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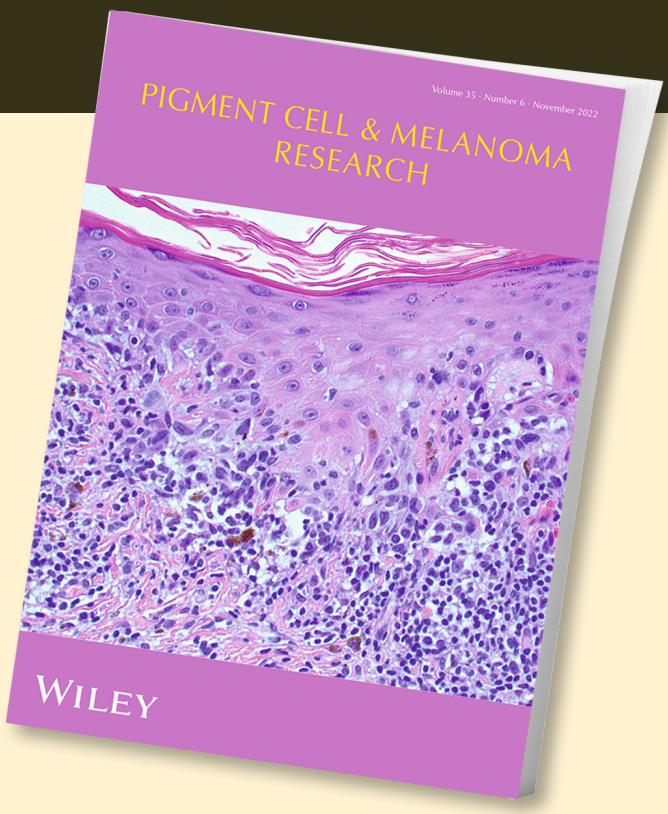

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ORIGINAL ARTICLE

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Retrospective review of outcomes associated with metastatic melanoma patients treated with 1st-line BRAF-targeted therapy

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Abstract

BRAF-mutant melanoma patients can theoretically access both immunotherapy and BRAF-targeted therapy as treatment for metastatic disease. BRAF-targeted therapy is increasingly used 1st line for poorer prognostic patients, so we wanted to assess realistic expectations of these patients accessing 2nd-line immunotherapy. We conducted a retrospective review of clinical outcomes in 25 patients treated over the last 3 years with 1st-line BRAF-targeted therapy in a real-world clinical setting at a UK-based tertiary centre. Compared with the registration trials, our patients receiving 1st-line BRAF-targeted therapy had poorer performance status, higher disease burden, shorter median progression-free survival (5.05 months, 95% CI: 3.96–8.88) and shorter median overall survival (11.5 months, 95% CI: 6.24 – not reached). Overall response rate was similar, at 64%. On disease progression, median survival was 2.34 months (95% CI: 1.62 – not reached). Only five patients went on to receive 2nd-line immunotherapy. Metastatic melanoma patients treated with 1st-line BRAF-targeted therapy now have different demographics compared with those recruited to registration trials conducted over the last 10 years. In a modern-day, real-world setting, these patients should be counselled that only 1 in 5 are likely to receive 2nd-line immunotherapy and their survival times are expected to be short.

KEYWORDS
BRAF, dabrafenib, encorafenib, immunotherapy, melanoma

1 | INTRODUCTION

BRAF gene driver mutations are found in 40%–50% of patients with metastatic melanoma, and oral kinase inhibitors targeting the MAP kinase pathway have been routinely available in clinical practice for almost a decade (Carlino et al., 2015; Kong et al., 2016). Patients with advanced *BRAF*-mutant melanoma generally have access to two different treatment modalities: immunotherapy (with immune checkpoint inhibitors) and BRAF-targeted therapies. Understanding how best to sequence these different treatment modalities is a key research priority (Giunta et al., 2020; Pavlick et al., 2019).

The apparent advantages of MAP kinase pathway inhibition over immunotherapy include a very high initial response rate which can be achieved within a few weeks of starting treatment,

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associated with few, if any, life-threatening side effects of treatment (Long et al., 2014; Robert et al., 2015). Objective response rates up to 70% have been reported in prospective trials of BRAF + MEK inhibitors (BRAF + MEKi), with nearly all treated patients having some degree of tumour shrinkage and median survival extending beyond 2 years (Gogas et al., 2020; Robert et al., 2019). High response rates can also be achieved in patients with multiple brain metastases—hitherto having been considered a sanctuary site (Glitza Oliva et al., 2018). However, few patients treated with BRAF ± MEKi achieve a complete response and secondary resistance with disease progression is almost inevitable (Gogas et al., 2020; Long et al., 2014; Robert et al., 2015). Those patients with poor performance status, high number of metastatic sites and raised serum LDH level have shorter durations of benefit (Menzies et al., 2015). In contrast, whilst response rates achieved with immune checkpoint blockade are generally lower than with BRAF + MEKi, those patients who do respond to immunotherapy can gain durable responses akin to long-term remission and, potentially, cure (Larkin et al., 2019). Immune-related adverse events can be both potentially life-threatening and/or life-changing, but clinicians are now familiar with managing these complex side effects (Brahmer et al., 2018). With longer patient follow-up, indirect clinical trial comparisons suggest that whilst BRAF + MEKi benefits patients in the short term, survival gains are likely to be superior with immunotherapy (Ugurel et al., 2020). Furthermore, initial data from two prospective randomised trials have reported superior outcomes with an immunotherapy first approach (Ascierto et al., 2021; Atkins et al., 2021).

What is also clear is that when patients progress on 1st-line therapy, some patients progressing after targeted therapy do so with rapid growth rates and do not have time to respond to 2nd-line immunotherapy, which generally requires several months to induce a T cell-driven immune response (Ackerman et al., 2014; Ascierto et al., 2014). Thus, it appears potentially easier to salvage a patient progressing off immunotherapy with BRAF-targeted therapy than the reverse order. Patients with advanced *BRAF*-mutant melanoma are nowadays therefore receiving immunotherapy 1st line.

The exception to this is a small group of patients who present with high volume, rapidly progressing disease, multiple brain metastases, highly symptomatic disease, and/or have poor performance, a high degree of frailty or a contraindication to immunotherapy (Michielin et al., 2019). These patients can expect to derive some degree of response to BRAF-targeted therapy, even in the face of what are mainly poor prognostic factors (Long et al., 2014; Robert et al., 2015). However, their response may be short-lived, and the chances of them actually receiving second-line therapy are less clear (Czarnecka et al., 2019; Luke et al., 2019; Schilling et al., 2019).

We undertook a retrospective audit to assess the outcomes for this patient subgroup in a real-world setting, with the following aims: (1) to compare the demographics of our patients receiving 1st-line BRAF-targeted therapy with the sample population enrolled in the BRAF + MEKi registration trials; (2) measure the modern day survival benefits of 1st-line BRAF-targeted therapy; and (3) determine the likelihood of this group of patients starting, and benefiting from, 2nd-line immunotherapy.

Understanding the outcomes from 1st- and 2nd-line therapy in the current, real-world, *BRAF*-mutant melanoma population should help manage clinician and patient expectations and ensure better-informed decision-making regarding treatment options at a time when clinical practice is evolving rapidly and patient anxiety is high (Fox et al., 2020).

Significance

This case series demonstrates worse outcomes for patients receiving 1st-line BRAF-targeted therapy than reported in the original registration trials for these agents, reflecting a recent shift in clinical practice towards immunotherapy as the default treatment of choice based on longer term survival gains. Despite the theoretical expectation that BRAF-mutant melanoma patients have access to both treatment modalities, those patients treated with 1st-line BRAF-targeted therapy have particularly aggressive disease and few patients are well enough to receive or benefit from 2nd-line immunotherapy. These results are important for fully informing clinicians and patients regarding realistic expectations of modern melanoma therapeutics.

2 | MATERIALS AND METHODS

We performed a single-centre, retrospective case notes audit of patients who received BRAF-targeted therapy as 1st-line treatment for metastatic melanoma at Cambridge University Hospitals NHS Foundation Trust. Patients started treatment between 1 January 2019 and 31 December 2020. Eligible patients were identified by review of hospital electronic chemotherapy prescription records. Patients treated with dabrafenib monotherapy, dabrafenib + trametinib, or encorafenib + binimetinib were included. Two patients treated on the control arm of the INTERIM study (EduraCT number 2016-005228-27) with standard continuous dabrafenib + trametinib were also included. Electronic medical records were then assessed by the study team. Data were collected to a cut-off date of 30 June 2021, ensuring all patients had had at least 6 months of follow-up and one staging assessment after starting treatment. Patients were staged by AJCC 8th edition.

Data were analysed using RStudio, with Kaplan–Meier plots generated using the 'survival', 'survminer' and 'dplyr' packages.

This study was registered at Addenbrooke's Hospital as a local retrospective audit of patient case notes (Local Clinical Project ID 4174, PRN 10174). The study was performed in accordance with the Declaration of Helsinki.

3 | RESULTS

3.1 | Demographics

Twenty-five patients fulfilling the eligibility criteria were identified. Patient demographics and clinical details prior to starting treatment are summarised in Table 1. Median age at diagnosis of metastatic melanoma was 65 years; 30% of patients had Eastern Cooperative Oncology Group performance status (PS) of two or worse prior to starting treatment.

The most common treatment regimens prescribed were encorafenib + binimetinib (48%), dabrafenib + trametinib (28%) and dabrafenib monotherapy (24%) (Table 2). The median age of patients treated with dabrafenib was higher (76 years) than with combination BRAF + MEKi regimens, and all of them had brain metastases.

3.2 | Comparison with BRAF-targeted therapy registration trials

We compared the demographics of our modern-day patient cohort to those of patients recruited to the major randomised phase III trials Combi-V, Combi-D and COLUMBUS (Gogas et al., 2020; Robert et al., 2019) that led to the registration of dabrafenib + trametinib and encorafenib + binimetinib for the treatment of *BRAF*-mutant metastatic melanoma (Table 1). Our real-world cohort was an older patient group, with poorer prognostic characteristics including worse PS and higher baseline disease burden (36% patients had brain metastases that would have excluded them from the registration trials and a higher proportion had raised LDH levels).

3.3 | Outcomes associated with 1st-line BRAF-targeted therapy

3.3.1 | Efficacy outcomes

Assessment of best objective response was based on standard CT radiologist reporting and clinical assessment of the patient, not by formal RECIST measurements (Table 2). Complete response was reported in 16% and partial response in 48% of patients, giving an overall response rate of 64%. Eight percentage of patients had stable disease as their best response and a mixed response was seen in 20% of patients, so the overall disease control rate was 92%. Eight percentage of patients had progressed at the time of their first surveillance imaging, conducted 7–8 weeks after starting treatment.

TABLE 1 Patient demographics and disease characteristics at the time of initiation of first-line therapy compared with patients included in registration trials

	CUH cohort ($n = 25$)	Combi-D ($n = 423$)	Combi-V ($n = 70$)	COLUMBUS ($n = 192$)
Gender				
Male	48%	53%	55%	60%
Age at diagnosis (years)				
Median	65 years	56 years	55 years	57 years
ECOG PS				
0	24%	72%	71%	71%
1	36%	28%	29%	29%
2	28%			
3	12%			
M status	**AJCC 8th ed (7th ed)[a]**	**AJCC 7th ed (%)**		
Inoperable nodal (M0)	8% (8%)	4	6	5
M1a	4% (4%)	12	15	14
M1b	8% (8%)	18	18	18
M1c	44% (80%)	66	61	64
M1d	36% (NA)	0	0	0
≥3 Organ sites involved				
Yes	52%	46	46	45
No	48%	54	54	55
LDH > ULN				
Yes	48%	35	33	29
No	52%	65	67	71

[a]Our cohort is staged using the AJCC 8th edition. Seventh edition stage is shown in brackets for comparison to the registration trials.

TABLE 2 Features of treatment with first-line BRAF-directed therapy in CUH cohort

	Overall (25)	Dabrafenib monotherapy (6)	Combination treatment (19) dab. + tram. (7) enco. + bini. (12)
Age at diagnosis			
Median	65 years	76 years	64 years
ECOG PS			
0	24% (6)	17% (1)	26% (5)
1	36% (9)	50% (3)	32% (6)
2	28% (7)	33% (2)	26% (5)
3	12% (3)		16% (3)
M status (AJCC 8th ed.)			
M1d	36% (9)	100% (6)	16% (3)
Best response			
Complete response	16%	17%	15%
Partial response	48%	50%	47%
Mixed response	20%	17%	21%
Stable disease	8%	–	11%
Progressive disease	8%	17%	5%
Treatment switching and discontinuation rates			
Switched due to toxicity and continued until progression	24%	–	32%
Discontinued due to progression	72%	66%	73%
Discontinued due to toxicity	4%	–	5%
Continuing treatment at end of study	24%	33%	21%
Choice of treatment upon switching due to toxicity (number of patients)			
Dabrafenib	3	–	3
Encorafenib	1	–	1
Encorafenib and binimetanib	1	–	1
Dabrafenib and trametinib	1	–	1

Median progression-free survival (PFS) was 5.05 months (95% CI: 3.96–8.88) (Figure 1a). The median PFS for patients treated with dual BRAF + MEKi (5.05 months, 95% CI: 3.96–20.3) or dabrafenib monotherapy (6.14 months, 95% CI: 1.78 – NR) was not significantly different ($p = .86$). Median OS was 11.5 months (95% CI: 6.24 – NR) (Figure 1b). There was a trend towards better OS for patients treated with BRAF + MEKi (11.55 months, 95% CI: 6.24 – NR), compared with dabrafenib monotherapy (8.15 months, 95% CI: 3.14 – NR), though this was not significant ($p = .18$). Poor PS, having three or more organ sites involved at the time of diagnosis, and raised baseline LDH level were all associated with poorer OS (Figures 1c,e,f). However, the presence of symptoms at diagnosis was not associated with overall survival outcome (Figure 1d).

3.3.2 | Reasons for stopping treatment

The median time on 1st-line treatment was 5.78 months. At the time of data cut-off, six patients remained on 1st-line BRAF-targeted therapy. Of the remaining patients, 18 had their treatment stopped due to radiological or clinical disease progression. One patient had their treatment stopped completely due to toxicity (severe arthralgia & myalgia).

Six patients were switched to a different BRAF-targeted therapy due to toxicity and were able to continue treatment (Table 2). Toxicities leading to discontinuation of the first choice of BRAF/MEKi in these cases included dermatological toxicities (grade 3 rash, erythema nodosum), arthralgia, myalgia, hyponatremia, liver impairment, fatigue, nausea, vomiting and anorexia. For the purposes of this real-world analysis, we have considered the total time on any BRAF-targeted therapy as the primary measure, rather than considering the independent combinations as separate lines of treatment. Best response and discontinuation rates have also been assessed based on each patient's time on any first line BRAF/MEKi.

3.4 | Treatment on disease progression after 1stline BRAF-targeted therapy

Nineteen (76%) patients progressed on 1st-line BRAF-targeted therapy, and their median OS calculated from date of documented progression to date of death or censoring was 2.34 months (95% CI: 1.62 – NR) (Figure 2a). At the time of progression, 36% of patients (7/19) were less fit, with PS 3 or 4 and poor PS was

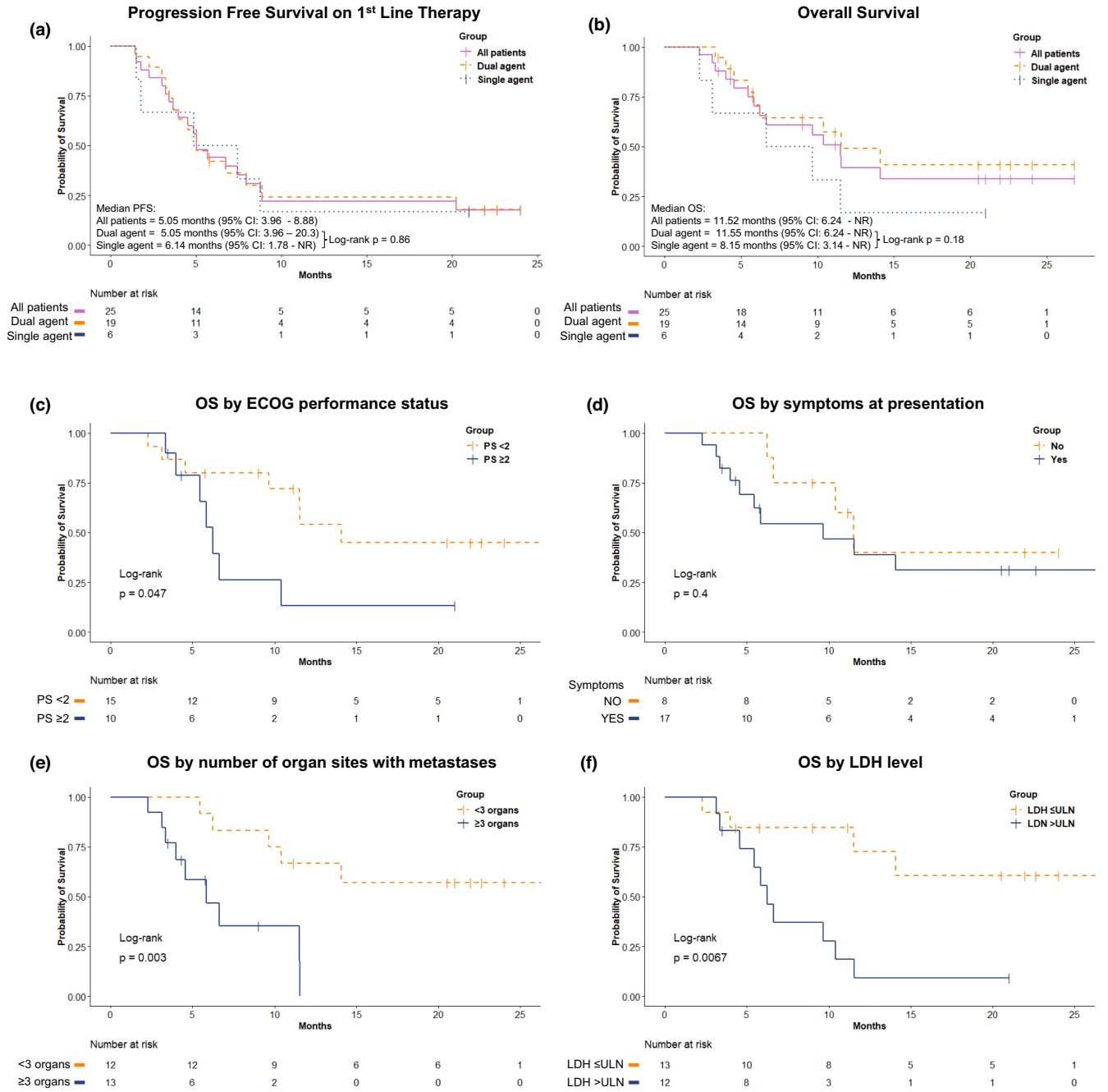

FIGURE 1 Survival analysis from time of starting first line BRAF-directed treatment. (a) Progression-free survival from time of starting first line BRAF-directed treatment to documented radiological or clinical progression. (b) Overall survival from time of starting first line BRAF-directed treatment. (c–f) overall survival curves divided by prognostic subgroup. Log-rank test *p*-values shown.

clearly associated with worse survival (Figure 2b). There were no significant differences in survival amongst subgroups stratified by number of organ sites involved (Figure 2d) or LDH level (Figure 2e).

3.4.1 | Patients receiving 2nd-line immunotherapy

Of the 19 patients who progressed on 1st-line BRAF-targeted therapy, only eight were well enough for 2nd-line treatment to be considered and planned. Of these eight patients, three progressed rapidly and were unable to start their planned treatment.

Five patients went on to start 2nd-line therapy. Their treatment and clinical characteristics are summarised in Table 3. Three patients received ipilimumab + nivolumab, and two patients started pembrolizumab. Two patients achieved a partial response, one of whom was still on pembrolizumab at time of data cut-off, the other had treatment discontinued due to immune- related enteritis but remained on active surveillance. The other three patients progressed on treatment, which was discontinued, and they were

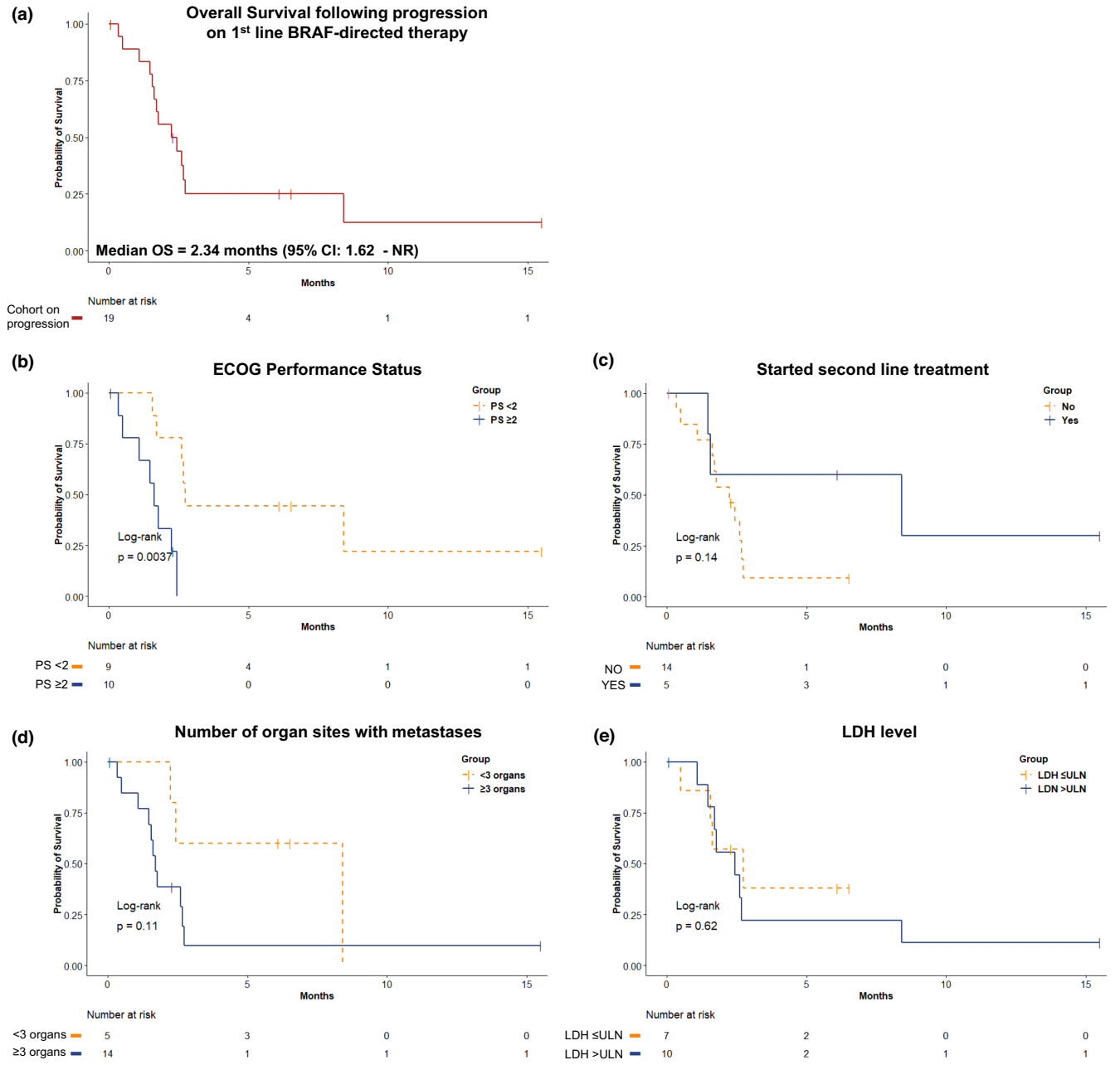

FIGURE 2 Survival following progression on BRAF-directed therapy. (a) Overall survival from date of documented progression on 1st-line BRAF-directed therapy. (b–e) Overall survival from date of documented progression on 1st-line BRAF-directed therapy, divided by subgroup. Log-rank test *p*-values shown.

offered best supportive care. One patient required treatment for immune-related nephritis.

All five patients who received 2nd-line treatment had been treated with dual BRAF + MEKi as the 1st line. The median 1st-line PFS and overall survival data for these patients were no different to that of the whole cohort.

Those patients who went on to receive 2nd-line immunotherapy had better PS than those who did not and were offered best supportive care: four patients starting 2nd-line immunotherapy were PS 1, one patient was PS 2, whereas 10 of the 14 patients who did not receive immunotherapy were recorded to be PS 2 or worse. The three patients who were planned for but did not start immunotherapy were initially PS 0 or 1, but deteriorated rapidly such that they were no longer fit to start treatment. There were no other obvious differences in the clinical characteristics of the patients who received 2nd-line immunotherapy when compared to the whole patient cohort, either at start of 1st-line treatment or on disease progression.

Survival from the time of first disease progression was not significantly different between those patients who received 2nd-line immunotherapy and those who received best supportive care (Figure 2c); however, the two longest surviving patients both received 2nd-line immunotherapy.

TABLE 3 Summary of patients treated with second-line immunotherapy

	First-line therapy							Second-line therapy									
		Features at start of 1st-line treatment								Features at start of 2nd-line treatment							
Patient	Treatment plan	ECOG PS	Stage	≥3 organs	LDH > ULN	Best response	PFS [5.05]	Treatment plan	Time to start treatment (days)	ECOG PS	Stage	≥3 organs	LDH > ULN	Best response	Time on treatment	Reason for stopping	Survival from date of 1st-line progression [2.34]	Overall survival [11.52]
41M	Encorafenib and binimetanib	1	M1c	YES	YES	SD	3.00	Ipilimumab and nivolumab	7	1	M1d	YES	NO	PD	1.12	Toxicity and progression	1.55	4.55
61F	Encorafenib and binimetanib	3	M1c	NO	YES	MR	3.96	Pembrolizumab	27	2	M1c	YES	YES	PD	0.30	Progression	1.49	5.45
70F	Encorafenib and binimetanib	1	M1c	NO	NO	PR	5.05	Pembrolizumab	36	1	M1c	NO	NO	PR	5.25	Treatment ongoing	6.11	11.16
66F	Encorafenib and binimetanib	0	M0	NO	NO	MR	5.68	Ipilimumab and nivolumab	40	0	M0	NO	YES	PD	3.50	Progression	8.42	14.09
63M	INTERIM continuous	1	M1c	NO	NO	SD	5.05	Ipilimumab and nivolumab	26	1	M1d	YES	YES	PR	2.38	Toxicity	15.48	20.53

Note: All patients stopped first-line treatment due to disease progression. All times values are months. Medians in square brackets refer to whole patient cohort for comparison.
Abbreviations: MR, mixed response; PD, progressive disease; PR, partial response; SD, stable disease.

3.4.2 | Additional lines of treatment

There were 11 patients for whom an active decision to manage with best supportive care was made after discontinuation of 1st-line treatment. These patients all died within the study period; the time between discontinuation of treatment and death was short with a median of 26 days. No patients were planned for, or received, a 3rd line of systemic therapy. No patients received a rechallenge of BRAF ± MEKi after progression on immunotherapy.

4 | DISCUSSION

Our real-world study confirms that patients treated with 1st-line BRAF-targeted therapy are now generally more advanced, with higher disease burden and poorer PS compared with those patients recruited to the original BRAF + MEKi registration trials. Despite this changing practice, most treatment-naive BRAF-mutant metastatic melanoma patients are generally counselled that they have two lines of therapy available to them. Our patient cohort had a high objective response rate comparable with published BRAF + MEKi registration trial data (Robert et al., 2019). However, by stark comparison, disease control was short-lived, due to the earlier development of resistance. Most of our patient cohort progressed on BRAF-targeted therapy within the first year, with a median PFS of 5.05 months, which is considerably shorter than that reported in COMBI-D and COMBI-V (11.1 months) (Robert et al., 2019) and COLUMBUS (14.9 months) (Gogas et al., 2020). Median overall survival was also shorter than seen in registration trials, at 11.52 months for our cohort, compared to 25.9 months in COMBI-D and COMBI-V (Robert et al., 2019) and 33.6 months in COLUMBUS (Gogas et al., 2020). Thus, whilst the registration trial populations were selected for good performance status patients excluding active brain metastases, 1st-line BRAF-targeted therapy is now more likely to be offered to patients with aggressive or high burden disease (Giunta et al., 2020; Michielin et al., 2019; Pavlick et al., 2019), whose outcomes are generally extremely poor. Our findings are not unexpected; for example, the BREAK MB study of dabrafenib + trametinib in patients with brain metastases reported a PFS of less than 6 months and OS of 12 months (Long et al., 2012). Our important observation is the very low proportion of patients (20%) who went on to receive 2nd-line immunotherapy.

Despite initial results of the DREAMseq (Atkins et al., 2021) and SECOMBIT (Ascierto et al., 2021) trials both supporting the immunotherapy first approach, there will continue to be a demand for rapid disease control in a subgroup of *BRAF*-mutant patients exemplified by those in this retrospective analysis. Defining the role of 2nd-line treatment in these patients has received much less attention, which is something we were particularly interested in when conducting this audit. Whilst there is retrospective evidence that immunotherapy is less effective when given 2nd-line as compared to 1st-line (Ackerman et al., 2014; Ascierto et al., 2014; Johnson et al., 2017; Mason et al., 2020), most publications focus on the outcomes of patients who actually received the 2nd-line treatment rather than

assessing the overall outcome data for all patients from the point of receiving their 1st-line treatment. Our finding that only 20% of our patients received 2nd-line treatment contrasts with previous retrospective studies reporting that approximately half of patients receive immunotherapy after BRAF-targeted therapy (Czarnecka et al., 2019; Luke et al., 2019; Schilling et al., 2019).

Retrospective analysis of 2nd-line therapy suggests a PFS around 2.5 months after 1st-line BRAF-targeted agents (Czarnecka et al., 2019). In our cohort, prognosis was considerably worse, with median OS of 2.3 months from the date of disease progression. PFS data after first progression on BRAF-targeted therapy were not assessed in our cohort, as most patients were managed with best supportive care. Upon progression, outcomes were poor regardless of LDH level, or number of disease sites involved. The key reasons for adopting a best supportive care approach in our cohort, rather than proceeding to 2nd-line immunotherapy, were poor PS and rapidly progressive disease. In those who are well enough to be considered for 2nd-line immunotherapy, the outcome data are particularly concerning, as immunotherapy often has a delayed treatment effect due to the time taken to induce a T-cell response. For example, median time to response for patients with advanced melanoma treated with pembrolizumab was 2.8 months in the KEYNOTE 001 study (Hamid et al., 2019). It has also been suggested that patients with longer duration of response (>6 months) to BRAF-targeted therapy have better response rates to 2nd-line anti-PD-1 immunotherapy (Johnson et al., 2017); however, none of our patients who received 2nd-line immunotherapy had 1st-line PFS longer than 6 months.

Strategies to improve the overall outcomes with patients needing first line BRAF/MEK targeted therapy are clearly needed. Triplet therapy combining immune checkpoint blockade with BRAF + MEKi has proved disappointing: the COMBI-I trial combining spartalizumab (anti-PD-1) with dabrafenib + trametinib did not meet its primary PFS end-point (Dummer et al., 2022). A pre-specified subgroup analysis did, however, suggest that patients with higher burden of disease (>3 metastatic sites or sum of baseline lesions diameters >66 mm) might benefit more from this combination. Intermittent dosing schedules of BRAF + MEKi have also been explored, with the hope that this would delay emergence of resistant clones. However, two randomised phase II intermittent dosing studies have failed to demonstrate improved outcomes (Algazi et al., 2020; Gonzalez-Cao et al., 2021). The most promising experimental arm of the SECOMBIT comprised 'induction' treatment with 8 weeks of encorafenib + binimetinib, followed by a switch to ipilimumab + nivolumab. (Ascierto et al., 2021). The CACTUS trial (NCT03808441) aims to utilise circulating tumour DNA as a mechanism to guide switching between BRAF-targeted therapy and immunotherapy (Lee et al., 2021), and the results of these exploratory approaches are awaited.

5 | CONCLUSIONS

Our results are important for setting expectations of those BRAF-mutant metastatic melanoma patients in whom BRAF-targeted therapy is recommended because they are not suitable for 1st-line immunotherapy. These patients are a particularly poor prognostic group. Despite an expectation of a good initial response to treatment, the duration of benefit is likely to be short-lived. In contrast to an assumption that these patients can access immunotherapy as 2nd line, our findings suggest that they are very unlikely to either receive, or benefit from, a subsequent line of therapy and therefore preparing for best supportive care should be a priority when counselling patients. It is vital that we continue to undertake research in this challenging space in order to better inform clinical practice.

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CONFLICT OF INTERESTS

JJ and RL have no conflicts of interest. PC has received speaker fees from Novartis, Bristol Myers Squibb, Merck, Sharp & Dohme and Pierre Fabre; advisory board fees from Bristol Myers Squibb and Merck, Sharp & Dohme; research funding from Pierre Fabre.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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