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Selection Rather than Resensitisation? The Drug-Free Interval Does Not Predict Response to BRAF and MEK Inhibitor Rechallenge in Melanoma

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Abstract

Background: Most patients with BRAF V600-mutant melanoma progress on BRAF and MEK inhibition. Rechallenge after an interval of other therapy produces responses in a substantial minority, and the mechanism usually invoked is that resistance is partly epigenetic and reverses during time off drug. That mechanism makes a testable prediction. **Objectives:** To quantify rechallenge efficacy against first-course efficacy in the same patients; to test whether the duration of the drug-free interval predicts rechallenge response as the resensitisation model requires; and to identify what does predict response. **Methods:** Cohorts reporting outcomes of BRAF-directed rechallenge in advanced melanoma were eligible. Reported response and disease control rates were compared between first course and rechallenge within cohorts, and reported associations between interval duration and outcome were extracted. No new pooling was performed. Analyses were performed in Python 3. **Results:** Pooled across cohorts totalling 400 patients, rechallenge produced an objective response rate of 34.25% (95% CI 28.50-40.00), disease control in 65.01% (57.31-72.72), median progression-free survival of 5.0 months (4.0-5.9) and median overall survival of 9.8 months (9.3-20.4). Within cohorts, rechallenge retained 38% of the first-course objective response rate (27% against 72%) and 63% to 68% of the disease control rate. Three independent cohorts examined the drug-free interval and none found an association with response, disease control, progression-free survival or overall survival. The single predictive factor identified was depth of response to the first course: all patients achieving complete response initially achieved disease control on rechallenge, against 60% of those achieving partial response ($p = 0.002$). Among patients who did respond, median duration of response was longer on rechallenge than on first exposure (14.0 against 10.7 months), and toxicity was reported lower. **Conclusions:** Rechallenge is a worthwhile option in a setting with few alternatives. The mechanism usually invoked to justify it is not supported by the data: the drug-free interval, which the resensitisation model predicts should matter, consistently does not, while prior response depth does. Rarer but longer responses on rechallenge point the same way. These observations are better explained by selection of intrinsically sensitive tumours than by resistance reversing during time off drug, which has implications for whom to rechallenge and for whether scheduling a drug holiday is worthwhile.

Keywords: *Melanoma, BRAF inhibitor, MEK inhibitor, Rechallenge, Acquired resistance, Drug holiday*

1. Introduction

Roughly half of cutaneous melanomas carry an activating BRAF V600 mutation, and combined BRAF and

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MEK inhibition produces responses in around 70% of patients with advanced disease (Long *et al.*, 2014). Most of those responses are temporary; approximately half of patients progress within a year through acquired resistance.

Rechallenge—reintroducing BRAF-directed therapy after an interval of something else—has become a recognised option, and reported response rates in the region of a third are substantial in a setting where alternatives are limited.

The rationale offered is mechanistic and appealing. Alongside genetic resistance mechanisms, resistance to BRAF inhibition has an epigenetic and phenotypic component that appears reversible in preclinical systems: resistant cells drift back toward a sensitive state when drug pressure is removed (Das Thakur *et al.*, 2013; Sun *et al.*, 2014). If that is what happens in patients, then time off drug is the active ingredient of rechallenge, and the model makes a clear prediction—longer drug-free intervals should produce better rechallenge outcomes.

That prediction is testable with existing data, because contributing cohorts recorded the interval and related it to outcome. This review asks whether it holds, and if not, what alternative account fits the observations better.

The question is not academic. If the interval matters, then deliberately scheduling a drug holiday, or lengthening the interval before rechallenge, is a therapeutic decision. If it does not, then the interval is incidental and the clinical task is identifying which patients to rechallenge rather than when.

2. Methods

2.1. Design and reporting

This is a structured synthesis of published rechallenge cohorts. No new pooling of response rates was performed, since a pooled estimate already exists and the object of this review is the mechanistic inference drawn from these data rather than the magnitude of the effect. Reporting follows the PRISMA 2020 statement (Page *et al.*, 2021). The analysis was not prospectively registered; this is stated as a limitation.

2.2. Review question (PICO)

Population: Adults with unresectable or metastatic BRAF V600-mutant melanoma who had previously received and discontinued BRAF-directed therapy.

Intervention: Rechallenge with a BRAF inhibitor with or without a MEK inhibitor.

Comparator: Where available, the same patients' first course of BRAF-directed therapy.

Outcomes: Objective response rate, disease control rate, progression-free and overall survival, duration of response, and any reported association between the drug-free interval and outcome.

Unit of analysis: The published cohort.

2.3. Eligibility criteria

Inclusion criteria:

- Cohort of at least ten patients rechallenged with BRAF-directed therapy after prior exposure.
- Advanced or metastatic BRAF V600-mutant melanoma.
- Reporting of response or disease control on rechallenge.
- Full peer-reviewed publication or conference abstract with extractable outcomes.

Exclusion criteria:

- Studies without a rechallenge cohort.
- Case reports and series of fewer than ten patients.
- Tumour types other than melanoma.
- Reports of the same registry cohort already included.

2.4. Testing the resensitisation prediction

The resensitisation model asserts that resistance decays during the drug-free interval. Its central empirical prediction is a positive association between interval duration and rechallenge outcome. We extracted every reported analysis of that association, whether positive or negative, and report them together. We also extracted reported predictors of rechallenge response, to establish what does associate with outcome where the interval does not.

Two auxiliary observations bear on the same question. If rechallenge resensitises a broad population, responses should be comparably durable to first-course responses. If it instead selects a subgroup that was always sensitive, responses should be rarer but at least as durable. We therefore compared duration of response between courses where both were reported.

2.5. Statistical analysis

Reported rates were extracted as published. Retention of efficacy was computed as the rechallenge rate divided by the first-course rate within the same cohort, which is a descriptive ratio rather than a treatment effect. No new pooling, heterogeneity estimation or significance testing was performed on the response data. Analyses were performed in Python 3 using NumPy (Eisenhauer *et al.*, 2009).

3. Results

3.1. Included cohorts

Seven sources met the inclusion criteria and six contributed outcome data: a systematic review and meta-analysis pooling 400 patients (J Clin Oncol., 2023); a multi-institutional retrospective study of 116 patients across 14 centres (Valpione *et al.*, 2018); a multicentre analysis of 51 patients rechallenged after progression on both targeted therapy and immunotherapy (Melanoma Res., 2020); a retrospective study of 60 patients reporting both courses in detail (Oncotarget, 2018); a prospective observational registry contributing 24 patients (Clin Transl Oncol., 2025); and a stratified registry study reporting response by prior treatment setting (BRAF/MEK inhibitor rechallenge in patients with non-resectable or metastatic BRAF V600-mutated melanoma: a stratified, controlled, retrospective EUMelaReg multicenter study, 2026). Characteristics are in Table 1.

Table 1: Characteristics of the contributing cohorts

Source	Design	Patients	Rechallenge outcome
Systematic review and meta-analysis	Pooled analysis	400	ORR 34.25%; DCR 65.01%
Multi-institutional retrospective	14 centres, retrospective	116	RR 43%; OS 9.8 mo; PFS 5 mo
Multicentre post-immunotherapy cohort	Retrospective	51	ORR 27%; DCR 63%; PFS 5.9 mo
Two-course retrospective cohort	Retrospective	60	DCR 57%; PFS 5.0 mo; DoR 14.0 mo
Prospective registry (GEM-1801)	Prospective observational	24	ORR 20% retreatment; PFS 5.5 mo
Stratified registry study	Retrospective, matched control	184	ORR 26.2% after adjuvant exposure
Narrative review	Context	–	–

Note: ORR, objective response rate; DCR, disease control rate; RR, response rate; DoR, duration of response. Cohorts overlap with the pooled analysis, so the totals are not additive.

3.2. What rechallenge achieves

Pooled across 400 patients, rechallenge produced an objective response rate of 34.25% (95% CI 28.50–40.00) and disease control in 65.01% (57.31–72.72), with median progression-free survival of 5.0 months (4.0–5.9), median overall survival of 9.8 months (9.3–20.4) and one-year survival of 42.63% (30.25–55.02). Before

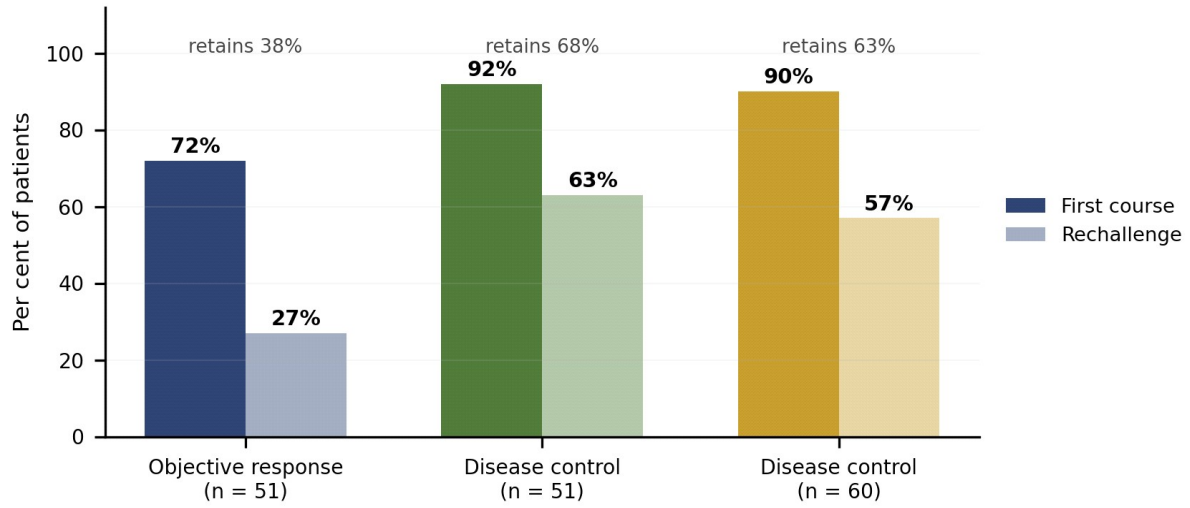

Figure 1: Response and disease control on first course and on rechallenge within the same cohorts. Solid bars are the first course, pale bars the rechallenge. Objective response retains 38% of its original rate while disease control retains around two thirds

rechallenge, 83% had received immunotherapy as interval treatment and 10% had been on a drug holiday; 79% were rechallenged with a combination and 21% with a BRAF inhibitor alone.

Within cohorts reporting both courses, the retention of efficacy is shown in Figure 2. Objective response fell from 72% to 27%, retaining 38% of the original rate. Disease control fell from 92% to 63% in one cohort and from 90% to 57% in another, retaining 68% and 63% respectively. Median progression-free survival roughly halved, from 10.5 to 5.9 months and from 9.9 to 5.0 months.

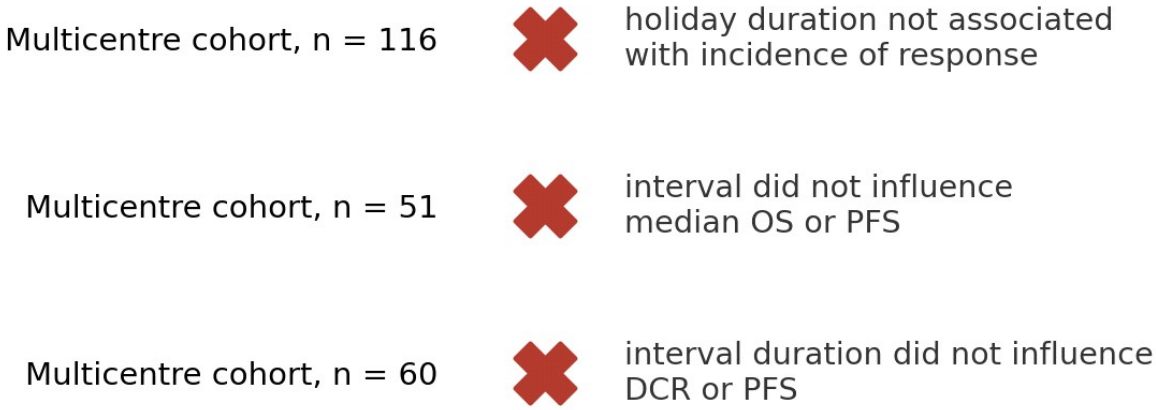

Figure 2: The prediction entailed by the resensitisation model—that a longer drug-free interval yields better rechallenge outcomes—tested in three independent cohorts. None found an association. Crosses mark the failed prediction rather than any deficiency in the studies

These are meaningful results in a population that has progressed on both targeted therapy and immune checkpoint blockade, where the realistic alternatives are a clinical trial or best supportive care. Toxicity was also reported to be lower on rechallenge than on first exposure.

3.3. The interval does not predict outcome

This is the central analysis, shown in Figure 3. Three independent cohorts examined the drug-free interval and none found it associated with outcome. The 116-patient study reported that the duration of the drug holiday was apparently not associated with the incidence of response. The 51-patient study reported that the time

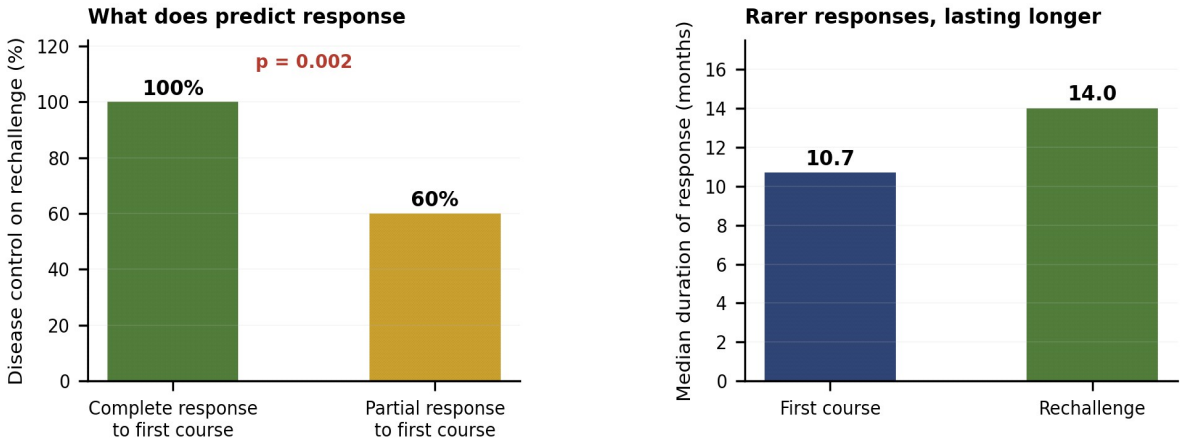

Figure 3: Left: disease control on rechallenge according to depth of response to the first course, the only predictive factor identified. Right: median duration of response by course. Responses on rechallenge are rarer but longer, which is what selection of an intrinsically sensitive subgroup would produce

interval between the end of first treatment and rechallenge did not influence median overall or progression-free survival. The 60-patient study reported that neither the duration of the treatment interval nor the treatment given during it influenced disease control or progression-free survival.

The resensitisation model predicts the opposite. If resistant clones drift back toward sensitivity when drug pressure is removed, then more time off drug should mean more reversion and better rechallenge outcomes. Three cohorts, in different countries and with different interval treatments, found no such gradient.

We are cautious about how strongly to state this. These are retrospective analyses of modest size, intervals were not randomised and were determined by clinical circumstance, and none reported a formal power calculation for the interval analysis. A real but modest association could have been missed. What can be said is that the prediction most directly entailed by the mechanism has been tested three times and has not been confirmed.

3.4. What does predict outcome

Where the interval failed, prior response succeeded. In the 60-patient cohort the only predictive factor identified for response to rechallenge was the depth of response to the first course. Every patient who achieved a complete response initially achieved disease control on rechallenge, against 60% of those who had achieved only a partial response ($p = 0.002$).

The 116-patient study reported a consistent pattern from a different angle: the greatest benefit was in patients who had responded to the initial targeted therapy and who had not responded to interval immunotherapy. The pooled analysis found that brain metastases and elevated lactate dehydrogenase, both strong general prognostic markers in melanoma, were not statistically significant predictors of rechallenge outcome.

One further observation points the same way. In the cohort reporting both, median duration of response was 10.7 months on first exposure and 14.0 months on rechallenge—responses are rarer the second time but last 1.31 times longer among those who achieve them. Adding MEK inhibition at rechallenge to patients previously treated with a BRAF inhibitor alone did not significantly improve disease control or progression-free survival.

3.5. Reading the pattern

Three observations sit together: the interval does not predict outcome, prior response depth does, and responses on rechallenge are rarer but more durable. Each is individually compatible with resensitisation, but the combination is what a selection account predicts directly.

On a selection reading, rechallenge does not restore sensitivity to a resistant population. It identifies the subgroup whose tumours were intrinsically and durably BRAF-dependent—the patients who achieved deep responses first time and whose residual disease retained that dependence. Those patients respond again and respond durably. Patients whose initial response was shallower had tumours less dependent on the pathway to begin with, and rechallenge does not change that.

We should be clear that the two accounts are not mutually exclusive, and neither is established here. Epigenetic reversion may occur and simply be too fast or too variable for interval duration to track it, in which case a threshold rather than a gradient would be expected. What the data do not support is the stronger version of the resensitisation claim in which time off drug is itself therapeutic.

Table 2: Rechallenge outcomes and predictors

Quantity	Value	Source
Objective response rate, pooled	34.25% (28.50–40.00)	400 patients
Disease control rate, pooled	65.01% (57.31–72.72)	400 patients
Median progression-free survival	5.0 months (4.0–5.9)	Pooled
Median overall survival	9.8 months (9.3–20.4)	Pooled
One-year overall survival	42.63% (30.25–55.02)	Pooled
ORR, first course vs rechallenge	72% vs 27% (retains 38%)	n = 51
DCR, first course vs rechallenge	92% vs 63% (retains 68%)	n = 51
DCR, first course vs rechallenge	90% vs 57% (retains 63%)	n = 60
Duration of response, first vs rechallenge	10.7 vs 14.0 months	n = 60
Drug-free interval as predictor	No association in 3 cohorts	n = 116, 51, 60
Prior complete response, disease control	100%	n = 60
Prior partial response, disease control	60% (p = 0.002)	n = 60
Brain metastases, LDH as predictors	Not significant	Pooled

Note: ORR, objective response rate; DCR, disease control rate; LDH, lactate dehydrogenase. Retention percentages are descriptive ratios within cohorts and are not treatment effects.

5. Discussion

Rechallenge with BRAF-directed therapy produces objective responses in about a third of patients and disease control in about two thirds, with median progression-free survival of five months. In a population that has exhausted both targeted therapy and immune checkpoint blockade, and with lower toxicity than first exposure, that is a worthwhile option and the practice is justified on outcomes alone.

The mechanism usually cited to justify it is another matter. The resensitisation account holds that resistance decays during time off drug, which entails that longer intervals should work better. Three independent cohorts tested that and none found it. The one factor that did predict rechallenge outcome was how deeply the tumour had responded the first time, and among patients who do respond, responses on rechallenge last longer than they did originally.

That combination is more economically explained by selection than by resensitisation. Tumours that were deeply and durably dependent on the BRAF pathway respond again when the pathway is blocked again, and their responses last because the dependence is real. Tumours that were less dependent do not, and time off drug does not make them so. On this reading rechallenge is not a way of reversing resistance but a way of identifying who never fully acquired it.

The preclinical account has become more specific since it was first proposed. Reversible resistance is now attributed substantially to rare pre-existing cell states that expand under drug pressure and contract without it, rather than to uniform reprogramming of the whole population (Shaffer *et al.*, 2017). That refinement is itself closer to a selection model than to a resensitisation one, and case-level reports of salvage rechallenge have been interpreted along similar lines (Front Oncol., 2021).

Two qualifications are needed. The first is that the accounts are not exclusive. Epigenetic reversion is well demonstrated in preclinical systems and may well occur in patients; it may simply operate on a timescale too short, or with variability too great, for interval duration to track it, in which case one would expect a threshold rather than a gradient. The second is evidential: these are retrospective cohorts of modest size, intervals were clinically rather than randomly determined, and no interval analysis reported a power calculation (Sterne *et al.*, 2016). Absence of an association is weaker evidence than presence of one.

For practice the implications are reasonably clear even under that uncertainty. Depth of prior response is a usable selection criterion and is available in every patient record without additional testing; a patient who achieved a complete response to first-line targeted therapy is a substantially better rechallenge candidate than one who achieved a partial response. Conversely, there is no evidential basis for deliberately extending a drug-free interval in order to improve rechallenge odds, and deferring effective therapy on that reasoning would be unsupported.

For research, the useful next step is a prospective cohort with prespecified interval strata and serial circulating tumour DNA, which would distinguish the two accounts directly: resensitisation predicts declining resistance-mutation fractions during the interval, while selection predicts that responders are identifiable from their first-course dynamics before the interval begins.

6. Limitations

- All contributing cohorts except one registry study are retrospective, and rechallenge was given at clinician discretion, so the rechallenged population is selected in ways that cannot be reconstructed.
- The comparison between first course and rechallenge within cohorts is not a randomised comparison and the two courses differ in disease burden, prior therapy and performance status.
- The absence of an interval effect rests on three analyses none of which reported a power calculation. A modest true association could have been missed, and absence of evidence is weaker than evidence of absence.
- Interval treatments differed substantially—83% received immunotherapy and 10% a drug holiday—so the interval is confounded with what happened during it.
- Rechallenge regimens differed, with 21% receiving a BRAF inhibitor alone, and one cohort found that adding MEK inhibition at rechallenge did not improve outcomes.
- The prior-response predictor derives from a single 60-patient cohort with small subgroup numbers, and the complete-response subgroup was very small.
- Duration of response was reported by both courses in only one cohort, so the durability observation is not replicated.
- The pooled estimates derive from a conference abstract, which limits the methodological detail available for appraisal.
- Cohorts overlap with the pooled analysis, so the sources are not independent.
- Interpreting the pattern as selection rather than resensitisation is an inference advanced by this review and is not established by these data.
- No new pooling was performed and no formal evidence grading was applied.
- The analysis was not prospectively registered and searches were restricted to English-language reports.

7. Conclusion

Rechallenge with BRAF and MEK inhibitors after progression produces objective responses in 34.25% (95% CI

28.50–40.00) of patients and disease control in 65.01% (57.31–72.72), retaining roughly two thirds of the first-course disease control rate and 38% of its objective response rate. In a heavily pretreated population with lower toxicity than first exposure, it is a worthwhile option.

The resensitisation rationale usually invoked predicts that longer drug-free intervals improve outcomes, and three independent cohorts found no such association. What did predict outcome was depth of response to the first course, and responses on rechallenge were rarer but longer-lasting. These observations fit selection of intrinsically sensitive tumours better than reversal of acquired resistance. The practical consequences are that prior response depth is a usable and freely available selection criterion, and that deliberately extending a drug-free interval to improve rechallenge odds has no evidential support.

Competing interests

The authors declare no competing interests.

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