Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced *BRAF*^{V600} mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background IMspire150 aimed to evaluate first-line combination treatment with BRAF plus MEK inhibitors and immune checkpoint therapy in *BRAF*^{V600} mutation-positive advanced or metastatic melanoma.

Methods IMspire150 was a randomised, double-blind, placebo-controlled phase 3 study done at 112 institutes in 20 countries. Patients with unresectable stage IIIc–IV, *BRAF*^{V600} mutation-positive melanoma were randomly assigned 1:1 to 28-day cycles of atezolizumab, vemurafenib, and cobimetinib (atezolizumab group) or atezolizumab placebo, vemurafenib, and cobimetinib (control group). In cycle 1, all patients received vemurafenib and cobimetinib only; atezolizumab placebo was added from cycle 2 onward. Randomisation was stratified by lactate dehydrogenase concentration and geographical region. Blinding for atezolizumab was achieved by means of an identical intravenous placebo, and blinding for vemurafenib was achieved by means of a placebo tablet. The primary outcome was investigator-assessed progression-free survival. This trial (ClinicalTrials.gov, NCT02908672) is ongoing but no longer recruiting patients.

Findings Between Jan 13, 2017, and April 26, 2018, 777 patients were screened and 514 were enrolled and randomly assigned to the atezolizumab group (n=256) or control group (n=258). At a median follow-up of 18·9 months (IQR 10·4–23·8), progression-free survival as assessed by the study investigator was significantly prolonged with atezolizumab versus control (15·1 *vs* 10·6 months; hazard ratio [HR] 0·78; 95% CI 0·63–0·97; p=0·025). Common treatment-related adverse events (>30%) in the atezolizumab and control groups were blood creatinine phosphokinase increased (51·3% *vs* 44·8%), diarrhoea (42·2% *vs* 46·6%), rash (40·9%, both groups), arthralgia (39·1% *vs* 28·1%), pyrexia (38·7% *vs* 26·0%), alanine aminotransferase increased (33·9% *vs* 22·8%), and lipase increased (32·2% *vs* 27·4%); 13% of patients in the atezolizumab group and 16% in the control group stopped all treatment because of adverse events.

Interpretation The addition of atezolizumab to targeted therapy with vemurafenib and cobimetinib was safe and tolerable and significantly increased progression-free survival in patients with *BRAF*^{V600} mutation-positive advanced melanoma.

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Introduction

Immune checkpoint inhibitors and BRAF and MEK inhibitors have significantly improved treatment outcomes in patients with *BRAF*^{V600} mutation-positive metastatic melanomas.[1–8] Although BRAF and MEK inhibitors are associated with high objective response rates, most responses are short-lived.[9] Immune checkpoint inhibitors provide more durable responses, but response rates are relatively lower.[10] Because of these complementary clinical characteristics, the combination of the two approaches is appealing. A combination approach is also supported by preclinical and translational data showing the immunological effects of BRAF and MEK inhibitors, such as the influx of CD4 and CD8 T cells into tumours, the upregulation of melanoma antigens and expression of major histocompatibility complex class I and major histocompatibility complex class II on tumour cells, and a cytokine shift toward an interferon γ tumour milieu.[11–14] Early phase studies have shown promising antimelanoma activity and manageable safety with such combinations.[15–19]

The programmed cell death ligand 1 (PD-L1) inhibitor atezolizumab is approved as a monotherapy or combination for selected patients with urothelial, lung, and breast cancer,[20] and has shown activity as a monotherapy in advanced melanoma (objective response rate of

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Research in context

Evidence before this study

At the time of the drafting of these results, the approved systemic options for patients with advanced melanoma were immunotherapy (all patients) or BRAF and MEK inhibitors for the subset of patients with *BRAF* mutations in their tumours. Although immunotherapy provides durable responses, a substantial proportion of patients with melanoma have a poor response to immunotherapy; conversely, although most patients respond to MAPK pathway inhibitors, responses are often short-lived. It is clinically desirable to combine the higher response rates observed with targeted therapy with long-term clinical benefit associated with immune modulation, without compromising patient safety. On the basis of emerging preclinical and clinical evidence for potential synergy between immune checkpoint inhibition and BRAF and MEK inhibitors, IMspire150 explored whether a combination of atezolizumab, vemurafenib, and cobimetinib would prolong progression-free survival in patients with *BRAF*-mutation-positive advanced melanoma versus vemurafenib and cobimetinib. We searched PubMed for any clinical reports published until Feb 20, 2020, that explored similar systemic options. We used the search string "melanoma AND ((BRAF OR MEK inhibitor) AND (immune checkpoint inhibitor))" restricted to articles reporting on a clinical trial. We identified two previous publications reporting data from early phase clinical reports (KEYNOTE 022 and GP28384/NCT01656642) investigating this combination in melanoma, but no controlled phase 3 clinical studies.

Added value of this study

IMspire150 is the first phase 3 study to evaluate an immune checkpoint inhibitor combined with BRAF plus MEK inhibitors in patients with advanced *BRAF*^{V600} mutation-positive melanoma. The IMspire150 study met its primary progression-free survival endpoint and provided high-level evidence to show that combined inhibition with vemurafenib, cobimetinib, and atezolizumab prolongs progression-free survival in previously untreated patients with *BRAF* mutation-positive advanced melanoma. Reassuringly, the safety profile and treatment discontinuation rates with this combination were similar to those of the control group of vemurafenib and cobimetinib, which is an approved treatment option for patients with *BRAF*-mutation-positive advanced melanoma.

Implications of all the available evidence

The analysis reported here shows that atezolizumab combined with vemurafenib and cobimetinib is a safe and efficacious treatment option for patients with *BRAF* mutation-positive advanced melanoma. Survival data from this and other ongoing studies on treatment sequencing will inform the optimal treatment paradigm in this patient population.

30%; median duration of response of 62 months in a cohort of 43 patients).[21] Combination therapy with the BRAF inhibitor, vemurafenib, and the MEK inhibitor, cobimetinib, is approved for patients with *BRAF*^{V600} mutation-positive advanced or metastatic melanoma.[2,22] A phase 1b study in patients with *BRAF*^{V600} mutation-positive advanced melanoma showed that initiating vemurafenib and cobimetinib 4 weeks before atezolizumab and reducing vemurafenib dosing from 960 mg twice-daily to 720 mg twice-daily after 3 weeks was tolerable and efficacious (objective response rate of 71·8%; median duration of response of 17·4 months).[16] Moreover, the initial period of targeted therapy was associated with favourable changes in the tumour immune microenvironment.[16]

See Online for appendix

We therefore did a randomised, controlled, phase 3 study that incorporated this dosing schedule to compare atezolizumab, vemurafenib, and cobimetinib versus atezolizumab placebo, vemurafenib, and cobimetinib in patients with previously untreated *BRAF*^{V600} mutation-positive advanced or metastatic melanoma.

Methods

Study design and participants

IMspire150 was a multicentre, phase 3, double-blind, placebo-controlled study. Eligible patients from 112 institutes in 20 countries were aged 18 years and above with histologically confirmed stage IV or unresectable stage IIIc melanoma per the *American Joint Committee on Cancer's Staging Manual*, 7th edn.[23] Patients had documented *BRAF*^{V600} mutation-positive tumours by a locally approved test; Eastern Cooperative Oncology Group Performance Status of 0 or 1; measurable disease by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST version 1.1);[24] and adequate haematological and organ function. In addition, patients had not received previous systemic treatment for metastatic melanoma. Patients with untreated or actively progressing brain metastases, active malignancy other than melanoma, or history of serious autoimmune disease were excluded. All patients provided written informed consent. The study protocol was approved by an independent ethics committee at each site. The protocol and statistical analysis plan are available online (appendix pp 17, 211).

Randomisation and masking

We randomly assigned patients 1:1 to atezolizumab, vemurafenib, and cobimetinib (atezolizumab group) or atezolizumab placebo, vemurafenib, and cobimetinib (control group). Randomisation was based on a stratified, permuted block randomisation scheme implemented via an interactive web-based response system. Stratification factors were geographical region (North America *vs* Europe *vs* Australia, New Zealand, and others) and baseline lactate dehydrogenase concentrations (≤upper limit of normal [ULN] *vs* >ULN).

To ensure blinding, vemurafenib dosing from cycle 1 day 22 onward was masked by use of three vemurafenib 240 mg tablets and one identical placebo tablet in the atezolizumab group and four vemurafenib 240 mg tablets in the control group.

The study investigators could unblind a patient's treatment assignment for safety concerns.

Study treatment continued until investigator-determined disease progression per RECIST version 1.1 (or confirmed disease progression 4–8 weeks later for clinically stable patients), death, unacceptable toxicity, or pregnancy, whichever occurred first.

Procedures

Treatment was administered in 28-day cycles (appendix p 14). In cycle 1, all patients received twice-daily oral vemurafenib 960 mg for 21 days plus once-daily oral cobimetinib 60 mg followed by either twice-daily vemurafenib 720 mg in the atezolizumab group or 960 mg for 7 days in the control group. From cycle 2 onwards, patients in the atezolizumab group received intravenous atezolizumab 840 mg (day 1 and 15), twice-daily vemurafenib 720 mg, and once-daily cobimetinib 60 mg (21 days on–7 days off). Patients in the control group received intravenous placebo (day 1 and 15), twice-daily vemurafenib 960 mg, and once-daily cobimetinib 60 mg (21 days on–7 days off). Dose modifications of vemurafenib and cobimetinib, including dose reductions and treatment interruptions, were allowed for the management of adverse events (appendix p 103). No dose reductions were allowed for atezolizumab, although treatment interruptions were allowed.

Outcomes

The primary efficacy endpoint was investigator-assessed progression-free survival (time from randomisation to first occurrence of disease progression or death from any cause). Secondary endpoints included progression-free survival assessed by an independent review committee, objective response (confirmed by observations at least 4 weeks apart), duration of response, overall survival, time to deterioration in global health status and time to deterioration in physical function (where deterioration was defined as ≥10-point decrease sustained over two consecutive assessments in EORTC QLQ-C30 linearly transformed scores in items 29 and 30 for global health and items 1–5 for physical functioning).

All measurable and non-measurable lesions were documented at screening. Tumour assessments were done every 8 weeks (plus or minus 1 week) from the date of treatment initiation through to the end of 24 months and then every 12 weeks (plus or minus 1 week) thereafter. Tumour assessments were done per schedule in patients who discontinued treatment for reasons other than disease progression. Blinded independent central review of tumour assessments was also done. Adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. All protocol-specified primary and secondary endpoints are reported in the manuscript, except for time to deterioration in global health status and time to deterioration in physical functioning, both of which will be reported in a separate quality-of-life-focused manuscript.

Statistical analysis

Analysis of progression-free survival was based on the intention-to-treat population and used a stratified log-rank test at a two-sided significance level of 0·05. Data for patients who had not had disease progression or who were alive at database close were censored at the last tumour assessment date. Data for patients without post-baseline tumour assessment were censored at the randomisation date. Subgroup analyses of progression-free survival were exploratory.

Key assumptions underlying the sample size considerations included a dropout rate of 7% and a median progression-free survival of 17 in the atezolizumab group and 12 months in the control group. Approximately 300 progression-free survival events were estimated to be necessary to provide 80% power to detect an improvement in progression-free survival corresponding to a hazard ratio (HR) of 0·70 with a two-sided significance level of 0·05. The updated minimum clinically relevant difference for HR based on the 327 progression-free survival events that accrued by database close was 0·79.

Final analysis of overall survival was to occur when approximately 385 deaths had accrued. This would provide approximately 80% power to detect an improvement in overall survival corresponding to a HR of 0·75 with a two-sided significance level of 0·05. The interim analysis of overall survival was prespecified per protocol to occur at the time of the primary analysis of progression-free survival and is reported here.

A stratified Cox model was used to estimate the HR and two-sided 95% CIs for progression-free survival and overall survival. Only baseline lactate dehydrogenase concentration (≤ULN *vs* >ULN) was included in the stratified analysis owing to potential risk of over-stratification. The proportional hazards assumption was assessed graphically by assessing the cumulative hazard function. Kaplan-Meier estimates were used to estimate the medians of time-to-event endpoints. A univariate unstratified Cox model was used to estimate the HR and two-sided 95% CIs for each predefined subgroup. For objective response rates, 95% Clopper-Pearson CIs were estimated. Baseline characteristics and safety were summarised descriptively. A weighted log-rank analysis that weights more on late events was done to assess a potential delayed treatment effect.[25,26] All efficacy analyses were done in the intention-to-treat population unless specified otherwise. The safety populations comprised patients who had received at least one dose of study drug and were grouped by actual treatment received. All efficacy and safety analyses were according to the final

	Atezolizumab + vemurafenib + cobimetinib (n=256)	Placebo + vemurafenib + cobimetinib (n=258)
Median age, years (range)	54·0 (44·8–64·0)	53·5 (43·0–63·8)
Age		
<65 years	195 (76%)	199 (77%)
≥65 years	61 (24%)	59 (23%)
Female sex	106 (41%)	109 (42%)
Male sex	150 (59%)	149 (58%)
White race	243 (95%)	246 (95%)
Geographical region		
North America	13 (5%)	14 (5%)
Europe	203 (79%)	203 (79%)
Australia, New Zealand, or other	40 (16%)	41 (16%)
Eastern Cooperative Oncology Group performance status		
0	195 (76%)	198 (77%)
1	61 (24%)	56 (22%)
Unknown	0	4 (2%)
Disease stage		
IIIC	14 (5%)	16 (6%)
IV	242 (95%)	240 (93%)
Unknown	0	2 (1%)
Elevated lactate dehydrogenase concentration (>upper limit of normal)	84 (33%)	85 (33%)
Stage, distant metastases at study entry		
M0	13 (5%)	16 (6%)
M1A	41 (16%)	35 (14%)
M1B	56 (22%)	42 (16%)
M1C	145 (57%)	163 (63%)
Unknown	1 (<1%)	2 (1%)
Histological subtype		
Superficial spreading	85 (33%)	83 (32%)
Nodular	84 (33%)	80 (31%)
Other	86 (34%)	93 (36%)
Unknown	1 (<1%)	2 (1%)
(Continued from previous column)		
Number of lesions		
1–3	113 (44%)	111 (43%)
>3	143 (56%)	144 (56%)
Unknown	0	3 (1%)
Sum of longest diameters		
<44 mm	109 (43%)	103 (40%)
≥44 mm	147 (57%)	155 (60%)
Previously treated brain metastases	5 (2%)	8 (3%)
BRAF mutation genotype*		
V600E	197 (77%)	182 (71%)
V600K	27 (11%)	29 (11%)
V600D/R	4 (2%)	3 (1%)
Missing	28 (11%)	44 (17%)
Baseline PD-L1 status†		
Immune cells 1/2/3	160 (63%)	158 (61%)
Immune cells 0	85 (33%)	86 (33%)
Unknown	11 (4%)	14 (5%)
Previous adjuvant therapy	41 (16%)	30 (12%)

Data are n (%) or median range. Due to rounding, percentages may not add up to 100. PD-L1=programmed cell death ligand 1. *All patients are reported *BRAF*^{V600} mutation-positive status in melanoma tumour tissue by a locally approved test. *BRAF* mutation genotype is reported missing when sample was not centrally analysed owing to insufficient tumour sample. †PD-L1 positivity based on the proportion of cells per tumour area occupied by PD-L1–expressing tumour-infiltrating immune cells of any intensity (% immune cells). For percentage of immune cells, immunohistochemistry staining was scored as 0 (<1%), 1 (≥1%–<5%), 2 (≥5%–<10%), or 3 (if ≥10% of cells per area were PD-L1 positive).

Table 1: **Baseline characteristics**

statistical analysis plan. Analyses were performed using SAS Software version 9.4 (SAS Institute, Cary, NC, USA). Details of statistical considerations and the statistical analysis plan are available online. An independent data and safety monitoring committee regularly reviewed safety data.

Role of the funding source

The funder of the study provided the study drugs and collaborated with the authors on study design, data collection, data analysis, data interpretation, and writing of the report. The trial was done in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. All authors had full access to all the data. All authors had final responsibility for the decision to submit for publication.

Results

Between Jan 13, 2017, and April 26, 2018, 514 patients were enrolled and randomly assigned to the atezolizumab group (n=256) or the control group (n=258) and comprised the intention-to-treat analysis population. Baseline demographic and disease characteristics can be seen in table 1.

The atezolizumab safety population comprised patients who received at least one dose of atezolizumab (n=230). The control safety population comprised patients who received at least one dose of study drug but no atezolizumab (n=281). 26 patients from the atezolizumab intention-to-treat population did not receive atezolizumab and thus were part of the control safety population (figure 1).

At data cutoff (Oct 11, 2019), median follow-up in the overall study population was 18·9 months (IQR 10·4–23·8); 115 (45%) of 256 patients in the atezolizumab group and 131 (51%) of 258 patients in the control group had discontinued the study. The most common reason for study discontinuation was death, which occurred in 93 (36%) of 256 patients in the atezolizumab group and 112 (43%) of 258 patients in

the control group. Approximately 25% of all patients were continuing study treatment at the data cutoff: 71 (28%) of 256 patients in the atezolizumab group and 55 (21%) of 258 patients in the control group.

At data cutoff, 327 patients had progressive disease by investigator assessment or had died, including 148 (58%) patients in the atezolizumab group and 179 (69%) of 258 patients in the control group. The addition of atezolizumab to vemurafenib and cobimetinib significantly prolonged median progression-free survival per investigator assessment from 10·6 months (95% CI 9·3–12·7) in the control group to 15·1 months (11·4–18·4) in the atezolizumab group (HR 0·78; 95% CI 0·63–0·97; log-rank p=0·025; figure 2A).

Median progression-free survival as assessed by the independent review committee also favoured atezolizumab (16·1 months; 95% CI 11·3–18·5) compared with control (12·3 months; 95% CI 10·8–14·7; HR 0·85; 95% CI 0·67–1·07; log-rank p=0·16; appendix p 15).

In evaluating the concordance between progressive disease assessed by independent review committee versus progressive disease assessed by the study investigators, a high concordance rate of 375 (77%) of 484 concordance-evaluable patients was observed. However, among the 109 patients with discordant results, the primary reason was assessment of progressive disease per the study investigators but not per independent review committee, which was observed in 90 (83%) of 109 patients and was balanced across treatment groups. This led to informative censoring in independent review committee analyses, resulting in fewer progression-free survival events contributing to the independent review committee analysis, and was the probable reason for the differences observed between progression-free survival per independent review committee and progression-free survival per study investigators.

Analysis of progression-free survival benefit across predefined patient subgroups showed a trend favouring the atezolizumab group on the basis of the directionality of the hazard ratio, consistent with results observed for the overall study population (figure 2B).

The analysis of the cumulative hazard function for the primary endpoint showed that the proportional hazards assumption was not met owing to a delayed separation. To further assess the effect of delayed separation, exploratory analyses were done by means of the weighted log-rank test, which weighted late events more heavily. The Fleming-Harrington weight function was applied and weights were specified as (0,1), (1,1), and (2,2). The corresponding stratified weighted log-rank test p values were 0·0040, 0·0038, and 0·0020, further supporting the results of the primary analysis.

At this interim analysis of overall survival, 205 patients had died: 93 (36%) of 256 patients in the atezolizumab group and 112 (43%) of 258 patients in the control group (HR 0·85; 95% CI 0·64–1·11; log-rank p=0·23). The estimated 2-year event-free rate for overall survival was

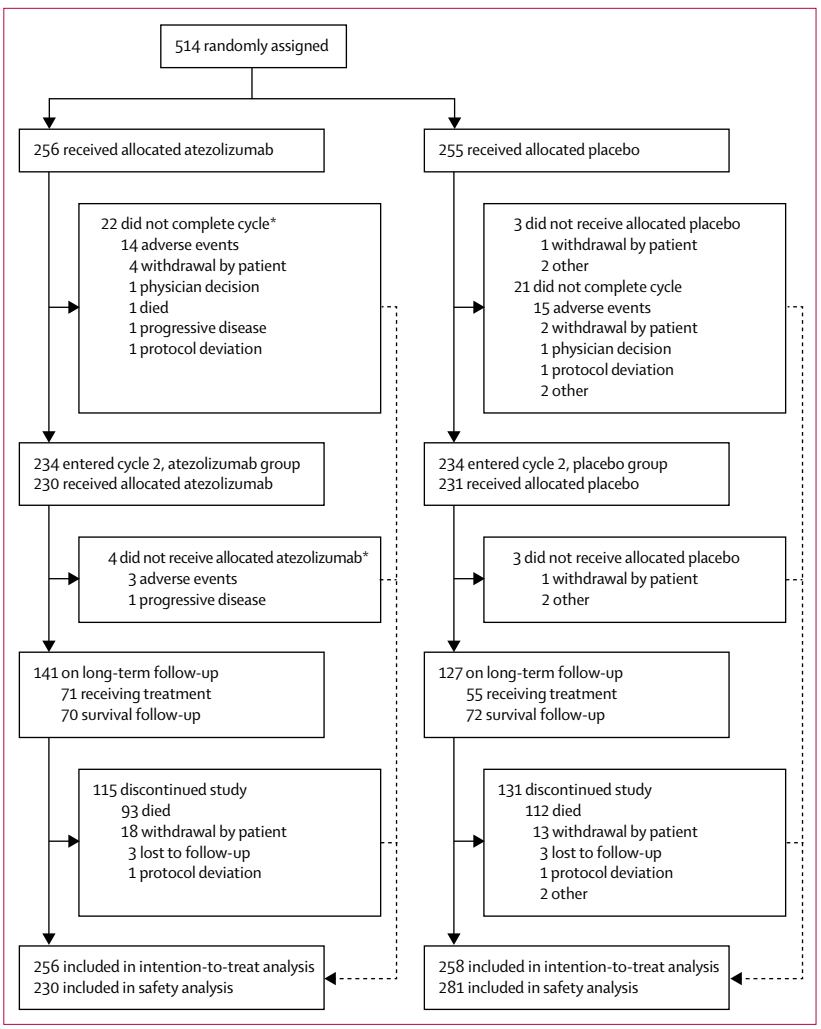


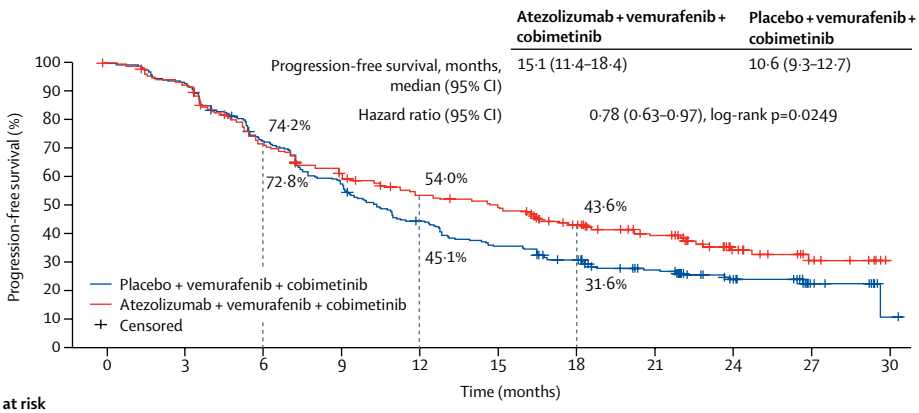
Figure 1: **Trial profile**
*These patients did not receive any dose of atezolizumab and were therefore included in the safety population for the control group.

60% in the atezolizumab group versus 53% in the placebo group (appendix p 16).

Investigator-assessed confirmed objective response rates were similar between the atezolizumab (66·3%; 95% CI 60·1–72·1) and control groups (65·0%; 58·7–71·0). Rates of complete response (15·7% *vs* 17·1%), partial response (50·6% *vs* 48·0%), and stable disease (22·7% *vs* 22·8%) were also similar between the atezolizumab and control groups. However, median duration of response was longer in the atezolizumab group (21·0 months; 95% CI 15·1 to not estimable) compared with the control group (12·6 months; 10·5–16·6; figure 3).

Overall, 511 patients (>99%) received at least one dose of study drug and were included in the safety analyses. In the atezolizumab group, median duration of treatment was 9·2 months (IQR 3·3–19·0) for atezolizumab, 9·8 months (IQR 4·5–19·8) for vemurafenib, and 10·0 months (IQR 4·8–20·1) for cobimetinib. In the

A



Number at risk

Placebo + vemurafenib + cobimetinib	258	230	179	143	107	86	71	51	27	11	1
Atezolizumab + vemurafenib + cobimetinib	256	229	174	149	123	114	90	66	34	11	

B

	Atezolizumab + vemurafenib + cobimetinib (n=256)		Placebo + vemurafenib + cobimetinib (n=258)		Hazard ratio	95% Wald CI
	n	Events	n	Events		
Randomised treatment group	**256**	**148**	**258**	**179**	**0·77**	**(0·62–0·96)**
Age group, years						
<65	195	114	199	134	0·82	(0·64–1·06)
≥65	61	34	59	45	0·63	(0·40–0·99)
Race						
White	243	138	246	170	0·76	(0·60–0·95)
Non-white	13	10	12	9	1·07	(0·43–2·65)
Sex						
Male	150	81	149	101	0·75	(0·56–1·01)
Female	106	67	109	78	0·81	(0·58–1·13)
Geographical region (IWRS)						
North America	13	7	14	10	0·85	(0·32–2·27)
Europe	203	124	203	142	0·79	(0·62–1·00)
Australia, New Zealand, or other	40	17	41	27	0·69	(0·37–1·27)
Serum lactate dehydrogenase at baseline (IWRS)						
≤upper limit	172	88	173	106	0·76	(0·57–1·01)
>upper limit	84	60	85	73	0·81	(0·58–1·14)
Eastern Cooperative Oncology group performance status						
0	195	103	198	136	0·68	(0·53–0·88)
1	61	45	56	42	1·08	(0·71–1·65)
Melanoma staging						
IIIC	14	4	16	11	0·37	(0·12–1·17)
IV	242	144	240	168	0·80	(0·64–1·00)
Previous adjuvant therapy						
Yes	41	20	30	22	0·57	(0·31–1·04)
No	215	128	228	157	0·81	(0·64–1·03)
PD-L1 expression						
IC 1/2/3	160	89	158	108	0·80	(0·60–1·06)
IC 0	85	53	86	62	0·76	(0·53–1·10)
Organ involvement						
<3	205	109	197	131	0·74	(0·58–0·96)
≥3	51	39	57	48	0·94	(0·61–1·44)
Sum of longer diameter						
<44 mm	109	55	99	65	0·70	(0·49–1·01)
≥44 mm	147	93	155	114	0·83	(0·63–1·10)
Histological subtype (initial diagnosis)						
Superficial spreading	85	54	83	58	0·86	(0·59–1·24)
Nodular	84	49	80	56	0·72	(0·49–1·06)
Other	86	44	93	65	0·72	(0·49–1·07)
Distant metastasis, stage (study entry)						
M0	13	4	16	11	0·42	(0·13–1·33)
M1A	41	18	35	20	0·72	(0·38–1·37)
M1B	56	29	42	27	0·80	(0·47–1·36)
M1C	145	97	163	121	0·86	(0·66–1·13)

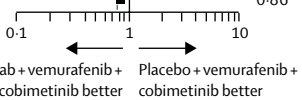


Figure 2: **Progression-free survival in the intention-to-treat population as assessed by the study investigators**
(A) Progression-free survival in the intention-to-treat population by key prognostic subsets as assessed by the study investigators. (B) Unstratified hazard ratios are displayed. IWRS=interactive web-based response system.

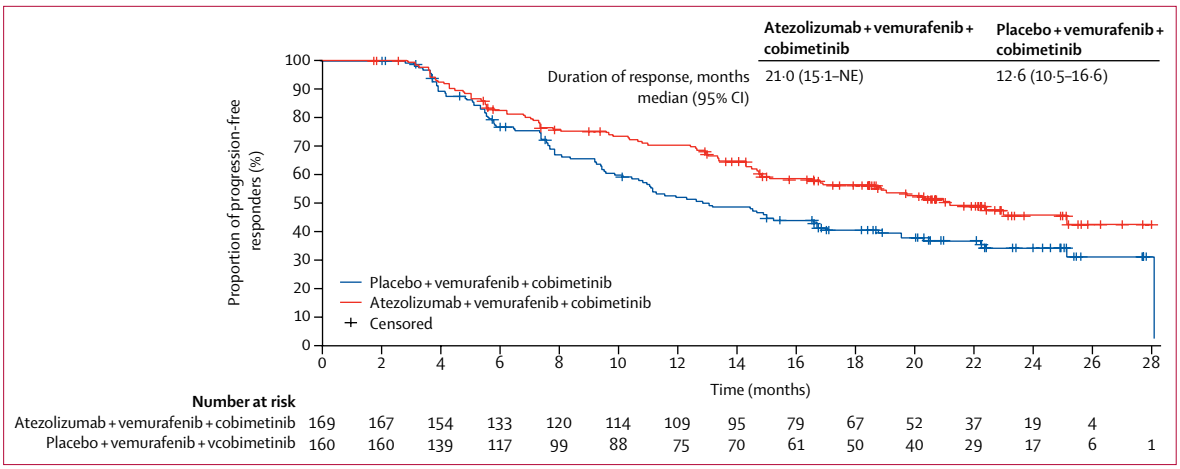


Figure 3: Kaplan-Meier estimate of duration of response in the intention-to-treat population
NE=not estimable.

control group, median duration of treatment was 9·0 months (IQR 4·2–17·3) for placebo, 7·9 months (IQR 3·3–17·3) for vemurafenib, and 7·8 months (IQR 2·6–17·2) cobimetinib.

Treatment-related adverse events occurred in 228 (99%) of 230 patients in the atezolizumab group and 279 (99%) of 281 patients in the control groups. Common treatment-related adverse events (≥10% in any group) that occurred more frequently with atezolizumab versus control (≥5% difference) were increased blood creatine phosphokinase, pyrexia, arthralgia, myalgia, liver enzymes and bilirubin, hyperthyroidism, hypothyroidism, pneumonitis, pruritus, and peripheral oedema (table 2). The prevalence of treatment-related grade 3 or 4 adverse events was 182 (79%) of 230 in the atezolizumab group and 205 (73%) of 281 in the control group. Common grade 3 or 4 treatment-related adverse events that occurred more frequently with atezolizumab (≥2% difference) versus control were blood creatine phosphokinase increased, alanine aminotransferase increased, maculopapular rash, amylase increased, aspartate aminotransferase increased, photosensitivity reactions, nausea, and infusion-related reactions. Among the common treatment-related adverse events, grade 4 events reported with a frequency of 1% or more in either the atezolizumab or control groups were blood creatine phosphokinase increased (16 [7·0%] *vs* 15 [5·3%]), lipase increased (18 [7·8%] *vs* 15 [5·3%]), alanine aminotransferase increased (2 [0·9%] *vs* 3 [1·1%]), and amylase increased (2 [0·9%] *vs* 3 [1·1%]). The prevalence of treatment-related serious adverse events was similar between atezolizumab (77 [33%] of 230) and control (81 [29%] of 281; appendix p 2).

Immune-mediated adverse events of special interest, defined as adverse events with potential immune-related cause where systemic corticosteroids were used within 30 days of onset, were higher in the atezolizumab (145 [63%] of 230) versus the control group (142 [51%] of 281). Immune-mediated adverse events of special interest that occurred more frequently in the atezolizumab group (≥2% difference *vs* control group) were aspartate aminotransferase increased, alanine aminotransferase increased, pneumonitis, amylase increased, dermatitis acneiform, uveitis, hyperthyroidism, and acne (appendix p 3). In the atezolizumab group, immune-mediated adverse events requiring use of high-dose corticosteroids (≥40 mg prednisone or equivalent) in 2% of patients or more were alanine aminotransferase increased (29 [13%] of 230), aspartate aminotransferase increased (28 [12%]), lipase increased (13 [6%]), rash (13 [6%]), pneumonitis (11 [5%]), amylase increased (8 [3%]), maculo-papular rash (7 [3%]), blood bilirubin increased (5 [2%]), chorioretinopathy (5 [2%]), dermatitis acneiform (5 [2%]), and γ-glutamyltransferase increased (5 [2%]). The median duration of high-dose corticosteroid use for immune-mediated adverse events by type of event ranged from 3·0 to 16·5 days.

Discontinuation of all treatment because of adverse events occurred in 29 (13%) of 230 patients in the atezolizumab group and 44 (16%) of 281 patients in the control group, most commonly as a result of the following abnormal laboratory investigations: alanine aminotransferase increased (four [1·7%] *vs* four [1·4%]), aspartate aminotransferase increased (three [1%] *vs* one [<1%]), hepatitis (three [1%] *vs* one [<1%]), and lipase increased (two [1%] *vs* three [1%]; appendix p 4). Grade 5 adverse events were reported in seven patients in each treatment group and most events were considered unrelated to treatment, with no trend or pattern identified (appendix p 5). Grade 5 adverse events in the atezolizumab group were sepsis (two patients, 1%), as well as one patient each from cardiac arrest, pneumonia, septic shock, hepatic failure, and hepatitis fulminant (<1% each). Grade 5 adverse events in the control group were cardiac arrest, cardiac failure, left ventricular failure, cerebrovascular accident, hydrocephalus, gastrointestinal haemorrhage, and pulmonary haemorrhage (one patient

	Atezolizumab + vemurafenib + cobimetinib (n=230)		Placebo + vemurafenib + cobimetinib (n=281)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any treatment-related adverse event	228 (99%)	182 (79%)	279 (99%)	205 (73%)
Treatment-related adverse events with a prevalence ≥10%*				
Blood creatine phosphokinase increased†	118 (51%)	46 (20%)	126 (45%)	42 (15%)
Rash	94 (41%)	20 (9%)	115 (41%)	25 (9%)
Diarrhoea	97 (42%)	4 (2%)	131 (47%)	9 (3%)
Arthralgia	90 (39%)	7 (3%)	79 (28%)	6 (2%)
Pyrexia	89 (39%)	3 (1%)	73 (26%)	3 (1%)
Alanine aminotransferase aspartate increased†	78 (34%)	30 (13%)	64 (23%)	25 (9%)
Lipase increased†	74 (32%)	47 (20%)	77 (27%)	58 (21%)
Aminotransferase increased†	69 (30%)	19 (8%)	57 (20%)	12 (4%)
Fatigue	62 (27%)	3 (1%)	74 (26%)	1 (<1%)
Nausea	54 (23%)	1 (<1%)	74 (26%)	7 (2%)
Pruritus	49 (21%)	2 (1%)	45 (16%)	1 (<1%)
Myalgia	48 (21%)	2 (1%)	35 (12%)	1 (<1%)
Photosensitivity reaction	48 (21%)	2 (1%)	70 (25%)	9 (3%)
Maculopapular rash	47 (20%)	29 (13%)	53 (19%)	27 (10%)
Amylase increased	46 (20%)	23 (10%)	45 (16%)	19 (7%)
Hyperthyroidism	39 (17%)	2 (1%)	21 (8%)	0
Hypothyroidism	38 (17%)	0	17 (6%)	0
Asthenia	37 (16%)	4 (2%)	39 (14%)	2 (1%)
Blood creatinine increased	36 (16%)	0	33 (12%)	1 (<1%)
Chorioretinopathy	34 (15%)	0	37 (13%)	1 (<1%)
Blood alkaline phosphatase increased	33 (14%)	7 (3%)	38 (14%)	8 (3%)
Dermatitis acneiform	33 (14%)	5 (2%)	42 (15%)	5 (2%)
Vomiting	29 (13%)	2 (1%)	41 (15%)	5 (2%)
Anaemia	26 (11%)	3 (1%)	24 (9%)	7 (3%)
Erythema	26 (11%)	0	35 (12%)	0
Peripheral oedema	26 (11%)	0	17 (6%)	0
Sunburn	25 (11%)	0	26 (9%)	1 (<1%)
Decreased appetite	24 (10%)	0	34 (12%)	2 (1%)
Blood bilirubin increased	23 (10%)	2 (1%)	18 (6)	1 (<1%)
Dry skin	23 (10%)	0	24 (9%)	0
Pneumonitis	23 (10%)	2 (1%)	13 (5%)	0

*Listed adverse events were reported at a frequency of ≥10%, along with corresponding frequencies for grade 3–4 events. †Preferred terms for which grade 4 events were reported in either treatment group.

Table 2: **Prevalence of treatment-related adverse events**

[<1%] each). Hepatic failure and hepatitis fulminant in the atezolizumab group and pulmonary haemorrhage in the control group were considered related to treatment. Notably, the patients with hepatic failure and fulminant hepatitis in the atezolizumab group had liver lesions. The patient with pulmonary haemorrhage in the control group had a lung lesion.

Discussion

The addition of atezolizumab to vemurafenib and cobimetinib significantly prolonged the primary endpoint of investigator-assessed progression-free survival from 10·6 months to 15·1 months and reduced the relative risk for progression or death by 22% versus the comparator combination of vemurafenib and cobimetinib. The choice of the comparator was based on the prevailing standard-of-care at time of study design. Progression-free survival curves started to separate after 7 months and maintained benefit in favour of the atezolizumab group. Overall response rates in the atezolizumab (66%) and control groups (65%) were similar and the progression-free survival benefit was driven, in part, by the prolonged duration of response with atezolizumab versus control (21·0 *vs* 12·6 months). Although overall survival was immature, the curves appeared to diverge after 15 months in favour of the atezolizumab group. The estimated 12-month event-free survival rates were 77% and 76% in the control group and the 24-month event-free survival rates were 60% in the atezolizumab group and 53% in the control group. Given the late separation of the progression-free survival and overall survival curves, longer follow-up, particularly relevant for the tail end of the curves, might reveal more clinically meaningful benefit and inform the optimal treatment paradigm.

These findings are similar to published findings from the phase 2 study KEYNOTE-022, in which patients with *BRAF*^{V600}-mutated metastatic melanoma treated with the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab plus dabrafenib and trametinib had longer median progression-free survival (16·0 months) versus those treated with placebo plus dabrafenib and trametinib (10·3 months).[27,28] As in the current study, the progression-free survival curves separated later (starting in month 7), and progression-free survival benefit was driven by prolonged median duration of response (increased from 12·5 months with dabrafenib and trametinib to 18·7 months with dabrafenib, trametinib, and pembrolizumab), even though the overall response rate was numerically higher with placebo (72%) versus pembrolizumab (63%). Further, a delayed separation of the overall survival curves was also evident in KEYNOTE-022.[28] Thus, combining BRAF and MEK inhibitors with PD-L1 or PD-1-directed checkpoint inhibition provides response rates similar to those observed with BRAF and MEK inhibitor therapy alone, but prolongs the duration of response.

In this study, the proportion of patients in the control group with grade 3 or 4 adverse events was higher than that reported in the coBRIM study evaluating an identical regimen.[2,22] The increased frequency of grade 3 or 4 events in IMspire150 was probably the result of protocol-mandated monitoring of laboratory abnormalities and class-effect adverse events that were not routinely assessed in other clinical trials, including coBRIM and KEYNOTE-022.[22,28] Notably, in the current study, lipase and amylase increases were not associated with clinically significant adverse events, such as pancreatitis, and abnormal liver function tests and creatine phosphokinase elevations were largely asymptomatic. The addition of

atezolizumab only slightly increased the prevalence of treatment-related grade 3 or 4 adverse events (79%) versus control (73%) and did not escalate typical BRAF plus MEK inhibitor-associated adverse events. The frequency of some PD-L1 inhibitor-associated adverse events, such as thyroid function disorders, pneumonitis, and elevated liver function tests, was increased, but most of these adverse events were grade 1 or 2. Although the number of adverse events with concomitant use of corticosteroids was high in both treatment groups, use of high-dose corticosteroids in the atezolizumab group was relatively low; importantly, corticosteroid treatment duration was short (median <16·5 days). Nevertheless, discontinuation of all study treatment owing to adverse events was not increased in the atezolizumab group (13%) and was within the range observed with vemurafenib plus cobimetinib doublet therapy (16% in this study; 11% in coBRIM).[22] In contrast, in KEYNOTE-022, grade 3 and above adverse events increased from 45% with the doublet to 70% in the triplet arm, and discontinuations owing to adverse events also increased from 15% with the doublet to 25% with the triplet arm. Potential reasons for the relatively similar safety profiles between treatment groups in IMspire150 include the dosing schedule (doublet therapy only in cycle 1 and reduced-dose vemurafenib in the atezolizumab group), and the possibility that the PD-L1 inhibitor atezolizumab might be better tolerated than a PD-1 inhibitor as suggested by meta-analysis.[29] Previous analyses based on pooled data from clinical studies evaluating vemurafenib or vemurafenib and cobimetinib show that efficacy outcomes with full-dose versus reduced-dose vemurafenib are similar,[30] supporting the use of reduced-dose vemurafenib in this study. Furthermore, response rates observed in this study are similar to those reported in KEYNOTE-22 that dosed dabrafenib at the full approved dose.

The role of the triple combination of PD-1 or PD-L1, BRAF, and MEK inhibitors in the rapidly evolving melanoma treatment landscape remains to be determined, particularly with the increasing use of combined CTLA-4–PD-1 therapy. Ongoing studies, such as ImmunoCobiVem (NCT02902029), SECOMBIT (NCT02631447), DREAMseq (NCT02224781), and part 3 of COMBI-i (investigating dabrafenib and trametinib plus the PD-1 inhibitor spartalizumab or placebo), will certainly inform the treatment paradigm with regard to optimal combinations and sequencing. Our study shows that the triple combination is superior across prognostic subgroups, regardless of lactate dehydrogenase concentration and PD-L1 status. Other studies are investigating the combination of atezolizumab, vemurafenib, and cobimetinib in the neoadjuvant setting (NEO-VC/NCT02303951) and in patients with brain metastases (Tricotel/NCT03625141).

In conclusion, our study showed that the addition of the PD-L1 inhibitor atezolizumab to the BRAF pathway-targeted agents vemurafenib and cobimetinib represents a safe and efficacious treatment option for patients with *BRAF*^{V600} mutation-positive metastatic melanoma.

Contributors

RG, DS, HG, CR, KL, SP, RPP, TE, PR, LD, GMM, GAM, and PAA collected data. RG, KL, CR, AU, VM, GAM, and PAA provided clinical and scientific input on the study design and protocol. All authors had full access to the data output and interpreted the data. KC-H did the statistical analyses. YY provided biomarker input, data analysis, and interpretation. The first and senior authors (RG, GAM, and PAA) wrote the first draft of the manuscript. All authors critically reviewed the manuscript and participated in the revision of the manuscript.

Declaration of interests

RG reports other from Roche during the conduct of the study; personal fees and non-financial support from Bristol-Myers Squibb, Roche Pharma, and Merck Serono; grants, personal fees, and non-financial support from Amgen, Novartis, Pierre Fabre, and Sanofi Regeneron; personal fees from 4SC, Almirall Hermal, Merck Sharp & Dohme, and Sun Pharma; grants from Johnson & Johnson; and grants and personal fees from Pfizer. DS declares no competing of interests. HG reports grants and personal fees from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Roche; personal fees from Amgen; and personal fees from Pierre Fabre. CR reports personal fees and travel grants for participation in advisory boards for Amgen, Biothera, Bristol-Myers Squibb, Roche, Pierre Fabre, Merck, Novartis, Amgen, Merck Sharp & Dohme, Sanofi, and Ultimovacs. KL reports grants from Roche–Genentech during the conduct of the study and personal fees from Roche–Genentech. SP reports no competing interests. RPP reports grants from Roche–Genentech during the conduct of the study; grants from AstraZeneca, BeiGene, Myovant, Pfizer, Regeneron, and Sanofi; and grants and personal fees form Roche–Genentech. TE reports other from Roche during the conduct of the study; personal fees from Bristol-Myers Squibb, Leo Pharma, Merck Sharp & Dohme, Novartis, Roche, and personal fees from Sanofi. PR reports personal fees from Bristol-Myers Squibb, Novartis, Roche, Merck Sharp & Dohme, Pierre Fabre, and Blueprint Medicines. LD reports grants from Amgen, Bristol-Myers Squibb, Roche, Novartis, and Merck Sharp & Dohme. GMM reports grants from Roche–Genentech. YY, K-CH, AU, and VM report employment with Roche–Genentech. GAM reports other from Array Biopharma and Roche–Genentech. PAA reports grants and personal fees from Array, Bristol-Myers Squibb, and Roche–Genentech; and personal fees from Alkermes, AstraZeneca, Genmab, Idera, Immunocore, Incyte, Italfarmaco, Medimmune, Merck, Merck Sharp & Dohme, NewLink Genetics, Novartis, Pierre Fabre, Serono, Syndax, Sun Pharma, Sanofi, Ultimovacs, Sandoz, and 4SC.

Data sharing

Qualified researchers might request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Additional details on Roche's criteria for eligible studies are available here: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For more details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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