European Journal of Cancer 91 (2018) 116–124

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Rechallenge with BRAF-directed treatment in metastatic melanoma: A multi-institutional retrospective study☆

Sara Valpione [a,b], Matteo S. Carlino [c,d], Johanna Mangana [e], Meghan J. Mooradian [f], Grant McArthur [g], Dirk Schadendorf [h], Axel Hauschild [i], Alexander M. Menzies [c,j], Ana Arance [k], Paolo A. Ascierto [l], AnnaMaria Di Giacomo [m], Francesco de Rosa [n], James Larkin [o], John J. Park [c,d], Simone M. Goldinger [e], Ryan J. Sullivan [f], Wen Xu [g], Elisabeth Livingstone [h], Michael Weichenthal [i], Rajat Rai [c], Lydia Gaba [k], Georgina V. Long [c,j], Paul Lorigan [a,*]

[a] *The Christie NHS Foundation Trust, and University of Manchester, Manchester, UK*
[b] *CRUK Manchester Institute, Manchester, UK*
[c] *Melanoma Institute Australia and the University of Sydney, Sydney, NSW, Australia*
[d] *Westmead and Blacktown Hospitals, Westmead, Australia*
[e] *University Hospital of Zurich, Zurich, Switzerland*
[f] *Massachusetts General Hospital, Cancer Center, Boston, MA, USA*
[g] *Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia*
[h] *University Hospital Essen, Essen and German Cancer Consortium, Germany*
[i] *Schleswig-Holstein University Hospital, Kiel, Germany*
[j] *Royal North Shore and Mater Hospitals, Australia*
[k] *Hospital Clínic de Barcelona, Barcelona, Spain*
[l] *Istituto Nazionale Tumori "Fondazione G. Pascale"-IRCCS, Naples, Italy*
[m] *Medical Oncology and Immunotherapy University Hospital of Siena, Siena, Italy*
[n] *IRCCS – IRST (Istituto Scientifico Romagnolo per Lo Studio e La Cura Dei Tumori), Meldola, Italy*
[o] *The Royal Marsden NHS Foundation Trust, London, UK*

Received 29 November 2017; accepted 2 December 2017
Available online 19 January 2018

☆ The present study was partially presented at ASCO 2017 (abstract 9512).

* *Corresponding author*: University of Manchester and Christie NHS Foundation Trust, 550 Wilmslow Road, Manchester, M20 4BX, UK. Fax: +44 (0) 161 446 3299.
E-mail address: paul.lorigan@christie.nhs.uk (P. Lorigan).

https://doi.org/10.1016/j.ejca.2017.12.007

KEYWORDS
Metastatic melanoma;
BRAF inhibitors;
BRAFi;
MEKi

Abstract ***Background:*** Most metastatic melanoma patients treated with BRAF inhibitors (BRAFi) ± MEK inhibitors (MEKi) eventually progress on treatment. Along with acquired resistance due to genetic changes, epigenetic mechanisms that could be reversed after BRAFi discontinuation have been described. The purpose of this study was to analyse retrospectively outcomes for patients retreated with BRAF-directed therapy.

Patients and methods: One hundred sixteen metastatic melanoma patients who received BRAFi-based therapy and, after a break, were rechallenged with BRAFi ± MEKi at 14 centres in Europe, US and Australia were studied, respectively. Response rate (RR), overall survival (OS) and progression-free survival (PFS) from the start of retreatment were calculated.

Results: The median duration of treatment was 9.4 months for first BRAFi ± MEKi treatment and 7.7 months for the subsequent treatment (immunotherapy 72%, other 17%, drug holiday 11%) after BRAFi discontinuation. Brain metastases were present in 51 (44%) patients at BRAFi retreatment. The RR to rechallenge with BRAFi ± MEKi was 43%: complete response (CR) 3%, partial response (PR) 39%, stable disease (SD) 24% and progressive disease 30%, 4% missing. Of 83 patients who previously discontinued BRAFi due to disease progression, 31 (37.3%) responded (30 PR and 1 CR) to retreatment. The median OS from retreatment was 9.8 months, and PFS was 5 months. Independent prognostic factors for survival at rechallenge included number of metastatic sites (hazard ratio [HR] = 1.32 for each additional organ with metastases, $P < .001$), lactic dehydrogenase (HR = 1.37 for each multiple of the upper normal limit, $P < .001$), while rechallenge with combination BRAFi + MEKi conferred a better OS versus BRAFi alone (HR = 0.5, $P = .006$).

Conclusion: Rechallenge with BRAFi ± MEKi results in a clinically meaningful benefit and should be considered for selected patients.

1. Background

BRAF inhibitors (BRAFi) and the combination of BRAFi (vemurafenib, dabrafenib, encorafenib) with MEK inhibitors (MEKi) (trametinib, cobimetinib, binimetinib) have revolutionised the treatment of patients with BRAF-mutant melanoma. However, most patients responding to targeted therapy will subsequently develop resistance and progress, with a median progression-free survival of 6–10 (BRAFi monotherapy) to 11–15 months (BRAFi + MEKi). Treatment options after the development of BRAFi resistance include immunotherapy. While many patients will benefit from this, the majority progress, and the median survival remains approximately 24 months [1].

In addition to the development of acquired resistance based on a classical clonal Darwinian selection [2], acquired epigenetic mechanisms have been proposed as important mechanisms of resistance. There is evidence that BRAFi may induce cancer cell 'drug addiction,' matrix remodelling and secretome adaptation resulting in temporary resistance to BRAFi [3–5]. In this scenario of a plastic phenotype which may be reversible on withdrawal of the driving stimulus, retreatment with BRAFi after a treatment break would have a rationale. Rechallenge with targeted therapy has been shown to be effective in other cancers including lung cancer, gastrointestinal stromal tumours (GIST) and renal cell cancer [6–11]. At the start of this study, there was evidence of heterogeneous clinical and molecular patterns of resistance to BRAFi [12,13] and anecdotal reports of reversible resistance in melanoma patients [14–22]. More recently, a small prospective study in 25 patients showed a benefit for retreatment with BRAFi retreatment [22].

The aim of the present study was to draw together the experience of a large number of melanoma centres to understand if rechallenge with BRAFi therapy is a clinically useful approach and to identify factors to select patients with more probabilities to have a benefit.

2. Materials and methods

2.1. Patients

We carried out a retrospective review of patients who had received BRAFi-based treatment (with or without MEKi) and, after a break, were rechallenged with BRAFi-containing regimen. Eligible patients were treated between February 2011 and September 2016 at 14 centres in Europe, the US and Australia. Inclusion criteria were patients with BRAF-mutated melanoma in which treatment with BRAFi-based treatment had been interrupted, with another therapy regimen initiation or drug holiday of minimum 4 weeks and subsequently

rechallenged with a BRAFi-containing regimen. Data included in the analysis were patient demographics, disease stage and extent, treatments received, lactic dehydrogenase (LDH) level, duration of first BRAFi-based treatment, reason for first BRAFi discontinuation and interval between first BRAFi stop and rechallenge. Factors analysed for prognostic value for overall survival (OS), progression-free survival (PFS) and response rate (RR) included the duration of the first-line treatment, best response, reason for discontinuation, interval treatment, duration of interval duration, number of metastatic sites, presence of brain metastases, LDH and rechallenge therapy.

2.2. Statistical analysis

Covariates were studied in univariate and multivariate Cox regression models for their prognostic value for death or progression. Hazard ratios (HRs) and 95% confidence intervals (CIs) for each risk factor were based on maximum likelihood estimates for each covariate. Cox-Snell residual–based methodology was used to check the proportional hazard assumption of the Cox models. The two-sided χ^2 P values from Wald test with Bonferroni correction for multiple testing was used to assess the significance of each covariate included in the full multivariate models. Fast-backward method (with Akaike information criterion as a stopping rule instead of P values, in order to favour parsimonious models) was used to select the covariates included in the final models for prognostic factors of OS and PFS. Model performance was measured with calibration and discrimination; the slope factor is the slope of the calibration plot when the model is fitted to new data and allows to estimate model overfitting (and thus allows to estimate the likelihood that the model will reliably predict new observations) and was calculated after 100 bootstrap replications. The shrinkage factor (slope) of the final prognostic model was 0.90 (range of the parameter 0–1, where 1 would be the ideally fitted model). Discrimination was determined with Harrell's C-index. The cohort was not large enough to provide a separate validation set,; thus, the results were internally validated using bootstrap method (after 100 bootstrap replications). The prognostic model was validated internally with bootstrap (100 replications) and the C-index (the possible range of the parameter being 0–1, where 1 is the ideal model) resulted 0.66.

Multiple imputation methodology was used to compute missing values in the prognostic model analyses (first BRAFi-containing regimen data missing for 2 patients; best response at first BRAFi regimen was missing for 8 patients, best response at rechallenge was missing for 3 patients and baseline rechallenge LDH blood concentration missing in 7 cases). Performance status (PS) was missing for 20 patients (17%) and failed the imputation procedure quality control, thus had to be omitted from the prognostic analysis.

In addition, the variables were then assessed for their interactions using exponential regression tree analysis for risk of death. This allowed for the identification of homogeneous prognostic subgroups.

Logistic regression was used to examine potential association with RR at rechallenge with BRAFi-based therapy. Spearman rank test was used to assess pairwise associations between covariates at first BRAFi regimen and rechallenge. PFS was defined as the time from rechallenge start to disease progression or last follow-up. Overall survival was defined as the time from rechallenge start to the date of death or last follow-up.

Survival rates were calculated using the Kaplan–Meier estimator, log-rank test being used to compare survival estimates across different groups.

The study was conducted in compliance to local ethics regulations, approved by the institutional ethics committees or audited by the review boards; informed consent procedures were conducted according to local regulations, and patient data were anonymised.

Statistical analyses were performed using R (v 3.3.3; CRAN project, R Foundation for Statistical Computing, Vienna, Austria). Anonymised raw data could be available upon reasonable request to the first author.

3. Results

A total of 116 patients fulfilling the eligibility criteria were identified from 14 centres. Patients' characteristics prior to rechallenge are shown in Table 1, and Supplemental Table 1 shows the details of first BRAF-directed therapy. BRAFi regimen was the first-line systemic treatment in the majority of patients (N = 90, 77%); BRAFi-based therapies were given after chemotherapy in 19 of the remaining patients. Locoregional treatment for brain metastases was administered before the first targeted therapy in 26 patients (22.4%), with 5 intracranial complete responses (CRs), 7 partial responses (PRs), 8 stable diseases (SDs) and 6 disease progressions (PD).

Out of 116 patients, 68 (58.6%) were treated with single-agent BRAFi as first BRAFi regimen, 41 (35.3%) received a combination of BRAFi and MEKi and the remaining (N = 5, 4.3%) had a combination of single-agent BRAFi and immunotherapy; data were missing for 2 patients. Most patients received treatment at full dose, while 31 (27%) required a dose reduction for toxicity.

The median duration of first-line BRAFi was 9.4 months (range 0.5–42.9, interquartile range 4.8–16.22). The most common reasons for stopping treatment was disease progression in 83 patients (71.6%), toxicity in 16 (13.8%), treatment break after CR in 9 patients (7.8%)

Table 1
Patients demographics and disease characteristics at rechallenge.

Patient demographics prior to rechallenge	N = 116
Age, years (range)	51.9 (28.6–80.3)
Metastatic organs number (range)	3 (1–8)
Brain metastases	51 (44%)
Stage	
M1a	14 (12%)
M1b	6 (5%)
M1c	96 (83%)
LDH	
<UNL	45 (41%)
≥UNL	64 (59%)
Missing	*7 (6%)*
PS	
0	34 (35%)
1	37 (39%)
2	20 (21%)
3–4	5 (5%)
Missing	*20 (17%)*
BRAFi rechallenge drugs	
Dabrafenib	19 (16%)
Dabrafenib + trametinib	54 (47%)
Encorafenib	1 (1%)
Encorafenib + binimetinib	14 (12%)
Encorafenib + binimetinib + ribociclib	2 (2%)
Vemurafenib	19 (16%)
Vemurafenib + cobimetinib	7 (6%)

LDH, lactic dehydrogenase.

or other reasons in 5 patients (4.3%); information was missing in 3 patients.

The most frequent sites of treatment failure in the 83 patients who stopped first BRAFi due to disease progression were lymph nodes (32.5%), soft tissue (27.7%) and central nervous system (26.5%); 28 (33.7%) patients were treated beyond progression, for a median of 2.2 months (range 0.9–17.6 months).

The median time from first BRAFi regimen cessation to rechallenge was 7.7 months (range 0.9–34.9), and progression was the reason for discontinuation of the interval regime in the majority of patients (55.1%). Immunotherapy was the most commonly administered treatment between first and rechallenge BRAFi treatment (71.5%) (Table 1). One third of patients (33.6%) had more than one line of interval therapy, with 22 (18.9%) receiving sequential immunotherapy with anti-CTLA4 followed by anti-PD1 treatment.

At the time of BRAFi rechallenge, 83% of patients were stage M1c, 59% had a raised LDH (median value, 1.1 × upper normal limit (UNL); range, 0.5–6.9 × UNL) and 44% had brain metastases.

Most patients (62.9%) had single-agent BRAFi at first BRAF-directed therapy, whereas a combination regimen was the most commonly used treatment at rechallenge (66.3%), reflecting the changing standard of care. The overall RR to BRAFi rechallenge was 42.3% for evaluable patients: CR in 3 patients (2.6%), PR in 46 (39.7%), SD in 28 (24.1%), PD in 36 (31%) and data missing in 3 patients. There was no correlation between best response to first BRAFi and best response at rechallenge ($P = .331$). Of note, 4 patients who had PD as best response for first BRAFi (3 BRAFi monotherapy and 1 BRAFi + MEKi) achieved a PR at rechallenge (with BRAFi + MEKi). For the 83 patients who previously interrupted first BRAFi because of disease progression, 30 (36.1%) had PR and 1 CR (1.2%) at rechallenge. RR did not significantly differ between the combination and monotherapy group ($P = .392$); however, all patients achieving CR (N = 3) had received combination treatment and of them, 2 had monotherapy (one partial response and one complete response) and one had combination at first BRAFi (with complete response). The duration of first-line BRAFi therapy was associated with the RR to BRAFi rechallenge, with a median duration of first-line therapy of 14.8 months for responders versus 9.7 months for non-responders ($P = .014$). Responders to rechallenge had a longer median interval between initial and retreatment BRAFi (8.8 versus 6.7 months, respectively, $P = .011$) but patients with an interval as short as 0.9 months also responded. Of note, the duration of the interval between first BRAFi and rechallenge in the 3 patients who achieved CR from the rechallenge spanned from 5.9 months (a patient who had first-line dabrafenib) to 20.8 months (a patient who had first-line dabrafenib plus trametinib), while in patients who had PD as rechallenge best response the interval of BRAFi drugs was from 0.9 (dabrafenib plus trametinib as first BRAFi) to 24.6 months (a patient treated with dabrafenib as first BRAFi). Furthermore, response to the interval treatment was not associated with response to BRAFi rechallenge (not shown). Supplemental Fig. 1 shows an example of successful rechallenge in a patient who, after an initial benefit from single-agent dabrafenib, progressed, did not respond to immunotherapy and then had a partial response to the rechallenge with dabrafenib and trametinib.

With a median follow-up of 15.7 months from the start of retreatment, 68 (58.6%) patients have died and 89 (76.7%) have progressed. Median OS for rechallenge was 9.8 months (0.2–34.4), and median PFS was 5 months (0.2–31.7). The OS and PFS at 1 year were 42.8% and 23.1%, respectively. Of note, PFS from rechallenge was significantly longer than the PFS reported for first-line chemotherapy (2.7 months, $P = .005$) and similar to PFS for first-line dabrafenib (5.1 months, $P = .9$) in treatment-naive patients [23].

The results of the full model for prognostic factors of OS are shown in Supplemental Table 2. The proportional hazard verification by means of Cox-Snell residuals for the OS and PFS prognostic models are represented in Supplemental Fig. 2A and 2B, respectively. The significant prognostic factors were the number of metastatic sites, LDH level and the treatment administered during rechallenge. In particular, patients

with more organs involved by metastatic disease (HR = 1.32 for each additional metastatic site, 95% CI 1.09–1.59, $P < .001$) and high LDH (HR = 1.37 for every additional multiple of the UNL, 95% CI 1.07–1.57, $P < .001$) had a worse prognosis, while patient receiving combination of BRAF plus MEKi (BRAFi plus MEKi or MEKi plus ribociclib) had a better prognosis (HR = 0.5, 95% CI 0.24–0.76, $P = .006$).

The regression tree analysis for risk of death identified 5 prognostic subgroups (Fig. 1A). The worst prognostic group was patients treated with single-agent BRAFi, 3 or more metastatic organs and high LDH (median OS = 4.0 months), while patients treated with combination therapy and less than 3 metastatic organs had the best prognosis (OS not reached). Fig. 1B shows the survival curves for the 5 subgroups, while the survival curves for each single prognostic factor are represented in Fig. 2.

The prognostic factors identified for PFS were similar to those for OS: the number of metastatic sites (patients with more metastatic organs had a worse prognosis; HR = 1.44 for each added metastatic site, 95% CI 1.24–1.67, $P < .001$, Fig. 3A) and the rechallenge therapy (patients treated with combination of BRAF plus MEKi or MEKi + ribociclib had a better prognosis; HR = 0.45, 95% CI 0.28–0.70, $P < .001$) (Fig. 3B); prognostic factors not retained in the final model are reported in Supplemental Table 3. OS and PFS prognostic analyses were repeated, in the subgroup of patients who had interrupted first BRAFi-based therapy because of progression, with consistent results (not shown).

4. Discussion

In this study, we show that melanoma patients treated with BRAF-directed therapy, who discontinue due to progression or other causes, can benefit from retreatment at a later stage. This translates to a clinically meaningful survival benefit from the time of retreatment, with a median overall OS of 9.8 months and median PFS of 5 months, respectively.

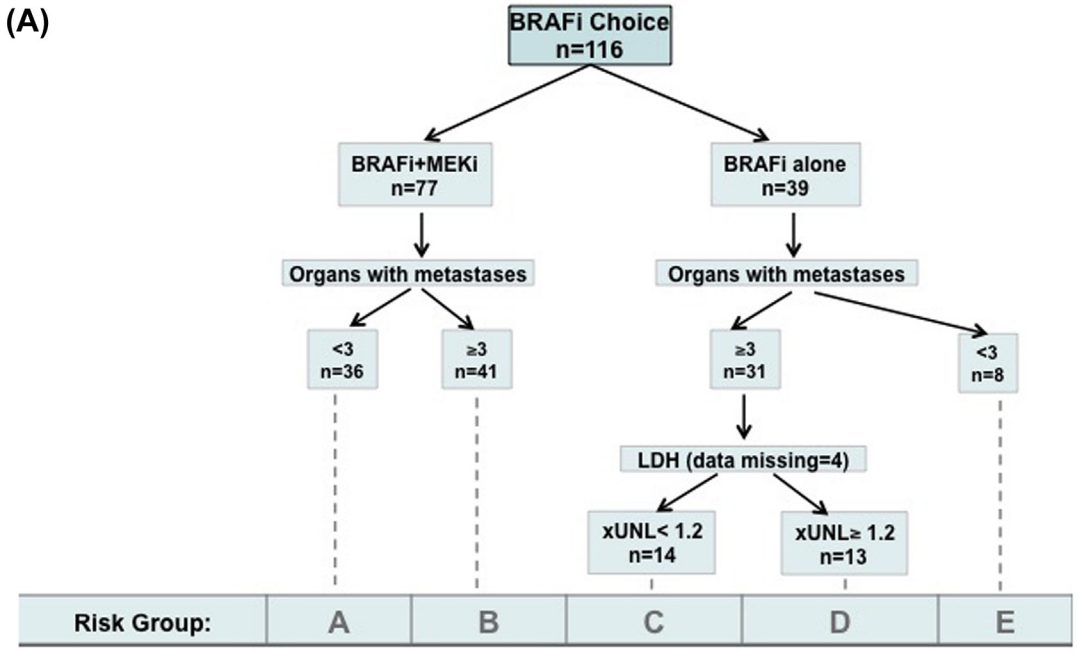
Targeted therapy has revolutionised the outcome for melanoma patients with a BRAF V600 mutation. The first phase III study with vemurafenib showed an improvement in OS from 9.7 to 13.6 months, with a HR of 0.70 coupled with a high RR and significant benefit in PFS [24]. Dual BRAF and MEK inhibition has extended the median OS to greater than 2 years and is now a standard of care [25]. The evolution of treatment from single to combination therapy is reflected in the treatments received by patients in this study. Single-agent therapy was the most common treatment administered initially (62.9%), and combination therapy was the preferred option (66.3%) on retreatment. Our results show that responses occur and survival may be extended with retreatment, with a median overall survival of 9.8 months from retreatment in patients that had exhausted standard therapeutic options.

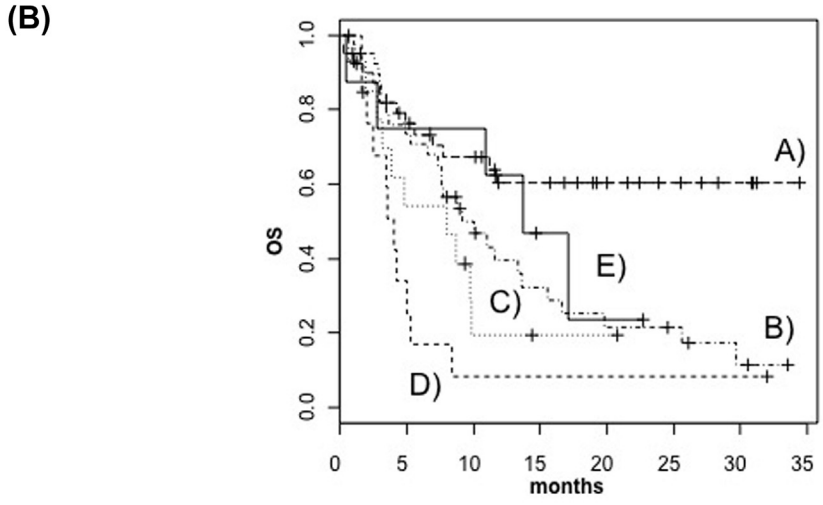
Retreatment with chemotherapy after a drug holiday is an established practice in many cancers, with the chance of a benefit being related to the initial response to treatment, duration of response and length of treatment break. However, in these instances, patients have usually completed a set course of treatment and were responding at the time of discontinuation. In this study, the majority of patients discontinued targeted therapy due to acquired resistance and disease progression. Of particular interest is that 37.8% of patients who had discontinued BRAFi initially due to progressive disease went on to respond to a rechallenge. Resistance to BRAF- and MEK-directed therapy has been shown to be mediated by a number of different mechanisms, largely due to reactivation of the MAPK signalling pathway, for example, spliced variants of BRAF, emergence of NRAS mutation of other multilineage kinases, loss of feedback inhibition leading to BRAF dimerisation and resistance to BRAFi; however, other pathways are also involved, including the PI3K-PTEN-AKT pathway [26–29].

Our results that were also corroborated by a prospective study in 25 patients who had progressed on BRAFi-based therapy and, after receiving immunotherapy for at least 12 weeks followed by progression, were rechallenged with dabrafenib and trametinib [22] where the RR was 32%, demonstrate that acquired resistance to targeted therapy is not always irreversible. The simple Darwinian model of selective pressure resulting in new mutations and selection of a resistant clone conferring survival advantage does not explain our observations. Similarly, the findings for PFS and RR recapitulated the observations from Schreuer *et al.* confirming the evidence of a clinical benefit from the rechallenge with BRAFi in metastatic melanoma patients. In our cohort, where the minimum duration of the break was less stringent, the length of the interval between first BRAFi cessation and rechallenge was not associated with survival, indicating that resensitisation can occur quickly.

Preclinical models suggest that clones resistant to BRAFi may have a fitness disadvantage relative to those sensitive to BRAFi, and the selective growth advantage in the face of BRAFi therapy could be lost on discontinuation of the BRAFi [3]. These findings would also support the evaluation of intermittent treatment regimens in melanoma, and these are already established in other cancers including renal cell carcinoma [3]. Other models for transient acquired resistance include signalling plasticity [27,30,31], phenotype switching [32], quiescence [33,34] or epigenetic changes [35].

Prognostic factors for patients treated with combination BRAF and MEK inhibition are now well





Risk Group	N	Deaths	Median	95% CI
A) BRAFi+MEKi (+/- LEE011), metastatic organs <3	36	12	NA	11.7 - NA
B) BRAFi+MEKi (+/- LEE011), metastatic organs ≥3	41	28	10.0	7.6 – 16.6
C) BRAFi monotherapy, metastatic organs ≥ 3 and normal LDH	14	10	8.0	3.2 - NA
D) BRAFi monotherapy, metastatic organs ≥3 and high LDH	13	11	4.0	2.5 - NA
E) BRAFi monotherapy, metastatic organs <3	8	5	13.7	10.9 - NA

Fig. 1. **Regression tree and risk classes for overall survival**. (A) Shows the regression tree and the 5 different risk classes identified for overall survival from the start of retreatment; (B) shows the Kaplan–Meier curves and corresponding survival data for the 5 risk classes.

established and include PS, number of metastatic sites and LDH level [36]. This study shows that number of metastatic sites and LDH level is prognostic for survival with retreatment. The performances of the prognostic studies were comparable to previously published models for rare tumours [37–39]. These allowed the identification of prognostic factors and risk classes, similarly to those observed for first-line BRAF-targeted therapy. Low tumour burden (less than 3 metastatic sites), the combination of BRAFi plus MEKi and low LDH were

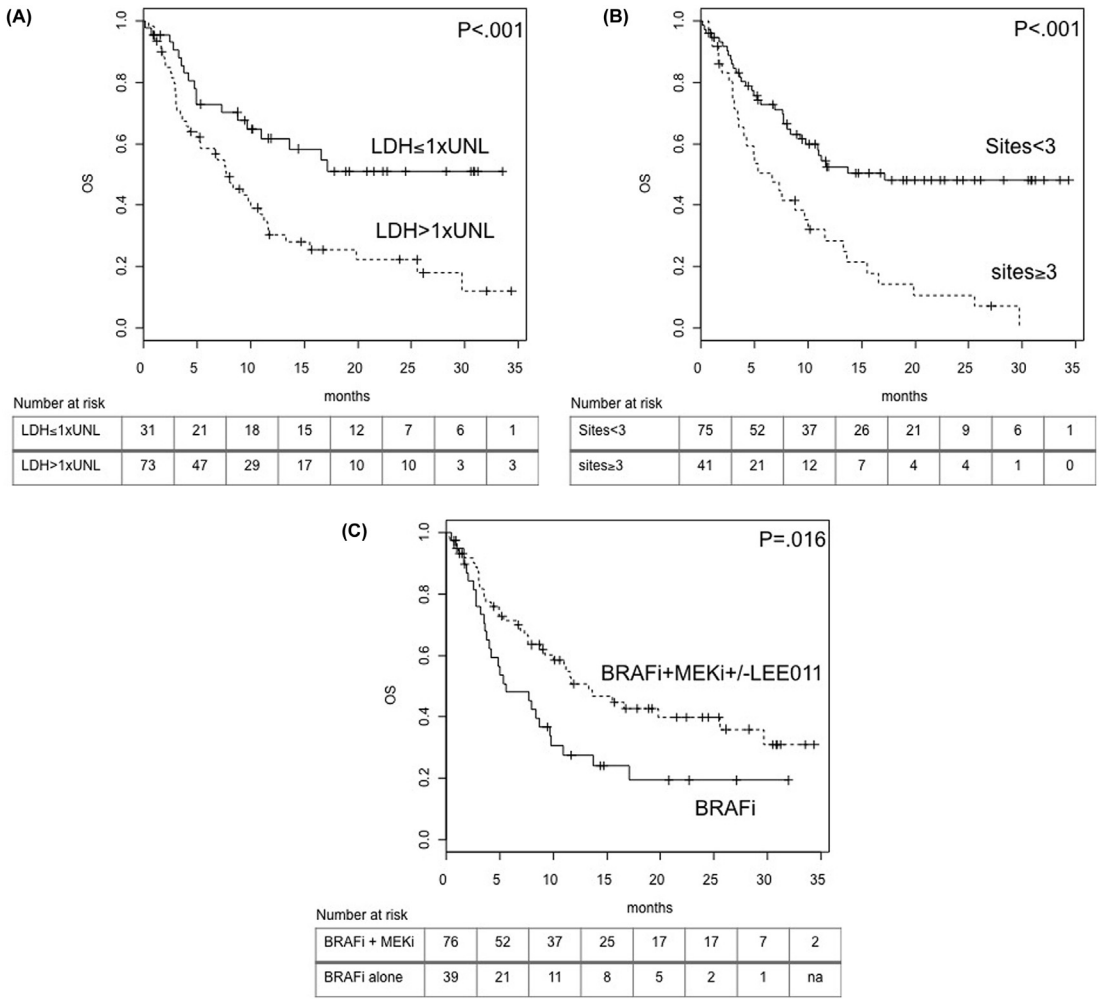


Fig. 2. Kaplan–Meier curves for the study cohort according to the prognostic factors for overall survival from the start of retreatment: (A) LDH above or below the upper normal limit, (B) more or less than 3 metastatic sites and (C) therapy with monotherapy BRAF inhibitors or combination of BRAF inhibitors and MEK inhibitors (plus ribociclib in 3 patients). LDH = lactic dehydrogenase; LEE011 = ribociclib.

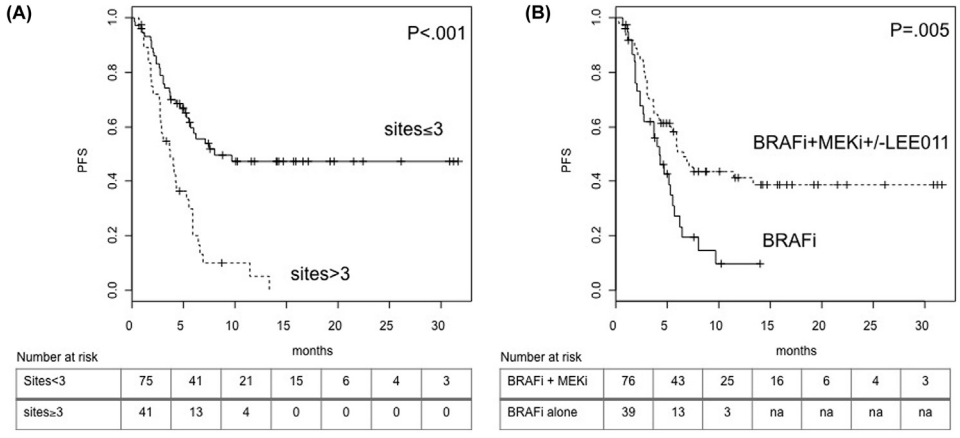


Fig. 3. Kaplan–Meier curves for the study cohort according to the prognostic factors for progression-free survival: (A) more or less than 3 metastatic sites and (B) therapy with monotherapy BRAF inhibitors or combination of BRAF inhibitors and MEK inhibitors (plus ribociclib in 3 patients). LEE011 = ribociclib.

associated with better overall survival, and the magnitude of the survival benefit was greater than the expected 6–9 months survival for treatment-naive patients in the pretargeted drugs and pre-immunotherapy era.

This study has a number of limitations, being a retrospective series of patients managed heterogeneously, although it reflects the heterogeneity of melanoma patients and its sample size is comparable to similar studies in rare tumours [37,38,40]. The frequency of tumour assessments was not standardised and so data on PFS are less robust. Patient selection will have contributed to the outcome, though it is interesting to note that many of these patients would have been expected to have a very poor prognosis, considering that most had a raised LDH (59%), and the cohort was enriched for patients with brain metastases (44%). Of note, PFS from rechallenge in this heavily pretreated population with adverse prognostic factors were similar to PFS for first-line dabrafenib [23]. While the absence of a control arm makes it difficult to quantify the benefits of the rechallenge, the results seen for PFS and OS are unexpected for heavily pretreated patients who have progressed through multiple lines of treatment [41].

In conclusion, our results support retreatment as a new therapeutic option for selected patients with BRAF-mutated melanoma who have progressed on BRAFi and have completed a subsequent treatment. In addition, the identification of different prognostic groups has implications for the design and stratification of clinical trials evaluating intermittent dosing strategies or rechallenge therapy with BRAFi after a different treatment.

Conflict of interest statement

A.M.M. is a member of the advisory board of MSD, Novartis and Pierre Fabre and received honoraria from BMS and Roche. G.V.L. is a consultant/advisor for Amgen, Array, BMS, Merck MSD, Novartis, Pierre Fabre and Roche. P.A.A. plays a consultant/advisory role in BMS, Roche-Genentech, MSD, Array, Novartis, Amgen, Merck-Serono, Pierre Fabre and Incyte and received research funds from BMS, Roche-Genentech and Array. A.D.G. plays a consultant/advisor role in BMS, Incyte and Pierre Fabre. D.S. plays a consultant/advisory role in BMS, Roche-Genentech, MSD, Array, Novartis, Amgen, Merck-Serono, Pierre Fabre and Incyte and received research funds from BMS and Novartis. S.M.G. has an intermittent advisory relationship with Roche, Novartis, BMS and MSD and received research support from the University of Zurich and medAlumni.

Acknowledgements

The authors are grateful to Prof. Simone Mocellin for the independent statistical review of the manuscript. The authors are grateful to Prof. Reinhard Dummer, Prof Keith Flaherty and Prof Michele Maio for their collaboration. S.V. would like to thank Dr. Tara Gangadhar for her advice. S.V. was supported by the ESMO Clinical Research Fellowship with the aid of a grant from Novartis (ESMO Clinical Research Fellowship 2015-2016). Any views, opinions, findings, conclusions or recommendations expressed in this material are those solely of the author(s) and do not necessarily reflect those of ESMO or Novartis.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2017.12.007.

References

[1] Ugurel S, Rohmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. Eur J Cancer 2017;83:247–57.
[2] Nowell PC. The clonal evolution of tumor cell populations. Science 1976;194(4260):23–8.
[3] Das Thakur M, Salangsang F, Landman AS, Sellers WR, Pryer NK, Levesque MP, et al. Modelling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance. Nature 2013;494(7436):251–5.
[4] Hirata E, Girotti MR, Viros A, Hooper S, Spencer-Dene B, Matsuda M, et al. Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin beta1/FAK signaling. Cancer Cell 2015;27(4):574–88.
[5] Obenauf AC, Zou Y, Ji AL, Vanharanta S, Shu W, Shi H, et al. Therapy-induced tumour secretomes promote resistance and tumour progression. Nature 2015;520(7547):368–72.
[6] Santini D, Vincenzi B, Addeo R, Garufi C, Masi G, Scartozzi M, et al. Cetuximab rechallenge in metastatic colorectal cancer patients: how to come away from acquired resistance? Ann Oncol 2012;23(9):2313–8.
[7] Lee DH, Kim SW, Suh C, Yoon DH, Yi EJ, Lee JS. Phase II study of erlotinib as a salvage treatment for non-small-cell lung cancer patients after failure of gefitinib treatment. Ann Oncol 2008;19(12):2039–42.
[8] Asahina H, Oizumi S, Inoue A, Kinoshita I, Ishida T, Fujita Y, et al. Phase II study of gefitinib readministration in patients with advanced non-small cell lung cancer and previous response to gefitinib. Oncology 2010;79(5–6):423–9.
[9] Italiano A, Cioffi A, Coco P, Maki RG, Schoffski P, Rutkowski P, et al. Patterns of care, prognosis, and survival in patients with metastatic gastrointestinal stromal tumors (GIST) refractory to first-line imatinib and second-line sunitinib. Ann Surg Oncol 2012;19(5):1551–9.
[10] Nozawa M, Yamamoto Y, Minami T, Shimizu N, Hatanaka Y, Tsuji H, et al. Sorafenib rechallenge in patients with metastatic renal cell carcinoma. BJU Int 2012;110(6 Pt. B):E228–34.
[11] Zama IN, Hutson TE, Elson P, Cleary JM, Choueiri TK, Heng DY, et al. Sunitinib rechallenge in metastatic renal cell carcinoma patients. Cancer 2010;116(23):5400–6.
[12] Menzies AM, Haydu LE, Carlino MS, Azer MW, Carr PJ, Kefford RF, et al. Inter- and intra-patient heterogeneity of response and progression to targeted therapy in metastatic melanoma. PLoS One 2014;9(1), e85004.
[13] Johnson DB, Menzies AM, Zimmer L, Eroglu Z, Ye F, Zhao S, et al. Acquired BRAF inhibitor resistance: a multicenter meta-

analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. Eur J Cancer 2015;51(18):2792–9.
[14] Seghers AC, Wilgenhof S, Lebbe C, Neyns B. Successful rechallenge in two patients with BRAF-V600-mutant melanoma who experienced previous progression during treatment with a selective BRAF inhibitor. Melanoma Res 2012;22(6):466–72.
[15] Romano E, Pradervand S, Paillusson A, Weber J, Harshman K, Muehlethaler K, et al. Identification of multiple mechanisms of resistance to vemurafenib in a patient with BRAFV600E-mutated cutaneous melanoma successfully rechallenged after progression. Clin Cancer Res 2013;19(20):5749–57.
[16] Roux J, Pages C, Malouf D, Basset Seguin N, Madjlessi N, Baccard M, et al. BRAF inhibitor rechallenge in patients with advanced BRAF V600-mutant melanoma. Melanoma Res 2015;25(6):559–63.
[17] Dooley AJ, Gupta A, Bhattacharyya M, Middleton MR. Intermittent dosing with vemurafenib in BRAF V600E-mutant melanoma: review of a case series. Ther Adv Med Oncol 2014;6(6):262–6.
[18] Vanhaecke C, Deilhes F, Chanal J, Regnier-Rosencher E, Boitier F, Boulinguez S, et al. BRAFV600 inhibitor discontinuation after complete response in advanced melanoma. A retrospective analysis of 16 patients. Br J Dermatol 2017;177(4):e94–5.
[19] Desvignes C, Abirached H, Templier C, Drumez E, Lepesant P, Desmedt E, et al. BRAF inhibitor discontinuation and rechallenge in advanced melanoma patients with a complete initial treatment response. Melanoma Res 2017;27(3):281–7.
[20] Rogiers A, Wolter P, Bechter O. Dabrafenib plus trametinib rechallenge in four melanoma patients who previously progressed on this combination. Melanoma Res 2017;27(2):164–7.
[21] Amann VC, Hoffmann D, Mangana J, Dummer R, Goldinger SM. Successful retreatment with combined BRAF/-MEK inhibition in metastatic BRAFV600-mutated melanoma. J Eur Acad Dermatol Venereol 2017 Oct;31(10):1638–40.
[22] Schreuer M, Jansen Y, Planken S, Chevolet I, Seremet T, Kruse V, et al. Combination of dabrafenib plus trametinib for BRAF and MEK inhibitor pretreated patients with advanced BRAFV600-mutant melanoma: an open-label, single arm, dual-centre, phase 2 clinical trial. Lancet Oncol 2017;18(4):464–72.
[23] Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380(9839):358–65.
[24] McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014;15(3):323–32.
[25] Long GV, Weber JS, Infante JR, Kim KB, Daud A, Gonzalez R, et al. Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. J Clin Oncol 2016;34(8):871–8.
[26] Shi H, Hugo W, Kong X, Hong A, Koya RC, Moriceau G, et al. Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. Cancer Discov 2014;4(1):80–93.
[27] Smith MP, Brunton H, Rowling EJ, Ferguson J, Arozarena I, Miskolczi Z, et al. Inhibiting drivers of non-mutational drug tolerance is a salvage strategy for targeted melanoma therapy. Cancer Cell 2016;29(3):270–84.
[28] Girotti MR, Lopes F, Preece N, Niculescu-Duvaz D, Zambon A, Davies L, et al. Paradox-breaking RAF inhibitors that also target SRC are effective in drug-resistant BRAF mutant melanoma. Cancer Cell 2015;27(1):85–96.
[29] Rizos H, Menzies AM, Pupo GM, Carlino MS, Fung C, Hyman J, et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. Clin Cancer Res 2014;20(7):1965–77.
[30] Solit D, Sawyers CL. Drug discovery: how melanomas bypass new therapy. Nature 2010;468(7326):902–3.
[31] Sun C, Wang L, Huang S, Heynen GJ, Prahallad A, Robert C, et al. Reversible and adaptive resistance to BRAF(V600E) inhibition in melanoma. Nature 2014;508(7494):118–22.
[32] Kemper K, de Goeje PL, Peeper DS, van Amerongen R. Phenotype switching: tumor cell plasticity as a resistance mechanism and target for therapy. Cancer Res 2014;74(21):5937–41.
[33] Touil Y, Segard P, Ostyn P, Begard S, Aspord C, El Machhour R, et al. Melanoma dormancy in a mouse model is linked to GILZ/FOXO3A-dependent quiescence of disseminated stem-like cells. Sci Rep 2016;6:30405.
[34] Goff D, Jamieson C. Cycling toward elimination of leukemic stem cells. Cell Stem Cell 2010;6(4):296–7.
[35] Vizoso M, Ferreira HJ, Lopez-Serra P, Carmona FJ, Martinez-Cardus A, Girotti MR, et al. Epigenetic activation of a cryptic TBC1D16 transcript enhances melanoma progression by targeting EGFR. Nat Med 2015;21(7):741–50.
[36] Long GV, Grob JJ, Nathan P, Ribas A, Robert C, Schadendorf D, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. Lancet Oncol 2016;17(12):1743–54.
[37] Valpione S, Mocellin S, Campana LG. Small datasets to develop and validate prognostic models may be a necessary evil to study rare tumours. Eur J Cancer 2016;54:169–71.
[38] Valpione S, Moser JC, Parrozzani R, Bazzi M, Mansfield AS, Mocellin S, et al. Development and external validation of a prognostic nomogram for metastatic uveal melanoma. PLoS One 2015;10(3), e0120181.
[39] Gold JS, Gonen M, Gutierrez A, Broto JM, Garcia-del-Muro X, Smyrk TC, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 2009;10(11):1045–52.
[40] Valpione S, Martinoli C, Fava P, Mocellin S, Campana LG, Quaglino P, et al. Personalised medicine: development and external validation of a prognostic model for metastatic melanoma patients treated with ipilimumab. Eur J Cancer 2015;51(14):2086–94.
[41] Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol 2008;26(4):527–34.