European Journal of Cancer 178 (2023) 180–190

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Phase 1b study of cobimetinib plus atezolizumab in patients with advanced *BRAF*^{V600} wild-type melanoma progressing on prior anti–programmed death-1 therapy

Shahneen Sandhu [a,*], Victoria Atkinson [b], Maria González Cao [c], Theresa Medina [d], Ainara Soria Rivas [e], Alexander M. Menzies [f,g,h], Ivor Caro [i], Louise Roberts [i], Yuyao Song [i], Yibing Yan [i], Yu Guo [i], Cloris Xue [i], Georgina V. Long [f,g,h]

[a] *Department of Medical Oncology, Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, Australia*
[b] *Department of Medical Oncology, Gallipoli Medical Research Foundation, Greenslopes Private Hospital, Greenslopes, and University of Queensland, Brisbane, Australia*
[c] *Department of Oncology, Instituto Oncológico Dr. Rosell, Hospital Universitario Dexeus, Barcelona, Spain*
[d] *Department of Medical Oncology, UC Health Cancer Care, University of Colorado Cancer Center, Aurora*
[e] *Department of Medical Oncology, University Hospital Ramón y Cajal, Madrid, Spain*
[f] *Melanoma Institute Australia, The University of Sydney, Sydney, Australia*
[g] *Faculty of Medicine and Health, The University of Sydney, Sydney, Australia*
[h] *Department of Oncology, Royal North Shore and Mater Hospitals, Sydney, Australia*
[i] *Department of Oncology, Roche Genentech, South San Francisco, CA, USA*

Received 28 July 2022; received in revised form 22 September 2022; accepted 20 October 2022
Available online 2 November 2022

KEYWORDS
Melanoma;
Drug therapy combination;
Immunotherapy;
Tumour biomarkers

Abstract ***Objective:*** To evaluate the efficacy and safety of cobimetinib plus atezolizumab in the treatment of patients with advanced *BRAF*^{V600} wild-type melanoma who had progressed on prior anti–programmed death-1 (PD-1) therapy.

Patients and methods: This phase 1b, open-label, international multicentre study enrolled 3 cohorts. Herein, we report on patients in cohorts A and B who had progressed on prior anti–PD-1 therapy. Patients in cohort A received cobimetinib 60 mg once daily for 21 days followed by a 7-day break and concurrent intravenous atezolizumab 840 mg every 2 weeks.

* *Corresponding author:* Department of Medical Oncology, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC 3052, Australia. Fax: +3 8559 7739.

E-mail addresses: shahneen.sandhu@petermac.org (S. Sandhu), Victoria.Atkinson@health.qld.gov.au (V. Atkinson), mgonzalezcao@oncorosell.com (M.G. Cao), theresa.medina@ucdenver.edu (T. Medina), ainarasoria@hotmail.com (A.S. Rivas), alexander.menzies@sydney.edu.au (A.M. Menzies), caro.ivor@gene.com (I. Caro), robertl9@gene.com (L. Roberts), yuyao.song@roche.com (Y. Song), yyan@gene.com (Y. Yan), guoy52@gene.com (Y. Guo), cloris.xue@roche.com (C. Xue), Georgina.Long@sydney.edu.au (G.V. Long).

@ProfGLongMIA (G.V. Long)

https://doi.org/10.1016/j.ejca.2022.10.019

Patients in cohort B received the same dosing regimen as cohort A except for cycle 1 in which patients received cobimetinib only for the first 14 days prior to initiation of atezolizumab on cycle 1 day 15. Coprimary end-points were objective response rate and disease control rate. Secondary end-points were duration of response, progression free survival and overall survival.

Results: Between 19th June 2017 and 12th December 2018, 103 patients were enrolled. Median follow-up was 6.9 months (interquartile range, 4.8–10.1 months); objective response rate was 14.6% and disease control rate was 38.8% (95% confidence interval, 29.39–48.94). The median duration of response, progression-free survival and overall survival was 12.7 months, 3.8 months and 14.7 months, respectively. The most common adverse events were diarrhoea (75/103; 72.8%), dermatitis acneiform (57/103; 55.3%) and nausea (52/103; 50.5%). Thirty-four patients (33.0%) died: 33 (91.7%) due to progressive disease and one (1%) due to treatment-related oesophagitis.

Conclusions: Combination therapy with cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} wild-type melanoma with disease progression on or after prior anti–PD-1 therapy demonstrated limited activity.

Clinical trial registration: This study is registered with ClinicalTrials.gov; NCT03178851;

1. Introduction

Treatment for advanced *BRAF*^{V600} wild-type melanoma following the failure of anti–programmed cell death 1 (PD-1) monoclonal antibodies is often limited to single-agent ipilimumab or clinical trials. Most immune checkpoint inhibitors (ICIs) in the second-line setting have limited effectiveness and can result in toxicities. With an estimated 22%–60% of patients with metastatic melanoma relapsing after ICIs [1], there remains a critical unmet need for additional effective treatments in these patients.

Targeting the mitogen-activated protein kinase pathway is highly effective in *BRAF*-mutated melanoma, which accounts for approximately half of all melanomas [2]. About 15%–30% of melanomas harbour an activating *NRAS* mutation and 14% harbour *NF1* mutations (>50% of which result in loss of function) [3]. Thus, even in melanomas that do not harbour constitutively active mutant *BRAF*, the activation of other components of the RAS/RAF/MEK pathway is common. Preclinical models have demonstrated antitumour response with MEK inhibition through its effects on T cells [4]. The phase 3 NEMO study demonstrated a modest increase in progression-free survival (PFS) with the MEK inhibitor binimetinib compared with dacarbazine in patients with *NRAS* mutation-positive melanoma [5]. In addition, combination therapy with MEK inhibition plus anti–PD-1/programmed death ligand-1 (PD-L1) has shown synergistic tumour growth inhibition in preclinical models [6].

Cobimetinib, a highly selective MEK1/MEK2 inhibitor, is approved for use in combination with vemurafenib for advanced *BRAF*^{V600} mutation-positive melanoma [7]. Atezolizumab, a humanised immunoglobulin G1 monoclonal antibody that targets PD-L1, enhances tumour-specific T-cell responses and has demonstrated an antitumour activity in multiple tumour types including metastatic melanoma [8–10]. In a phase 1b multicohort study of anti-PD-L1/PD-1–naive patients with solid tumours, cobimetinib plus atezolizumab showed an objective response rate (ORR) of 50% and median PFS of 15.7 months in 10 patients with *BRAF*^{V600} wild-type melanoma [11].

Herein, we report the results of a phase 1b study that evaluated the efficacy and safety of cobimetinib plus atezolizumab in patients with advanced *BRAF*^{V600} wild-type melanoma who had progressed on or after prior anti–PD-1 therapy.

2. Methods

2.1. Study design and participants

This open-label, multicentre phase 1b study (NCT03178851) was conducted at 18 sites in Australia, Spain and the United States. The study enrolled patients with *BRAF*^{V600} wild-type advanced melanoma who had progressed on or after prior anti-PD-1 therapy (cohorts A and B) or were treatment naive (cohort C). Data from cohorts A and B are presented here; results for cohort C are published separately [12].

Key eligibility criteria for cohorts A and B were aged ≥18 years with histologically confirmed stage IV or unresectable stage IIIc *BRAF*^{V600} wild-type melanoma, with measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, and disease progression on or after anti-PD-1 treatment (monotherapy or in combination with other agents) for metastatic melanoma. Patients in cohort B must have

progressed on or after anti-PD-1 treatment within 12 weeks before the study start and have had ≥2 accessible lesions amenable to a biopsy. Detailed eligibility criteria are available under Supplementary Materials Table A1.

The study was approved by the institutional ethics review board for each study site (Supplementary Materials Table A2) and was conducted in line with International Conference on Harmonization E6 guidelines for Good Clinical Practice and the regulations of the country in which it was conducted. All patients provided written informed consent before participation in the study.

2.2. Procedures and biopsies

Patients in cohort A received atezolizumab 840 mg intravenously every 2 weeks and cobimetinib 60 mg once daily for 21 days followed by a 7-day break in a 28-day cycle. Patients in cohort B had a regimen identical to cohort A, except for cycle 1, during which patients received cobimetinib 60 mg once daily only for the first 14 days and atezolizumab 840 mg intravenously beginning on cycle 1 day 15 and continued thereafter every 2 weeks.

Study treatment continued until disease progression (i.e. confirmed 4 weeks later for clinically stable patients with a favourable benefit-risk assessment), death, initiation of subsequent anticancer therapy or unacceptable toxicity, whichever occurred first. Measurable and non-measurable lesions were documented at screening, and response assessments were subsequently assessed at 8-week intervals per RECIST v1.1.

All patients were required to provide archival tissue (<5 years old) or a fresh biopsy for study entry (Supplementary Appendix Figure A1). Via a separate optional consent, patients in cohort A were requested to provide biopsies at baseline (before cycle 1 day 1) and 4–6 weeks after the first atezolizumab dose. Patients in cohort B consented to provide mandatory biopsies at baseline, on-treatment (cycle 1 days 10–14) and post-treatment (radiographic progression) and a second optional on-treatment biopsy (cycle 2 from 4 to 6 weeks after the first atezolizumab dose). Additional details on biopsy collection are provided under Supplementary Materials.

2.3. Outcomes

The coprimary efficacy end-points were ORR (proportion of patients with a complete response [CR] or a partial response [PR] on 2 consecutive occasions ≥4 weeks apart, per RECIST v1.1) and disease control rate (DCR; proportion of patients with a CR, PR, or stable disease [SD] at 16 weeks). Secondary efficacy endpoints were duration of response (DoR; time of first occurrence of a documented overall response to disease progression or death from any cause, whichever occurred first), overall survival (OS; time from Cycle 1, Day 1 to death from any cause) and PFS (time from Cycle 1, Day 1 to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurred first). Safety was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

Table 1
Patient demographics and baseline characteristics.

	Cohort A	Cohort B	All patients
N	92	11	103
Age, y, median (range)	62.5 (34–90)	62.0 (43–74)	62.0 (34–90)
Sex			
Male	59 (64.1)	8 (72.7)	67 (65.0)
Female	33 (35.9)	3 (27.3)	36 (35.0)
Geographic region			
Europe	22 (23.9)	2 (18.2)	24 (23.3)
North America	20 (21.7)	5 (45.5)	25 (24.3)
South Asia	50 (54.3)	4 (36.4)	54 (52.4)
ECOG performance status			
0	67 (72.8)	9 (81.8)	76 (73.8)
1	25 (27.2)	2 (18.2)	27 (26.2)
Distant metastasis[a]			
M0	5 (5.4)	1 (9.1)	6 (5.8)
M1a	9 (9.8)	1 (9.1)	10 (9.7)
M1b	18 (19.6)	4 (36.4)	22 (21.4)
M1c	59 (64.1)	5 (45.5)	64 (62.1)
Mx	1 (1.1)	0	1 (1.0)
Number of disease sites, median (range)	3 (1–11)	3 (2–7)	3 (1–11)
Liver metastasis			
Present	25 (27.2)	2 (18.2)	27 (26.2)
Absent	67 (72.8)	9 (81.8)	76 (73.8)
Lactate dehydrogenase level			
>ULN	40 (44.9)	6 (54.4)	46 (46.0)
≤ULN	49 (55.1)	5 (45.5)	54 (54.0)
PD-L1 status[b]			
IC0	26 (32.1)	5 (55.6)	31 (34.4)
IC1/2/3	55 (67.9)	4 (44.4)	59 (65.6)
Prior adjuvant therapy[c]			
Yes	37 (40.2)	7 (63.6)	44 (42.7)
No	55 (59.8)	4 (36.4)	59 (57.3)
Prior adjuvant ipilimumab			
Yes	12 (13.0)	2 (18.2)	14 (13.6)
No	80 (87.0)	9 (81.8)	89 (86.4)
Prior treatment for brain metastases	9 (9.8)	1 (9.1)	10 (9.7)
Median time from initial melanoma diagnosis to study entry, mo (range)	94.0 (15.2–942.7)	81.2 (49.8–362.1)	93.4 (15.2–942.7)
Biomarker evaluable population, *n*			
BRAF mutant/fusion	–	–	8
NF1 mutant	–	–	17
RAS mutant	–	–	42
Triple wild type	–	–	19

Data represent *N* (%), unless otherwise specified.
[a] Per American Joint Committee on Cancer Staging Manual, 7th edition.
[b] PD-L1 expression was assessed by immunohistochemistry using an SP142 antihuman PD-L1 rabbit monoclonal antibody (Ventana Medical Systems, Tucson, AZ, USA).
[c] All prior cancer therapies including radiotherapy. Tumour sections stained for PD-L1 were categorized into subgroups defined by threshold levels of staining for PD-L1 expressing tumour-infiltrating ICs of any intensity (IC0 <1%; IC1/2/3 ≥ 1%). Abbreviations: ECOG, Eastern Cooperative Oncology Group; IC, immune cell; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.

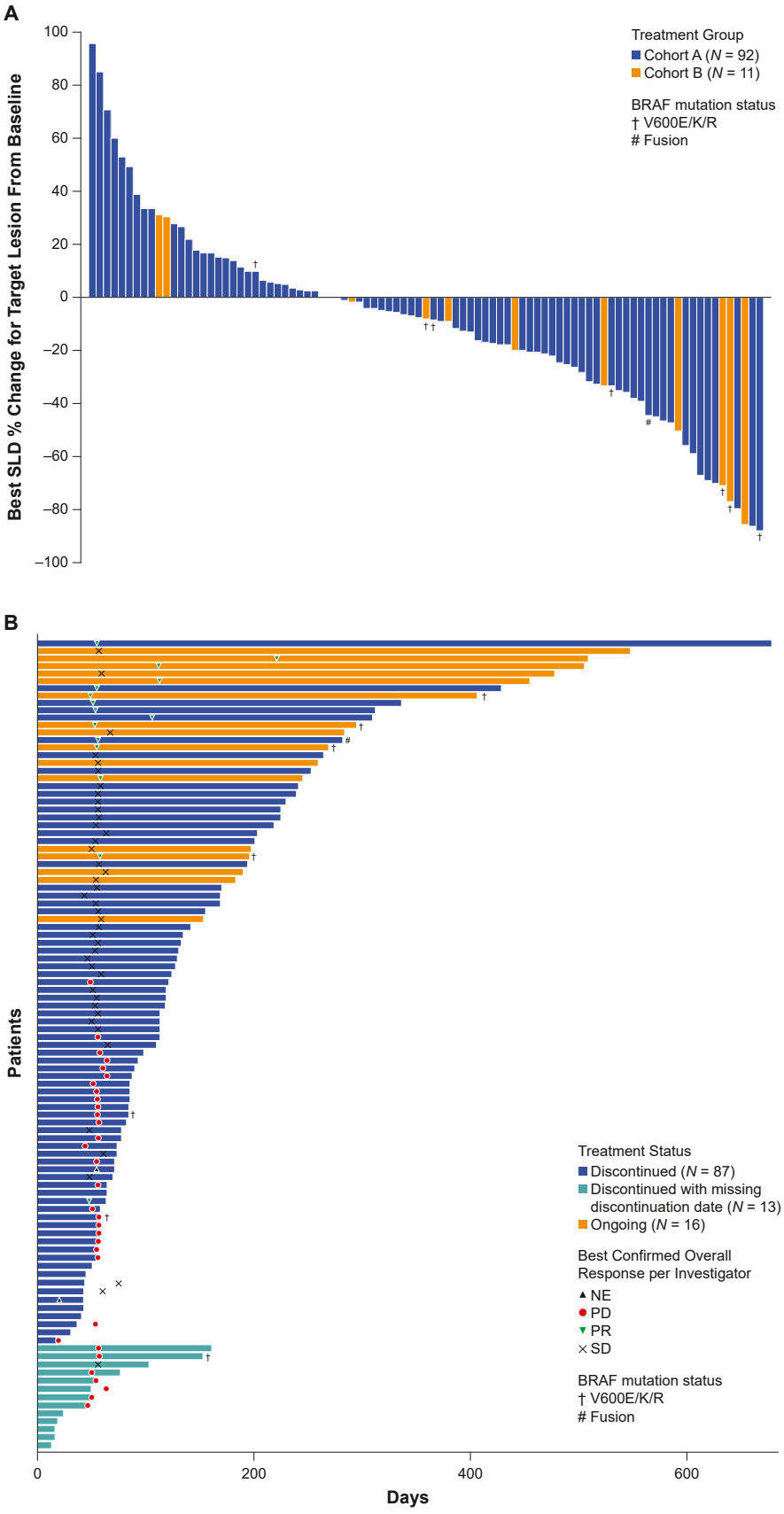


Fig. 1. Patient tumour outcomes. (A) Waterfall plot showing maximal reduction in target lesion size from baseline. (B) Swimmer plot showing individual patients' outcomes and time on treatment. For patients with missing discontinuation dates, date of treatment discontinuation has been substituted with the date of last exposure. NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters.

Table 2
Tumour response rates.

	Cohort A	Cohort B	All patients
N	92	11	103
Objective response rate	11 (12.0)	4 (36.4)	15 (14.6)
95% CI	6.12–20.39	10.93–69.21	8.39–22.88
Complete response	0 (0)	0 (0)	0 (0)
Partial response	11 (12.0)	4 (36.4)	15 (14.6)
Stable disease	40 (43.5)	3 (27.3)	43 (41.7)
Progressive disease	28 (30.4)	4 (36.4)	32 (31.1)
Disease control rate[a]	34 (37.0)	6 (54.5)	40 (38.8)
95% CI	27.12–47.66	23.38–83.25	29.39–48.94

All data are represented as *N* (%), unless otherwise specified.
[a] Disease control rate was defined as the confirmed objective response rate plus stable disease at 16 weeks posttreatment.

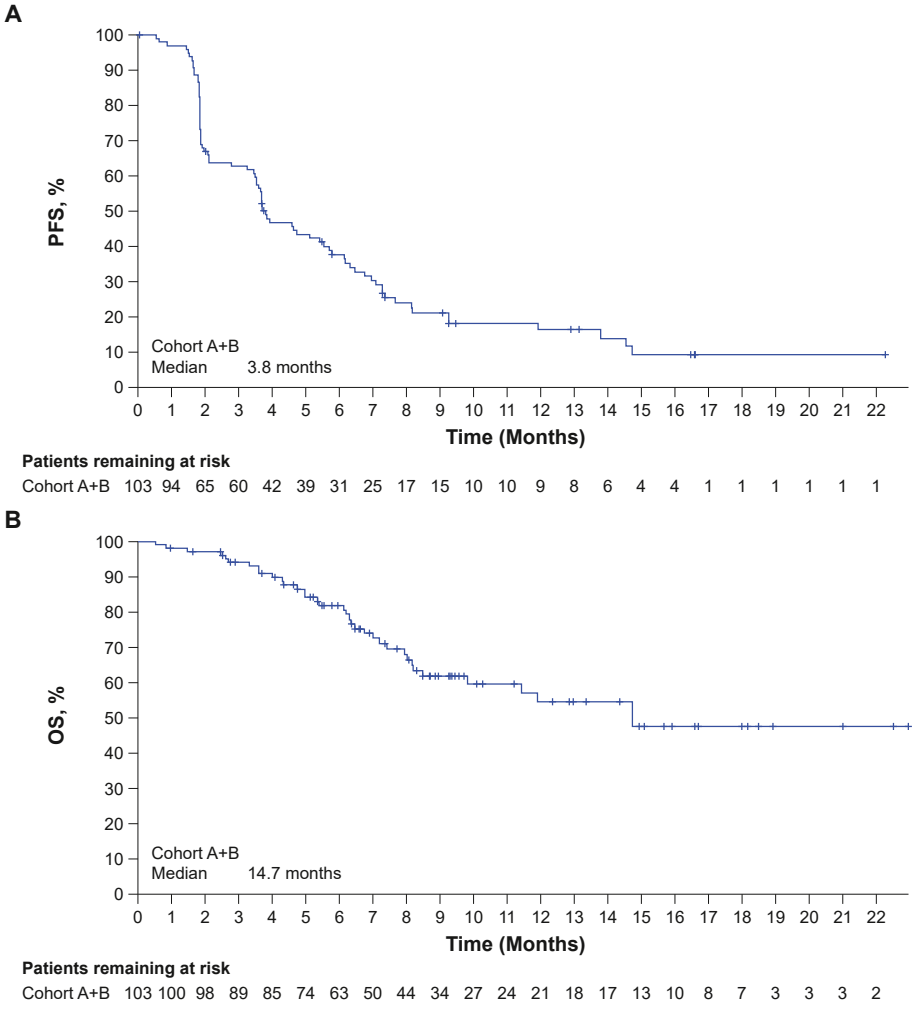


Fig. 2. Overall survival and progression-free survival. (A) Progression-free survival of all patients, cohorts A and B. (B) Overall survival of all patients, cohorts A and B. Tick marks indicate patients with censored data. NE, not estimable OS, overall survival; PFS, progression-free survival.

2.4. Biomarker analyses

Biomarker analyses were performed to evaluate outcomes according to tumour PD-L1 expression, tumour mutational burden (TMB), driver mutations and interferon expression on RNA sequencing. PD-L1 expression on tumour-infiltrating immune cells (ICs) was evaluated using PD-L1 monoclonal antibody (SP142; Ventana Medical Systems, Oro Valley, AZ, USA). CD8+ T cells in the tumour were determined by immunohistochemistry. TMB and driver mutation status were evaluated by next generation sequencing using the FoundationOne platform

(Foundation Medicine, Cambridge, MA, USA). Further details on the biomarker assays and analysis are outlined in the Supplementary Materials.

2.5. Statistical analyses

The efficacy and safety analyses populations included all patients who received ≥1 dose of both study drugs. Time-to-event analyses were summarised using Kaplan–Meier methodology. All other results were summarised using descriptive statistics. Comparisons of biomarker subgroups were performed using a chi-square, Fisher exact or Kruskal–Wallis test.

3. Results

3.1. Patients

Between 19th June 2017 and 12th December 2018, 103 patients were enrolled (n = 92 in cohort A, n = 11 in cohort B). Of these, the biomarker evaluable populations included 94 patients for the immunohistochemistry analysis, 85 patients for the FoundationOne™ next generation sequencing analysis and ≤6 patients for RNA sequencing analysis at different timepoints (Supplementary Table A3). All patients met eligibility criteria with $BRAF^{V600}$ wild-type tumours per local laboratory tests; however, subsequent central testing identified $BRAF^{V600}$ mutations in seven patients (V600E in 4 patients, V600K in 2 patients and V600R in 1 patient) and *BRAF* gene fusion in one patient.

At data cutoff (28th May 2019), 45 of 92 patients in cohort A (48.9%) and 2 of 11 patients in cohort B (18.2%) had discontinued the study. Median duration of follow-up was 7.1 months (interquartile range, 4.7–10.1 months) in cohort A and 5.6 months (4.8–13.3 months) in cohort B. The median age of patients was 62.0 years, with 65% males (Table 1). Patients had received 295 prior anti-cancer treatments. Overall, 81 patients had ≥1 documented best response to ≥1 prior immunotherapies. Best response to previous immunotherapy was CR (3/114; 2.6%), PR (11/114; 9.6%), SD (18/114; 15.8%), PD (75/114; 65.8%), not evaluable (NE; 2/114; 1.8%) or not available (5/114; 4.4%). There were 59 (72.8%) patients with a best response of PD to prior immunotherapies.

3.2. Efficacy

Best responses of target lesions are shown in the waterfall plot (Fig. 1A): 15 (14.6%) patients had PR, 43 (41.7%) patients had SD and 32 (31.1%) patients had PD (Table 2, Fig. 1B). The ORR was 14.6% (95% confidence interval [CI], 8.39–22.88) and the DCR was 38.8% (95% CI, 29.39–48.94) (Table 2).

At the time of primary analysis, 78 (75.7%) patients had an event contributing to PFS, including death (n = 11) and disease progression (n = 67). The median PFS was 3.8 months (95% CI, 3.5–5.7) (Fig. 2A) and the 12-month PFS rate was 16.4% (95% CI, 8.0%–24.7%).

Median duration of PR was 12.7 months (95% CI, 12.1–NE). Median duration of SD was 3.4 months (95% CI, 2.1–4.7). Median OS was 14.7 months (95% CI, 9.8–NE) (Fig. 2B).

Forty-two (40.8%) patients were treated with ≥1 post-trial therapy following disease progression; the most common treatments were nivolumab (n = 15; 14.6%), ipilimumab (n = 10; 9.7%) and radiotherapy (n = 5; 4.9%).

Thirty-four (33.0%) patients died: 33 due to PD (91.7%) and one due to grade 5 treatment-related oesophagitis. Median time to death after last therapy/last exposure was 7.8 months (95% CI, 5.0–11.6).

3.3. Biomarkers

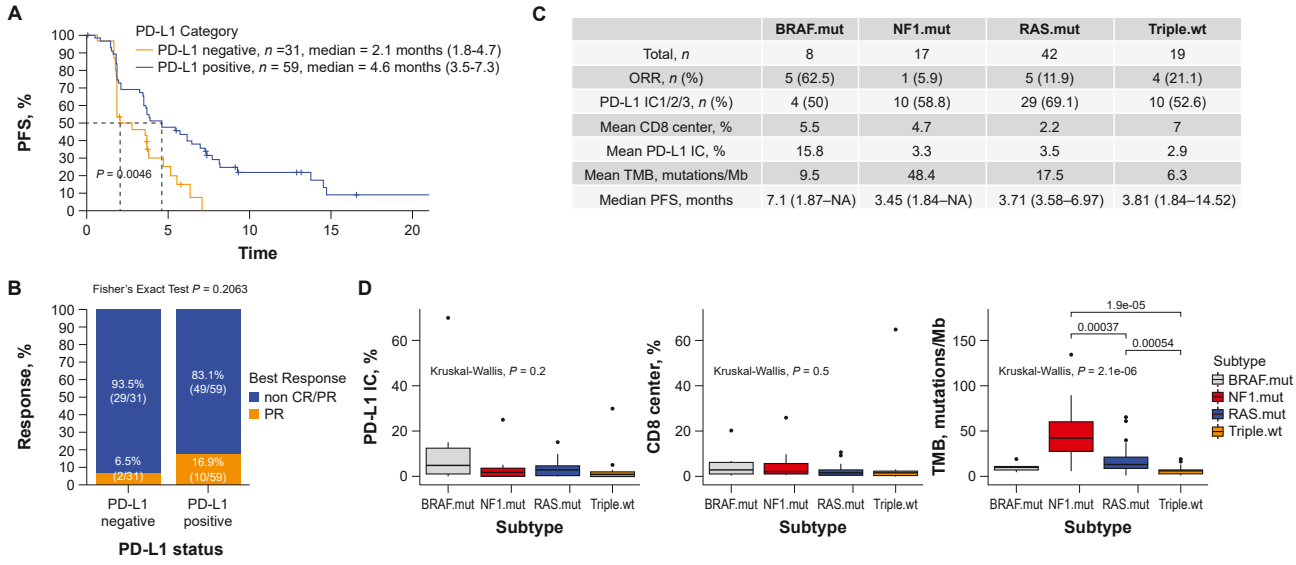
Genomic tumour profiling categorised the molecular subtypes: *BRAF* mutant/rearrangement (n = 8), *NF1* mutant (n = 17), *RAS* mutant (n = 42) and non-mutated *BRAF/NF1/RAS* triple wild-type (n = 19) (Supplementary Appendix Figure A2).

Patients with *BRAF* mutations had higher PD-L1 scores and PD-L1 tumour-infiltrating IC positivity was associated with a longer median PFS (4.6 months versus 2.1 months in PD-L1–positive and PD-L1–negative categories, respectively) (Fig. 3A), with 12/90 patients achieving PR (PD-L1 negative, n = 2; PD-L1 positive, n = 10) (Fig. 3B).

ORR by molecular subtype was 62.5% (5/8) in *BRAF* mutant/fusion, 5.9% (1/17) in *NF1* mutant, 11.9% (5/42) in *RAS* mutant and 21.1% (4/19) in *BRAF/NF1/RAS* triple wild-type. The overall mean interferon-gamma expression was similar across the molecular subtypes and ranged between 0.20 and 0.36. TMB was associated with melanoma molecular subtypes, with mean TMB of 6.3 mutations/MB in *BRAF/NF1/RAS* triple wild-type, 48.38 in *NF1* mutant and 17.53 in *NRAS* mutant subtypes (Fig. 3C and D). Best overall response or PFS showed no differences according to TMB (Supplementary Figure A3), whereas PFS was higher in favour of CD8+ >median versus ≤ median (4.2 months versus 3.7 months) with 11/77 patients achieving a PR (CD8+ >median, n = 6; CD8+ ≤median, n = 5) (Supplementary Figure A4). PD-L1 expression in ICs and CD8+ tumour infiltration was similar across molecular subtypes (Fig. 3D). Differential expression of hallmark cancer gene sets from baseline after single-agent cobimetinib is shown in Supplementary Figure A5.

3.4. Exposure and safety

Median atezolizumab exposure was 2.8 months (range, 0.0–20.0 months) and the median number of doses was 7.0 (range, 1.0–38.0). Median cobimetinib exposure was 2.9 months (range, 0.0–18.0). Any-grade adverse events (AEs) were observed in all patients except one, and 99.0% of patients had AEs related to study drugs.



C

	BRAF.mut	NF1.mut	RAS.mut	Triple.wt
Total, *n*	8	17	42	19
ORR, *n* (%)	5 (62.5)	1 (5.9)	5 (11.9)	4 (21.1)
PD-L1 IC1/2/3, *n* (%)	4 (50)	10 (58.8)	29 (69.1)	10 (52.6)
Mean CD8 center, %	5.5	4.7	2.2	7
Mean PD-L1 IC, %	15.8	3.3	3.5	2.9
Mean TMB, mutations/Mb	9.5	48.4	17.5	6.3
Median PFS, months	7.1 (1.87–NA)	3.45 (1.84–NA)	3.71 (3.58–6.97)	3.81 (1.84–14.52)

Fig. 3. Baseline biomarker characteristics. (A) Progression-free survival categorized by PD-L1 expression in immune cells (PD-L1 ICs). IC0 represents PD-L1 expression <1% (PD-L1 negative); IC1/2/3 represents PD-L1 ≥1% (PD-L1 positive). (B) Objective response rate by PD-L1 expression in immune cells (PD-L1 IC). Percentage and number of responders over total count as labelled. (C) Baseline biomarker characteristics in each melanoma molecular subtype. (D) PD-L1, CD8 and TMB by melanoma molecular subtypes. CD8, cluster of differentiation 8. CR, complete response; IC, immune cell; NA, not assessed; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; TMB, tumour mutational burden.

The most common treatment-related AEs (TRAEs) were diarrhoea (75/103; 72.8%), dermatitis acneiform (57/103; 55.3%) and nausea (52/103; 50.5%) (Table 3). TRAEs of grade ≥3 occurred in 57/103 patients (55.3%). One patient had a grade 5 AE of oesophagitis, which was assessed as treatment related by the investigator. Overall, 22 patients (21.4%) had AEs leading to any treatment discontinuation, including myocarditis ($n = 4$; 3.9%) and encephalitis ($n = 4$; 3.9%), and 16 patients (15.5%) had AEs leading to the discontinuation of both atezolizumab and cobimetinib (Table 4). All TRAEs except one case of myocarditis resolved with treatment. Seventy-six (73.8%) patients had ≥1 AE leading to dose reductions/interruptions.

4. Discussion

Results of this study demonstrated limited activity with atezolizumab plus cobimetinib in patients with advanced $BRAF^{V600}$ wild-type melanoma who had progressed on prior anti–PD-1 therapy. This was unexpected given the promising preclinical and early phase clinical data suggesting that MEK inhibition has beneficial immunomodulatory effects that may enhance response to ICIs [4,6,11,13–15], and the relatively good prognostic features of our cohort at the time of study entry (ECOG PS, 0–1; prior treatment for brain metastases, 10%; liver metastases, 26%) despite progression on prior anti-PD-1 therapy.

Results from the current study are consistent with the observations from the phase 3 IMspire170 study, in which combination therapy with cobimetinib plus atezolizumab did not improve PFS versus pembrolizumab in patients with previously untreated $BRAF^{V600}$ wild-type advanced melanoma [16]. At the time the present phase 1b study was conducted, limited data were available regarding treatment options for patients who progressed following anti–PD-1 therapy, and the results of IMspire170 were not available prior to patient recruitment.

Previous retrospective studies in melanoma patients who progressed on or after anti–PD-1 therapy demonstrated response rates of up to 16% with ipilimumab monotherapy and up to 31% with ipilimumab plus anti–PD-1 therapy [17,18]. In a recent meta-analysis of 14 studies, the pooled response rate was 8% for ipilimumab monotherapy and 23% for ipilimumab combined with nivolumab [19]. Prospective data from a phase 2 study reported a preliminary response rate of 47% ($n = 17$) with pembrolizumab plus low-dose ipilimumab in patients with melanoma who progressed on prior anti–PD-1 or non–CTLA-4 combination treatment [20], with the final results demonstrating a response rate of 31% ($n = 67$) [21]. In the present study, treatment with cobimetinib plus atezolizumab showed an ORR of 14.6% and a DCR of 38.8% in patients who had progressed on prior anti–PD-1 therapy. Although the response rate is relatively low, the patient population was treatment refractory, with 73% of the patients having demonstrated primary resistance to prior ICIs. Moreover, a substantial proportion of patients (58%) had also received prior ipilimumab.

Of patients who achieved PR ($n = 12$) in the biomarker evaluable population, most were PD-L1

Table 3
Treatment-related adverse events reported in ≥10% of patients (any grade) during the study.

Treatment-related adverse event, *n* (%)	Cohorts A and B (*n* = 103)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal					
Diarrhoea	75 (72.8)	36 (35.0)	28 (27.2)	11 (10.7)	0
Nausea	52 (50.5)	37 (35.9)	14 (13.6)	1 (1.0)	0
Vomiting	37 (35.9)	27 (26.2)	8 (7.8)	2 (1.9)	0
Constipation	31 (30.1)	21 (20.4)	10 (9.7)	0	0
Dry mouth	13 (12.6)	12 (11.7)	1 (1.0)	0	0
Mouth ulceration	11 (10.7)	8 (7.8)	3 (2.9)	0	0
Skin and subcutaneous tissue disorders					
Dermatitis acneiform	57 (55.3)	24 (23.3)	29 (28.2)	3 (2.9)	1 (1.0)
Rash	35 (34.0)	17 (16.5)	11 (10.7)	7 (6.8)	0 (0.0)
Pruritus	20 (19.4)	13 (12.6)	7 (6.8)	0	0
General disorders					
Fatigue	49 (47.6)	29 (28.2)	20 (19.4)	0	0
Pyrexia	38 (36.9)	24 (23.3)	9 (8.7)	5 (4.9)	0 (0.0)
Oedema peripheral	18 (17.5)	12 (11.7)	6 (5.8)	0	0
Chills	13 (12.6)	12 (11.7)	1 (1.0)	0	0
Asthenia	12 (11.7)	9 (8.7)	3 (2.9)	0	0
Metabolism and nutrition disorders					
Decreased appetite	22 (21.4)	14 (13.6)	7 (6.8)	1 (1.0)	0
Infections and infestations					
Urinary tract infection	13 (12.6)	2 (1.9)	9 (8.7)	2 (1.9)	0
Eye disorders					
MEK inhibitor-associated serious retinopathy	12 (11.7)	7 (6.8)	5 (4.9)	0	0
Nervous system disorders					
Dizziness	13 (12.6)	9 (8.7)	4 (3.9)	0	0
Headache	11 (10.7)	9 (8.7)	2 (1.9)	0	0
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	12 (11.7)	8 (7.8)	2 (1.9)	2 (1.9)	0
Blood and lymphatic system disorders					
Anaemia	14 (13.6)	6 (5.8)	6 (5.8)	2 (1.9)	0
Investigations	26 (25.2)	8 (7.8)	9 (8.7)	9 (8.7)	0
Blood creatine phosphokinase increased					
Aspartate aminotransferase increased	14 (13.6)	11 (10.7)	0	2 (1.9)	1 (1.0)
Alanine aminotransferase increased	11 (10.7)	7 (6.8)	1 (1.0)	3 (2.9)	0 (0.0)

Table 4
Adverse events leading to treatment discontinuation.

Treatment-related adverse event, *n* (%)	Atezolizumab	Cobimetinib	Both treatments
Total number of patients with at least one adverse event	18 (17.5)	20 (19.4)	16 (15.5)
Total number of events	19	23	17
Myocarditis	4 (3.9)	3 (2.9)	3 (2.9)
Encephalitis	4 (3.9)	4 (3.9)	4 (3.9)
Pneumonitis	2 (1.9)	2 (1.9)	2 (1.9)
Acute kidney injury	1 (1.0)	1 (1.0)	1 (1.0)
Alanine aminotransferase increased	1 (1.0)	1 (1.0)	1 (1.0)
Amylase increased	1 (1.0)	0	0
Anaemia	0	1 (1.0)	0
Blood creatine phosphokinase increased	0	1 (1.0)	0
Colitis	1 (1.0)	1 (1.0)	1 (1.0)
Ejection fraction decreased	0	1 (1.0)	0
Encephalopathy	1 (1.0)	1 (1.0)	1 (1.0)
Hepatitis	1 (1.0)	1 (1.0)	1 (1.0)
Immune-mediated hepatitis	1 (1.0)	1 (1.0)	1 (1.0)
Meningitis	1 (1.0)	1 (1.0)	1 (1.0)
Pruritus	0	1 (1.0)	0
Pyrexia	1 (1.0)	1 (1.0)	1 (1.0)
Rash	0	1 (1.0)	0
Tachycardia	0	1 (1.0)	0

For frequency counts by preferred term, multiple occurrences of the same AE in one individual are counted only once except for the "Total number of events" row, in which multiple occurrences of the same AE are counted separately.

positive ($n = 10$). Further, the PD-L1–positive subgroup had a longer median PFS than the PD-L1–negative subgroup (4.6 months versus 2.1 months, respectively). Taken together, these data suggest that combination therapy with cobimetinib and atezolizumab may be more effective in tumours with high PD-L1 expression. RNA sequencing results in cohort B were only available for a limited number of patients at each timepoint, likely due to patients not wanting to undergo repeated biopsies in the setting of disease progression.

In the biomarker-evaluable population, PD-L1 expression and cluster of differentiation 8 (CD8) tumour infiltration did not differ according to $BRAF^{V600}$ mutation, *NF1* mutation, *RAS* mutation or triple wild-type status. Consistent with previous findings [3,22], TMB was associated with melanoma molecular subtypes (*BRAF*, *NF1* or *RAS* mutants) and was higher in *NF1* mutant subtype. Despite the higher TMB in *NF1* mutant patients, the ORR was 5.9% and median PFS was 3.5 months, which was lower than all other molecular subtypes. This contrasts with a previous meta-analysis showing that high TMB was associated with better OS and PFS versus low TMB groups in patients who received ICIs [23]. However, enrolment in our trial was limited to patients with advanced melanoma who had progressed on prior anti–PD-1 therapy and therefore had treatment-resistant tumours irrespective of TMB status.

Treatment with ipilimumab alone or in combination with anti–PD-1 in patients with metastatic melanoma who were resistant to anti–PD-1 monotherapy was associated with a grade ≥3 AE rate of 21%–33% [18,21,24]. In the current study, 99% of patients experienced TRAEs with cobimetinib plus atezolizumab, with TRAEs of grade ≥3 in 55% of patients. The combination resulted in one reported treatment-related grade 5 oesophagitis. No new safety signals were identified. Similar to previous reports with this combination (15%–30%) [11,25], 21.4% of patients discontinued any study treatment due to AEs. Furthermore, immune-related myocarditis and encephalitis, which are rare but established AEs with ICIs [26,27], led to the withdrawal of any study treatment in 3.9% and 2.9% of patients, respectively.

5. Conclusion

Cobimetinib plus atezolizumab demonstrated limited activity in patients with advanced $BRAF^{V600}$ wild-type melanoma who had progressed on or after prior anti–PD-1 therapy. Efficacy and safety data from this study do not support the use of this combination in these patients. Further research may provide additional insight regarding genomic, molecular and immunological factors underlying these observations.

Author contributions

SS: Data curation, writing, review and editing. VA: Supervision, writing, review and editing, provision of data. MGC: Data curation, writing, review and editing, formal analysis. TM: Investigation. ASR: Investigation, writing, review and editing. AMM: Resources, data curation, investigation, writing, review and editing, provision of patients and data. IC: Supervision, investigation, writing, review and editing, medical monitor of the study. LR: Conceptualization, data curation, formal analysis, methodology, writing, review and editing. YS: formal analysis. YY: Conceptualization, data curation, investigation, writing, review and editing. YG: Data curation, formal analysis, investigation, visualization, methodology. CX: Data curation, formal analysis, methodology, writing, review and editing. GVL: Resources, data curation, investigation, project administration, writing, review and editing, provision of patients and data.

Funding

This analysis was funded by F. Hoffmann–La Roche Ltd. The study was sponsored by F. Hoffmann–La Roche Ltd and Genentech Inc. The sponsors provided the study drugs and collaborated with academic authors on study design and on data collection, analysis, and interpretation. All authors verified that this study was done according to the protocol and attest to data accuracy and completeness. All authors had full access to all study data. All drafts of the manuscript were prepared together with the authors, with professional writing assistance funded by the sponsor. All authors contributed to revisions and final approval of the manuscript and made the decision to submit the manuscript for publication.

Availability of data and material

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as

potential competing interests: SS reports personal fees and/or grants from AstraZeneca, Bristol Myers Squibb, Genentech, Merck Sharp & Dohme, Pfizer, and Novartis/Advanced Accelerator Applications directly to the institution. VA reports personal fees and/or nonfinancial support from Bristol Myers Squibb, Limbic, Merck, Merck Sharp & Dohme, Nektar, Novartis, Oncosec Medical, Pierre Fabre, QBiotics, and Roche. MGC reports personal fees and/or nonfinancial support from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, and Takeda. TM reports institutional funding from Alkermes, Array BioPharma, Checkmate Pharmaceuticals, Exicure, Immunocore, Iovance Biotherapeutics, Moderna, Nektar, Novartis, Oncosec Medical, Regeneron Pharmaceuticals, Replimune Group, Synlogic, and Taiga Biotechnologies. ASR reports no conflicts of interest. AMM reports personal fees from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Pierre Fabre, and QBiotics. IC, LR, YS, YY, YG, and CX report employment and stock ownership with Roche. GVL reports personal fees from Amgen, Array BioPharma, Boehringer Ingelheim International, Bristol Myers Squibb, Hexal AG, Highlight Therapeutics, Merck Sharpe & Dohme, Novartis, Pierre Fabre, QBiotics, Regeneron Pharmaceuticals, SkylineDx BV, and Specialised Therapeutics Australia Pty Ltd.

Acknowledgements

The authors thank Andres Aguilar for his contributions to the research team activities and data interpretation. Editorial assistance was provided by ApotheCom, San Francisco, CA, USA, and funded by F. Hoffmann–La Roche Ltd.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.10.019.

References

[1] Trujillo JA, Luke JJ, Zha Y, Segal JP, Ritterhouse LL, Spranger S, et al. Secondary resistance to immunotherapy associated with β-catenin pathway activation or PTEN loss in metastatic melanoma. J Immunother Cancer 2019;7(1):295.
[2] Ascierto PA, Kirkwood JM, Grob JJ, Simeone E, Grimaldi AM, Maio M, et al. The role of BRAF V600 mutation in melanoma. J Transl Med 2012;10:85.
[3] Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. Cell 2015;161(7):1681–96.
[4] Boni A, Cogdill AP, Dang P, Udayakumar D, Njauw CN, Sloss CM, et al. Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. Cancer Res 2010;70(13):5213–9.
[5] Dummer R, Schadendorf D, Ascierto PA, Arance A, Dutriaux C, Di Giacomo AM, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017;18(4):435–45.
[6] Ebert PJR, Cheung J, Yang Y, McNamara E, Hong R, Moskalenko M, et al. MAP kinase inhibition promotes T cell and anti-tumor activity in combination with PD-L1 checkpoint blockade. Immunity 2016;44(3):609–21.
[7] Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371(20):1867–76.
[8] Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387(10030):1837–46.
[9] Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387(10031):1909–20.
[10] Hamid O, Molinero L, Bolen CR, Sosman JA, Munoz-Couselo E, Kluger HM, et al. Safety, clinical activity, and biological correlates of response in patients with metastatic melanoma: results from a phase I trial of atezolizumab. Clin Cancer Res 2019;25(20):6061–72.
[11] Hellmann MD, Kim TW, Lee CB, Goh BC, Miller WH, Oh DY, et al. Phase Ib study of atezolizumab combined with cobimetinib in patients with solid tumors. Ann Oncol 2019;30(7):1134–42.
[12] de Azevedo SJ, de Melo AC, Roberts L, Caro I, Xue C, Wainstein A. First-line atezolizumab monotherapy in patients with advanced BRAF(V600) wild-type melanoma. Pigment Cell Melanoma Res 2021;34(5):973–7.
[13] Liu L, Mayes PA, Eastman S, Shi H, Yadavilli S, Zhang T, et al. The BRAF and MEK inhibitors dabrafenib and trametinib: effects on immune function and in combination with immunomodulatory antibodies targeting PD-1, PD-L1, and CTLA-4. Clin Cancer Res 2015;21(7):1639–51.
[14] Loi S, Dushyanthen S, Beavis PA, Salgado R, Denkert C, Savas P, et al. RAS/MAPK activation is associated with reduced tumor-infiltrating lymphocytes in triple-negative breast cancer: therapeutic cooperation between MEK and PD-1/PD-L1 immune checkpoint inhibitors. Clin Cancer Res 2016;22(6):1499–509.
[15] Ribas A, Butler M, Lutzky J, Lawrence DP, Robert C, Miller W, et al. Phase I study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib) and/or MEK (trametinib) inhibitors in advanced melanoma. J Clin Oncol 2015;33(15_suppl):3003.
[16] Gogas H, Dréno B, Larkin J, Demidov L, Stroyakovskiy D, Eroglu Z, et al. Cobimetinib plus atezolizumab in BRAF(V600) wild-type melanoma: primary results from the randomized phase III IMspire170 study. Ann Oncol 2020;32(3):384–94.
[17] Zimmer L, Apuri S, Eroglu Z, Kottschade LA, Forschner A, Gutzmer R, et al. Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. Eur J Cancer 2017;75:47–55.
[18] da Silva IP, Ahmed T, Reijers ILM, Weppler AM, Warner AB, Patrinely JR, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. Lancet Oncol 2021;22(6):836–47.
[19] Alrabadi NN, Abushukair HM, Ababneh OE, Syaj SS, Al-Horani SS, Qarqash AA, et al. Systematic review and meta-analysis efficacy and safety of immune checkpoint inhibitors in advanced melanoma patients with anti-PD-1 progression: a systematic review and meta-analysis. Clin Transl Oncol 2021;23(9):1885–904.
[20] Olson D, Luke JJ, Hallmeyer S, Bajaj M, Carll T, Krausz T, et al. Phase II trial of pembrolizumab (pembro) plus 1mg/kg ipilimumab

(ipi) immediately following progression on anti-PD-1 Ab in melanoma (mel). J Clin Oncol 2018;36(suppl_15). Abstract 9514.

[21] Olson D, Luke JJ, Stewart Poklepovic A, Bajaj M, Higgs E, Carll TC, et al. Significant antitumor activity for low-dose ipilimumab (IPI) with pembrolizumab (PEMBRO) immediately following progression on PD1 Ab in melanoma (MEL) in a phase II trial. J Clin Oncol 2020;38(15_suppl). Abstract 10004.

[22] Johnson DB, Frampton GM, Rioth MJ, Yusko E, Xu Y, Guo X, et al. Targeted next generation sequencing identifies markers of response to PD-1 blockade. Cancer Immunol Res 2016;4(11):959–67.

[23] Kim JY, Kronbichler A, Eisenhut M, Hong SH, van der Vliet HJ, Kang J, et al. Tumor mutational burden and efficacy of immune checkpoint inhibitors: a systematic review and meta-analysis. Cancers 2019;11(11):1798.

[24] Da Silva IP, Ahmed T, Lo S, Reijers ILM, Weppler A, Warner AB, et al. Ipilimumab (IPI) alone or in combination with anti-PD-1 (IPI+PD1) in patients (pts) with metastatic melanoma (MM) resistant to PD1 monotherapy. J Clin Oncol 2020; 38(15_suppl). Abstract 10005.

[25] Eng C, Kim TW, Bendell J, Argiles G, Tebbutt NC, Di Bartolomeo M, et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol 2019;20(6):849–61.

[26] Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A. Immune checkpoint inhibitor myocarditis: pathophysiological characteristics, diagnosis, and treatment. J Am Heart Assoc 2020; 9(2):e013757.

[27] Dalakas MC. Neurological complications of immune checkpoint inhibitors: what happens when you 'take the brakes off' the immune system. Ther Adv Neurol Disord 2018;11. 1756286418799864.