and hepatic failure) were considered by the investigator to be associated with triplet combination therapy with atezolizumab, vemurafenib, and cobimetinib. One grade 5 adverse event in the control group (pulmonary haemorrhage) was considered to be associated with cobimetinib.

Discussion

This interim analysis of the phase 3 IMspire150 study reports mature overall survival outcomes for triplet combination with atezolizumab, vemurafenib, and cobimetinib in patients with previously untreated *BRAF*^{V600} mutation-positive advanced or metastatic melanoma. In line with overall survival outcomes from the primary analysis,[17] this second interim overall survival analysis shows numerically, but not significantly, longer overall survival in the atezolizumab group (median overall survival 39·0 months) versus the control group (25·8 months). The late separation of overall survival curves after 12 months suggests a delayed treatment effect in the atezolizumab group, as evident during additional follow-up. The median follow-up duration was shorter for patients in the control group (22·8 months) than in the atezolizumab group (29·1 months), probably due to a higher number of deaths and a higher rate of study discontinuation in the control group at the clinical cutoff date for this analysis.

The median overall survival of 25·8 months in the control group is consistent with that observed with vemurafenib plus cobimetinib (22·3 months [95% CI 20·3–not estimable]) in the randomised, double-blind, phase 3 coBRIM study.[15] The randomised, phase 2 KEYNOTE-022 study evaluated the efficacy of pembrolizumab plus dabrafenib and trametinib versus placebo plus dabrafenib and trametinib in patients with previously untreated *BRAF*$^{V600E/K}$-mutated advanced melanoma.[9,19] At median follow-up of 61·2 months, pembrolizumab plus dabrafenib and trametinib improved median progression-free survival (17·0 months *vs* 9·9 months; HR 0·46 [95% CI 0·29–0·74]) and median overall survival (46·3 months *vs* 26·3 months; HR 0·60 [0·38–0·95]) compared with placebo plus dabrafenib and trametinib.[20] These outcomes of the KEYNOTE-022 trial, together with the delayed separation of overall survival curves we report, suggest that longer follow-up might be needed to confirm whether a significantly longer overall survival can be achieved with immunotherapy plus BRAF

	Placebo plus cobimetinib and vemurafenib (n=280)			Atezolizumab plus cobimetinib and vemurafenib (n=231)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	93 (33%)	145 (52%)	39 (14%)	58 (25%)	134 (58%)	39 (17%)
Rash	94 (34%)	25 (9%)	0	85 (37%)	20 (9%)	0
Photosensitivity reaction	65 (23%)	8 (3%)	0	51 (22%)	2 (1%)	0
Pruritus	48 (17%)	1 (<1%)	0	63 (27%)	2 (1%)	0
Erythema	43 (15%)	0	0	38 (16%)	0	0
Dermatitis acneiform	37 (13%)	5 (2%)	0	32 (14%)	5 (2%)	0
Dry skin	28 (10%)	0	0	31 (13%)	0	0
Alopecia	28 (10%)	0	0	23 (10%)	1 (<1%)	0
Blood creatine phosphokinase increased	85 (30%)	34 (12%)	16 (6%)	72 (31%)	34 (15%)	17 (7%)
Lipase increased	24 (9%)	45 (16%)	17 (6%)	29 (13%)	36 (16%)	18 (8%)
Alanine aminotransferase increased	43 (15%)	23 (8%)	3 (1%)	51 (22%)	30 (13%)	2 (1%)
Aspartate aminotransferase increased	46 (16%)	11 (4%)	2 (1%)	53 (23%)	20 (9%)	1 (<1%)
Amylase increased	28 (10%)	19 (7%)	3 (1%)	24 (10%)	25 (11%)	2 (1%)
Blood creatinine increased	42 (15%)	1 (<1%)	0	48 (21%)	0	0
Blood alkaline phosphatase increased	39 (14%)	8 (3%)	0	31 (13%)	8 (3%)	0
Blood bilirubin increased	17 (6%)	1 (<1%)	0	26 (11%)	3 (1%)	0
Pyrexia	92 (33%)	5 (2%)	0	111 (48%)	4 (2%)	0
Fatigue	85 (30%)	1 (<1%)	0	67 (29%)	3 (1%)	0
Asthenia	50 (18%)	2 (1%)	1 (<1%)	48 (21%)	7 (3%)	0
Oedema peripheral	42 (15%)	0	0	49 (21%)	0	0
Diarrhoea	146 (52%)	11 (4%)	0	108 (47%)	7 (3%)	1 (<1%)
Nausea	84 (30%)	7 (3%)	0	69 (30%)	2 (1%)	0
Vomiting	67 (24%)	5 (2%)	0	48 (21%)	4 (2%)	0
Constipation	33 (12%)	0	0	35 (15%)	0	0
Abdominal pain	28 (10%)	0	0	29 (13%)	0	0
Abdominal pain upper	30 (11%)	0	0	20 (9%)	0	0
Arthralgia	92 (33%)	6 (2%)	0	93 (40%)	10 (4%)	0
Myalgia	48 (17%)	1 (<1%)	0	58 (25%)	2 (1%)	0
Pain in extremity	29 (10%)	0	0	32 (14%)	1 (<1%)	0
Cough	35 (13%)	0	0	34 (15%)	0	0
Pneumonitis	15 (5%)	1 (<1%)	0	28 (12%)	3 (1%)	0
Oropharyngeal pain	14 (5%)	0	0	24 (10%)	0	0
Hyperthyroidism	27 (10%)	0	0	48 (21%)	2 (1%)	0
Hypothyroidism	24 (9%)	0	0	45 (19%)	0	0
Headache	55 (20%)	3 (1%)	0	55 (24%)	2 (1%)	0
Hypertension	33 (12%)	21 (8%)	0	20 (9%)	23 (10%)	0
Sunburn	32 (11%)	1 (<1%)	0	27 (12%)	1 (<1%)	0
Anaemia	34 (12%)	10 (4%)	0	41 (18%)	4 (2%)	0
Nasopharyngitis	30 (11%)	0	0	24 (10%)	0	0
Urinary tract infection	11 (4%)	3 (1%)	0	22 (10%)	2 (1%)	0
Decreased appetite	40 (14%)	2 (1%)	0	35 (15%)	0	0
Chorioretinopathy	37 (13%)	1 (<1%)	0	34 (15%)	1 (<1%)	0
Chills	22 (8%)	1 (<1%)	0	23 (10%)	0	0
Upper respiratory tract infection	23 (8%)	1 (<1%)	0	22 (10%)	1 (<1%)	0
Rash maculopapular	26 (9%)	26 (9%)	1 (<1%)	18 (8%)	30 (13%)	0
Gamma-glutamyl transferase increased	12 (4%)	6 (2%)	3 (1%)	8 (3%)	5 (2%)	2 (1%)

(Table 2 continues on next page)

	Placebo plus cobimetinib and vemurafenib (n=280)			Atezolizumab plus cobimetinib and vemurafenib (n=231)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Ejection fraction decreased	5 (2%)	3 (1%)	0	11 (5%)	4 (2%)	0
Syncope	2 (1%)	3 (1%)	0	5 (2%)	4 (2%)	0
Hyperglycaemia	9 (3%)	7 (3%)	1 (<1%)	11 (5%)	5 (2%)	2 (1%)
Hypophosphataemia	10 (4%)	7 (3%)	0	11 (5%)	5 (2%)	0
Hypokalaemia	14 (5%)	2 (1%)	0	10 (4%)	6 (3%)	0
Hyponatraemia	6 (2%)	5 (2%)	1 (<1%)	5 (2%)	3 (1%)	2 (1%)
Infusion-related reaction	16 (6%)	1 (<1%)	0	18 (8%)	6 (3%)	0
Lymphopenia	14 (5%)	3 (1%)	0	8 (3%)	7 (3%)	1 (<1%)
Acute kidney injury	5 (2%)	1 (<1%)	0	5 (2%)	5 (2%)	1 (<1%)

Data are n (%). Adverse events of grade 1 or 2 occurring in 10% or more of patients and adverse events of grade 3 or worse occurring in 2% or more of patients are reported.

Table 2: **Treatment-emergent adverse events by highest grade per patient**

inhibitor and MEK inhibitor triplet combination versus vemurafenib plus cobimetinib. Primary results from the randomised, phase 3 COMBI-i study[21,22] showed no significant improvement in progression-free survival with spartalizumab in combination with dabrafenib and trametinib versus placebo plus dabrafenib and trametinib in patients with previously untreated *BRAF*^{V600}-positive metastatic melanoma (16·2 months *vs* 12·0 months; HR 0·82 [95% CI 0·66–1·03], p=0·042);[21] with a median follow-up of 42·8 months, median overall survival was not reached in the spartalizumab plus dabrafenib and trametinib group compared with 40·4 months with placebo plus dabrafenib and trametinib (HR 0·80 [95% CI 0·62–1·03]).[22]

Approximately 50% of patients with metastatic melanoma have *BRAF* mutations, of which up to 88% are Val600Glu mutations.[23,24] In our study, a post-hoc exploratory subgroup analysis showed that patients with centrally confirmed *BRAF*^{V600E} mutations had a longer overall survival in the atezolizumab group compared with the control group. The difference in median overall survival was larger in this subgroup than that observed in the intention-to-treat population, suggesting that this combination might be beneficial for the management of these patients. This subgroup of patients was specifically cited during regulatory approval of the triplet therapy in Switzerland. However, these subgroup analyses were not a prespecified secondary endpoint of overall survival, and there was no stratification of randomisation according to *BRAF* mutation subtype. Therefore, these findings should be considered hypothesis-generating. On the basis of the scarce evidence available, a difference in efficacy for targeted therapy, immunotherapy, or both between patients with Val600Glu and those with Val600Lys mutations remains unclear.[25] Determination of the optimal treatment for patients with Val600Lys mutations remains an area of unmet need.

The duration of response and progression-free survival benefits observed in the primary analysis of the IMspire150 phase 3 study[17] were also observed in this report, with longer follow-up confirming the durability of clinical benefit with the triplet combination. Although a similar objective response rate was observed between the two treatment groups, the atezolizumab, vemurafenib, and cobimetinib triplet combination significantly improved progression-free survival compared with placebo, vemurafenib, and cobimetinib. This progression-free survival benefit was probably driven by the improved duration of response in the atezolizumab group versus the control group. Although the optimal duration of treatment with the triplet combination remains unclear, future studies should explore the opportunity to stop atezolizumab after 2 years as is currently done with other anti-PD-1 or anti-PD-L1 treatments in real-world clinical practice.

The safety profile in the atezolizumab group reported in this follow-up study was generally in line with that observed in the primary analysis of the IMspire150 trial,[17] with a similar overall incidence of adverse events in the atezolizumab group and the control group. The observed safety profile was also consistent with the known safety profile of individual treatment components and the vemurafenib plus cobimetinib combination,[14,26–28] and no new safety signals were identified with this extended follow-up. A higher incidence of pyrexia was observed in the atezolizumab group versus the control group, although most events were grade 1–2 in severity in both treatment groups. Of note, the frequency of pyrexia reported in the atezolizumab group (115 [50%] of 231 patients) appears lower than that reported with the spartalizumab plus dabrafenib plus trametinib triplet combination (191 [72%] of 267 patients) in the COMBI-i study.[21] The incidence of other adverse events, including arthralgia, alanine aminotransferase increased, aspartate aminotransferase increased, pruritis, myalgia, hyperthyroidism, and hypothyroidism, were also slightly higher in the atezolizumab group than in the control group. Most of these adverse events were grade 1–2; therefore, they were not likely to affect the overall survival outcomes in the atezolizumab group. Also noteworthy is that the proportion of patients in the atezolizumab group who discontinued treatment (88 [38%]) was lower than the number of patients reported for other triplet combinations in this patient population (42–68%).[29,30]

COVID-19 had minimal effect on the interpretation of the study results. All patients included in this analysis were enrolled and had completed the study by December, 2019, around the time when the COVID-19 pandemic started. Efficacy analysis was not affected because of the small effect of missed tumour assessment on the endpoint of overall survival. Patients were stratified by geographical region, which additionally limited the potential for a differential effect of the pandemic between the treatment groups. Safety reporting was also minimally affected.

The limitations of the study include the absence of a-priori identification of subsets of patients likely to show greater benefit with addition of atezolizumab to vemurafenib plus cobimetinib, and the short duration of follow-up for overall survival. Furthermore, the sample size was calculated based on the primary endpoint of progression-free survival and the study might be underpowered to detect a clinically meaningful change in overall survival. Nevertheless, this is an interim analysis and outcomes of the final analysis will be needed to confirm these observations.

In conclusion, additional follow-up of the IMspire150 phase 3 study showed that overall survival was not significantly improved in the atezolizumab group versus the control group. Results from the final analysis are awaited to establish whether the atezolizumab, vemurafenib, and cobimetinib triplet combination can significantly improve overall survival in patients with previously untreated *BRAF*^{V600} mutation-positive advanced or metastatic melanoma.

Contributors

As members of the Steering Committee, PAA, CR, KL, GAM, and RG provided clinical and scientific input on the study design and protocol. PAA, DS, HG, CR, KL, SP, RPP, TE, PR, LD, NZ, JS, GAM, and RG recruited patients and collected data. CX did the statistical analyses. CX, YY, IC, CH, and LK verified the study data. PAA, GAM, and RG collaboratively wrote the first draft of the manuscript, verified the underlying data, and had final responsibility for the decision to submit for publication. All authors had full access to study data, interpreted the data, critically reviewed the manuscript, approved the final version, and had responsibility for the decision to submit for publication.

Declaration of interests

PAA reports grants from Bristol Myers Squibb, Roche/Genentech, Pfizer/Array, and Sanofi; consulting fees from Bristol Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Novartis, Merck Serono, Pierre Fabre, Sun Pharma, Sanofi, Idera, Sandoz, 4SC, Italfarmaco, Nektar, Pfizer/Array, Lunaphore, Medicenna, Bio-Al Health, ValoTx, and Replimmune; travel support from Pfizer; and advisory board member for Bristol Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Novartis, AstraZeneca, Immunocore, Boehringer-Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Oncosec, Nouscom, Seagen, and iTeos. HG reports honoraria from Bristol Myers Squibb, MSD Oncology, Pierre Fabre, and Sanofi/Regeneron; research funding from Bristol Myers Squibb, Roche, MSD Oncology, Amgen, Novartis, and Iovance Biotherapeutics; travel, accommodation, and expenses from Bristol Myers Squibb, Merck Sharp & Dohme, Amgen, and Pfizer; and a consulting or advisory role for Bristol Myers Squibb, MSD Oncology, Amgen, Pierre Fabre, and Sanofi/Regeneron. CR reports consulting fees from Roche, Novartis, Pierre Fabre, MSD, Bristol Myers Squibb, Sanofi, Pfizer, and AstraZeneca; and payment or honoraria from Roche, Novartis, Pierre Fabre, MSD, Bristol Myers Squibb, Sanofi, Pfizer, and AstraZeneca. KL reports honoraria from Array Biopharma and Iovance Biotherapeutics; a consulting or advisory role for Array Biopharma, Iovance Biotherapeutics, Merck, Nektar, Regeneron, Roche, and Sanofi; research funding from Alkermes, Amgen, Array Biopharma, Bristol Myers Squibb, Incyte, Iovance Biotherapeutics, Kartos Therapeutics, Merck, Nektar, Neon Therapeutics, OncoSec, Regeneron, Replimune, Roche/Genentech, Seagen, Senhwa Biosciences, and Ultimovacs; and travel, accommodations, or expenses from Alkermes, Merck, Neon Therapeutics, Regeneron, and Roche/Genentech. SP reports honoraria from Biocad, Roche, Bristol Myers Squibb, and Merck Sharp & Dohme; speakers bureau for Biocad, Roche, Bristol Myers Squibb, and Merck Sharp & Dohme; and research funding from Roche, Merck Sharp & Dohme, Amgen, Novartis, Bristol Myers Squibb, and Biocad. RPP reports speakers bureau for Roche and Bristol Myers Squibb and research funding from Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Bayer, and AstraZeneca. TE reports a consulting or advisory role for Bristol Myers Squibb/Medarex, Sanofi/Regeneron, Novartis, and Pierre Fabre and speakers bureau for Almirall Hermal. PR reports honoraria from Bristol Myers Squibb, MSD, Novartis, Roche, Pfizer, Pierre Fabre, Sanofi, and Merck; speaker's bureau for Pfizer, Novartis, and Pierre Fabre; consulting fee from Blueprint Medicines, Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, and Philogen; research funding from Bristol Myers Squibb, Novartis, and Roche; and travel, accommodations, or expenses from Orphan Europe and Pierre Fabre. LD reports honoraria from Roche, Merck Sharp & Dohme, Bristol Myers Squibb, and Novartis and research funding from Roche, Merck Sharp & Dohme, Bristol Myers Squibb, Novartis, and Amgen. NZ reports honoraria from Roche, Novartis, Bristol Myers Squibb/Celgene, MSD Oncology, and AstraZeneca/Merck; consulting fees from Roche, MSD Oncology, Merck; and travel and accommodation expenses from MSD Oncology and Roche. JS reports a consultant or advisory role for Merck Sharp & Dohme and Bristol Myers Squibb. YY and IC report employment with Genentech and stock or other ownership with Roche/Genentech. CH and CX report employment with Roche. LK reports employment and ownership non-voting shares for Roche. GAM reports research funding to his institution from Genentech/Roche and Bristol Myers Squibb. RG reports honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Roche/Genentech, Novartis, Merck Serono, Almirall Hermal, Amgen, Sun Pharma, Pierre Fabre, Sanofi/Regeneron, and Immunocore; a consulting or advisory role for Bristol Myers Squibb, Merck Sharp & Dohme, Roche/Genentech, Novartis, Almirall Hermal, 4SC, Amgen, Pierre Fabre, Merck Serono, Sun Pharma, Sanofi, and Immunocore; research funding from Pfizer, Novartis, Johnson & Johnson, Amgen, Merck Serono, Sun Pharma, and Sanofi; and travel, accommodations, or expenses from Bristol Myers Squibb, Roche, Merck Serono, Pierre Fabre, and Sun Pharma. DS declares no competing interests.

Data sharing

Qualified researchers can request access to individual patient-level data through the clinical study data request platform, which is available online. Roche's criteria for eligible studies are available online. Details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents are available online. Anonymised records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient reidentification.

For the **data request platform** see https://vivli.org/

For more on the **eligibility criteria** see https://vivli.org/members/ourmembers/

For more on **Roche's global policy** see https://go.roche.com/data_sharing

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