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BRAF^{V600E}-mutated central nervous system tumors benefit from treatment with dabrafenib plus trametinib: Results from the Drug Rediscovery Protocol

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ABSTRACT

Introduction: Dual MAPK pathway inhibition with dabrafenib and trametinib has demonstrated significant activity across several *BRAF*^{V600E}-mutated tumor types. The aim of this study was to evaluate the efficacy and safety of dabrafenib plus trametinib in patients with *BRAF*^{V600E}-mutated progressive or recurrent tumors of the central nervous system (CNS).

Methods: Adult patients with *BRAF*^{V600E}-mutated CNS-tumors, including pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and glioblastoma, progressive on their last treatment line, were treated in the Drug Rediscovery Protocol (2023–509152–33–00) with dabrafenib 150 mg twice daily plus trametinib 2 mg once daily, until disease progression or intolerable toxicity. The primary endpoints were clinical benefit (CB: confirmed complete or partial response [PR] or stable disease [SD] $\geq$ 16 weeks) and safety.

Results: Between January 2019 and May 2024, 30 patients started treatment, of whom 25 were evaluable for response after completing at least one full treatment cycle. CB was observed in 19 patients, including 11 with confirmed PR and eight with SD for $\geq$ 16 weeks, resulting in a CB-rate of 76% (95% CI, 54.9%–90.6%) and an objective response rate of 44% (95% CI, 24.4%–65.1%). After a median follow-up of 40.2 months, the median duration of response was 27.8 months (95% CI, 23.6 months–not reached). The median progression-free and overall survival were 18.1 months (95% CI, 8.4 months–not reached) and 32.3 months (95% CI, 22.0 months–not reached), respectively. No unexpected toxicities were observed.

Conclusions: Dabrafenib plus trametinib is highly effective in patients with recurrent or progressive *BRAF*^{V600E}-mutated CNS-tumors, representing a valuable therapeutic option for these vulnerable patients.

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1. Introduction

B-raf proto-oncogene serine/threonine kinase (*BRAF*)^{V600} mutations activate the mitogen-activated protein kinase (MAPK) signaling pathway and result in cell proliferation and survival [1]. These mutations are significant oncogenic drivers across multiple cancer types, including melanoma [2]. In gliomas, the most frequently occurring primary brain tumors with an annual global incidence of approximately four to six cases per 100,000 individuals, *BRAF*^{V600} mutations are also identified [3,4]. These mutations are most frequently observed in grade 2 or 3 pleomorphic xanthoastrocytomas (PXA), appearing in around 56% of cases. In low-grade gliomas, *BRAF*^{V600} mutations exhibit an overall prevalence of 11% (95% CI, 0.04–0.19), with higher frequencies observed in gangliogliomas (40%). In contrast, these mutations are rare in high-grade gliomas, including an estimated prevalence of only 1% in glioblastomas, most often in cases with epithelioid morphology [5].

With molecular diagnostics rapidly advancing, the 2021, 5th edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) further incorporated genomic features into the classification of CNS tumors [6]. Depending on subtype and histological grade, differences in overall survival can be observed and different treatment options are available. For patients with glioblastoma, a grade IV glioma without the presence of an isocitrate dehydrogenase (*IDH*) mutation, prognosis remains poor, with a 2-year survival of 18% [7]. Treatment options are limited to surgical resection, followed by the so-called *Stupp scheme* combining radiotherapy with the chemotherapy temozolomide [8]. For *IDH*-mutant grade IV gliomas, median overall survival is 2.5 years [9]. In contrast, *IDH*-mutant grade II and III gliomas, including astrocytomas and 1p/19q-codeleted oligodendrogliomas, are more sensitive to chemotherapy combined with radiotherapy after maximal safe resection, resulting in a median overall survival of 8–13 years [10,11]. For *IDH*-mutant low-grade gliomas, the IDH1/2 enzyme inhibitor vorasidenib was recently granted approval by the FDA and European Medicines Agency (EMA) [12,13]. Treatment options for recurrent disease remain limited, ranging from re-resection, re-irradiation, or re-introduction of systemic therapy if available. The presence of pre-existing genomic alterations, the formation of new treatment-induced alterations, intratumoral heterogeneity, and challenges posed by the blood-brain barrier (BBB) can further complicate effective treatment [14,15]. The BBB makes the tumor microenvironment in gliomas unique by limiting immune cell infiltration, resulting in an immunologically 'cold' environment dominated by microglia and glioma-associated macrophages, along with senescent tumor-infiltrating lymphocytes [16]. Through complex cytokine and signaling networks, tumor cells, immune cells, and other stromal components interact to establish an immunosuppressive state, which contributes to therapeutic resistance, including limited responses to immune checkpoint inhibitors [17,18].

In this context, targeted approaches have gained increasing relevance. Dual MAPK pathway blockade with combination therapy of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) has shown significant activity in various *BRAF*^{V600E}-mutant tumor types, including an objective response rate (ORR) in the ROAR-trial of 69% and 33% in treatment refractory or relapsed low- and high-grade gliomas, respectively [19]. Together with data from the NCI-MATCH trial, that observed an ORR of 38% across *BRAF*^{V600}-mutated tumors treated with dabrafenib plus trametinib after at least one treatment line, the FDA granted approval in 2022 to dabrafenib plus trametinib for all patients with advanced or metastatic *BRAF*^{V600E}-mutant solid tumors after all standard of care treatment options are exhausted [20–22].

Although clinically effective in several tumor types, dabrafenib was initially developed to exhibit poor BBB permeability in order to avoid potential neurotoxic effects from interaction with high levels of wild-type BRAF in the brain [23]. Furthermore, both dabrafenib and trametinib are substrates of the active efflux transporters P-glycoprotein and breast cancer resistance protein in the BBB [24,25]. Despite these properties, preclinical studies demonstrated dabrafenib and trametinib to be capable of penetrating brain tissue in mice, particularly when the BBB is impaired [24,25]. Moreover, its proven effectiveness against both melanoma brain metastases and various primary brain tumors further indicate that these compounds are able to penetrate the BBB [19,23].

In this study, we present the efficacy and safety data of a cohort of patients with *BRAF*^{V600E}-mutated CNS-tumors that were treated with dabrafenib plus trametinib in the Drug Rediscovery Protocol (DRUP).

2. Methods

2.1. Study design

DRUP (2023–509152–33–00) is a prospective, ongoing, non-randomized basket and umbrella trial designed to investigate efficacy and safety of off-label targeted therapies and immunotherapies when molecularly matched to patients with advanced solid tumors [26]. Patients are enrolled in parallel cohorts, each characterized by a molecular alteration, a matched study drug, and a histological tumor type or tumor-agnostic approach. The study has been approved by the Medical Ethics Committee of the Netherlands Cancer Institute in Amsterdam and the institutional review boards of every participating hospital across the Netherlands. The study is conducted in accordance with the International Conference on Harmonization of Good Clinical Practice and the Declaration of Helsinki.

2.2. Patient population

Adult patients with a CNS-tumor harboring either a class I *BRAF* mutation (V600-mutant), a class II *BRAF* mutation (non-V600-mutant), or a class III *BRAF* mutation (non-V600-mutant) with a concomitant upstream mutation in the RAS/RAF pathway [1], found during routine molecular testing, were eligible for enrollment if they were progressive on their last line of systemic treatment or lacked any systemic treatment options, with measurable disease according to Response Assessment in Neuro-Oncology (RANO) [27] or Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [28]. The general inclusion and exclusion criteria of DRUP applied to this cohort [26]. Specifically for primary brain tumors, patients who required anticonvulsant therapy were not allowed to take enzyme-inducing antiepileptic drugs (EIAED), but had to be switched to non-EIAED at least 2 weeks prior to treatment initiation. A stable or decreasing dose of steroids for at least 7 days preceding the baseline scan was required, and patients that received radiotherapy within 3 months prior to progression or exceeding 65 Gy were excluded. Additionally, drug-specific exclusion criteria included: eligibility for ongoing phase II/III trials; known hypersensitivity to the treatment or any of the excipients of the products; concomitant use of known potent CYP2C8 and CYP3A4 inducers; uncorrectable electrolyte abnormalities, long QT syndrome, or use of drugs known to prolong the QT interval; history of retinal vein occlusion or predisposing factors, including uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes.

2.3. Study procedures

Written informed consent was obtained from patients upon enrollment. Patients were treated with dabrafenib capsules of 150 mg twice daily, together with trametinib tablets of 2 mg once daily in 28-day cycles, until disease progression or intolerable toxicity. Dose reductions were allowed up to a minimum of 50 mg dabrafenib twice daily, in combination with 1 mg trametinib once daily, in accordance with the Summary of Product Characteristics. Tumor assessments were performed by contrast-enhanced magnetic resonance imaging at baseline and after every second treatment cycle (i.e., every 8 weeks). If patients continued treatment beyond 6 months, tumor assessments were

thereafter performed after every third treatment cycle (i.e., every 12 weeks).

2.4. Study endpoints

The primary endpoints of the study are clinical benefit (CB) and safety. CB is defined as confirmed complete or partial response (CR/PR), or stable disease (SD) for ≥ 16 weeks, according to the RANO [27] or RECIST v1.1 [28] criteria, based on two assessments at least 28 days apart. Safety is measured by evaluation of serious and treatment related grade ≥ 3 adverse events (SAEs; TRAEs), defined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, that occur between registration up until 30 days after last dose of study drug. Trial safety is assessed by an Independent Data Monitoring Committee, blinded to cohort-specific response rates during accrual. Secondary study endpoints include ORR (defined as CR or PR), duration of response (DoR), PFS, and overall survival (OS). All patients who started treatment were included in the safety analysis. Patients who received less than one full cycle of dabrafenib plus trametinib (< 28 days) were considered non-evaluable per protocol, and were replaced and excluded from the efficacy analysis.

2.5. Statistical analysis

In DRUP, a Simon-like two-stage "admissible" monitoring design is used to evaluate clinical activity in each cohort [29]. Enrollment starts with eight patients in stage I. If at least one patient shows CB, the cohort is expanded to stage II with an additional 16 patients (24 patients in total). If less than five patients experience CB, absence of clinically meaningful activity is suggested, while CB in five or more patients would warrant further investigation to confirm the findings in a stage III 'expansion' cohort [30]. The null hypothesis and alternative hypotheses to be tested are defined as clinical benefit rate (CBR) of 10% versus ≥ 30%. This monitoring rule has 85% power to reject the null hypothesis when the true CBR is 30%, at a one-sided alpha error rate of 7.8%.

Patient characteristics, tumor responses, and TRAEs were summarized using descriptive statistics. The Clopper-Pearson method was used to calculate exact 95% confidence intervals (CI) of the CBR and ORR. Associations between OR and baseline characteristics were calculated with the Fisher's exact test (categorical variables), Wilcoxon's test (continuous variables), and linear by linear association test (ordinal variables). The Kaplan–Meier method was used to estimate time on treatment, DoR, PFS, and OS. The reverse Kaplan–Meier method was used to estimate the duration of follow-up. Differences between groups were assessed by the log-rank test. P values < 0.05 were considered statistically significant. All analyses were performed on R version 4.2.0.

3. Results

3.1. Patients

Between January 2019 and May 2024, 40 adult patients with *BRAF*-mutated CNS-tumors, from 11 different hospitals, were submitted to the central study team for review of potential study participation. Of these, 30 patients were found eligible and started study treatment. Twenty-five patients completed at least one full cycle of dabrafenib plus trametinib (28 days) and were therefore evaluable for the primary endpoint. At time of data cut-off (November 21, 2025), six patients (24%) were still on treatment. Reasons for treatment discontinuation were disease progression (n = 18, 72%), and toxicity (n = 1, 4%). A full overview of the reasons for non-accrual, non-evaluability and treatment discontinuation is provided in Supplementary Figure S1.

Baseline characteristics of all included patients are presented in Table 1. In brief, the median age was 44.0 years (36.3–51.8 years), 56.7% of the patients were male (n = 17), and 15 patients (50.0%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. The majority of patients (n = 23, 76.7%) had a high-grade CNS-tumor, of which glioblastoma was the most common diagnosis (n = 12, 40.0%). Centralized pathological review of tissue samples was not performed, as molecular testing was part of routine diagnostics. Nevertheless, all pathology reports were re-evaluated by a pathologist. Following this review, two patients who were initially diagnosed as glioblastoma were reclassified according to the updated 2021 WHO classification: one as PXA WHO grade 3 and the other as diffuse midline glioma, H3K27-altered. For one patient, the distinction between glioblastoma and PXA WHO grade 3 was uncertain. All evaluable patients harbored a $BRAF^{V600E}$-mutation.

Table 1
Baseline characteristics of included patients.

	Included patients	Evaluable patients
	n = 30	n = 25
Sex, n (%)		
Male	17 (56.7)	15 (60.0)
Female	13 (43.3)	10 (40.0)
Age, median [IQR]	44.0 [36.3 – 51.8]	43.0 [34.0 – 51.0]
ECOG performance status, n (%)		
0	10 (33.3)	10 (40.0)
1	15 (50.0)	11 (44.0)
2	5 (16.7)	4 (16.0)
Primary tumor type[a], n (%)		
High-grade CNS-tumor	**23 (76.7)**	**18 (72.0)**
Glioblastoma	12 (40.0)	8 (32.0)
PXA WHO gr.3	8 (26.7)	7 (28.0)
High-grade glioneuronal tumor, NEC	1 (3.3)	1 (4.0)
Diffuse midline glioma, H3K27-altered	1 (3.3)	1 (4.0)
Glioblastoma or PXA WHO gr.3[b]	1 (3.3)	1 (4.0)
Low-grade CNS-tumor	**7 (23.3)**	**7 (28.0)**
PXA WHO gr.2	1 (3.3)	1 (4.0)
Pilocytic astrocytoma	5 (16.7)	5 (20.0)
DLGNT	1 (3.3)	1 (4.0)
BRAF alteration, n (%)		
V600E (class I)	27 (90.0)	25 (100.0)
non-V600E (class II + III)	3 (10.0)	-
MGMT promoter methylation, n (%)		
Yes	3 (10.0)	3 (12.0)
No	16 (53.3)	14 (56.0)
Unknown	11 (36.7)	8 (32.0)
Previous systemic treatment lines, n (%)		
0	8 (26.7)	8 (32.0)
1	15 (50.0)	13 (52.0)
2	4 13.3)	3 (12.0)
3	2 (6.7)	-
5	1 (3.3)	1 (4.0)
Previous radiotherapy, n (%)		
Yes	24 (80.0)	19 (76.0)
No	6 (20.0)	6 (24.0)

[a]According to the 2021 WHO Classification.
[b]No clear diagnosis.
Abbreviations: BRAF, B-raf proto-oncogene serine/threonine kinase; CNS, central nervous system; DLGNT, diffuse leptomeningeal glioneuronal tumor; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MGMT, O6-methylguanine-DNA methyl-transferase; NEC, not elsewhere classified; PXA, pleomorphic xanthoastrocytoma; WHO, World Health Organization.

3.2. Efficacy

In the 25 evaluable patients, CB was observed in 19 patients, of whom 11 had a confirmed PR and eight had SD for ≥ 16 weeks, resulting in a CBR of 76% (95% CI, 54.9%–90.6%) and an ORR of 44% (95% CI, 24.4%–65.1%). The median DoR was 27.8 months (95% CI, 23.6 months–not reached) after a median follow-up of 40.2 months (95% CI, 30.6 months–not reached). The median time on treatment was 17.4 months (95% CI, 5.6–30.6 months, Figure 1). Among the six patients who did not experience CB, three had disease progression upon their first response evaluation, two had SD < 16 weeks, and one experienced symptomatic deterioration before the first response evaluation. The

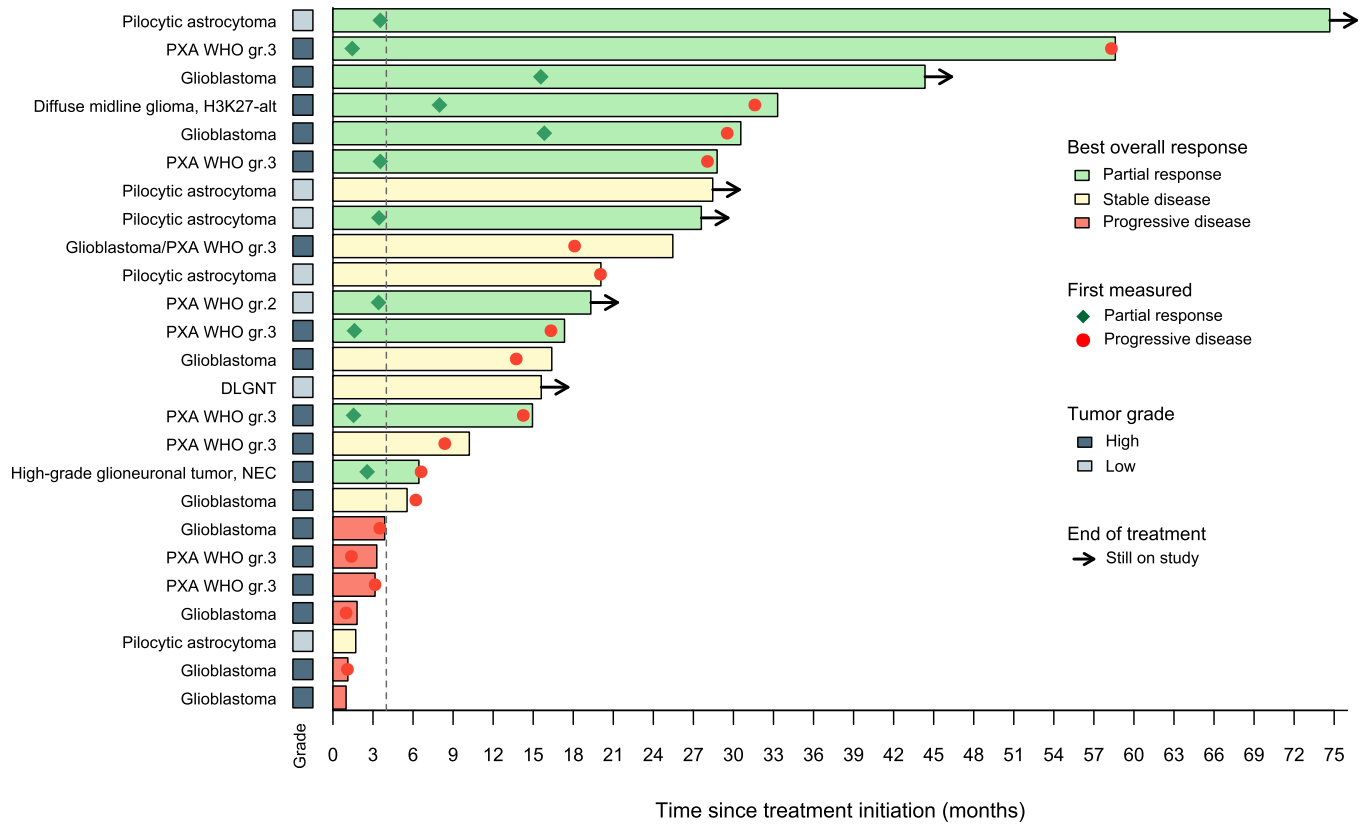

Fig. 1. Swimmer plot. **Figure legend**: Swimmer plot showing the time on treatment for all patients included in the efficacy analysis. Diamonds indicate the first measurements of partial response, and circles the first measurement of progressive disease. Arrows indicate continued treatment after data cut-off. The dashed line indicates 16 weeks. The plot is annotated with the tumor grade and type. **Abbreviations**: alt, altered; DLGNT, diffuse leptomeningeal glioneuronal tumor; gr, grade; NEC, not elsewhere classified; PXA, pleomorphic xanthoastrocytoma; WHO, World Health Organization.

greatest changes in the sum of target lesions is depicted in Figure 2. There were no significant differences in baseline characteristics between patients who had an objective response and those who did not (Supplementary Table S1). The median PFS and OS were 18.1 months (95% CI, 8.4 months–not reached) and 32.3 months (95% CI, 22.0 months–not reached), respectively (Figure 3).

When stratifying patients according to tumor grade, the ORR of the high-grade glioma group was 44% (95% CI, 21.5%–69.2%) with a median DoR of 24.1 months (95% CI, 14.7 months–not reached), whereas the low-grade glioma group had an ORR of 43% (95% CI, 9.9%–81.6%) with a median DoR that was not reached (Supplementary Figure S2). The median PFS and OS of the high-grade glioma group were 11.1 months (95% CI, 3.5 months–29.6 months) and 22.0 months (95% CI, 12.6 months–not reached), respectively. The median PFS and OS of the low-grade glioma group were not reached and 64.8 months (95% CI, 64.8 months–not reached), respectively (Supplementary Figure S3).

3.3. Safety

Overall, dabrafenib plus trametinib was well tolerated, as listed in Table 2. A total of three unique TRAEs grade ≥ 3 were reported in two patients (6.7%). One patient (3.3%) discontinued treatment due to a recurrent headache grade 2, possibly related to study treatment. No unexpected TRAEs were observed, and the overall safety profile was comparable to known toxicity profile of these compounds.

3.4. Biomarker analysis

All 25 evaluable patients harbored a *BRAF*^{V600E}-mutation, which had been identified through molecular diagnostics prior to study inclusion. Whole-genome sequencing (WGS) was performed in one patient, while the remaining 24 patients had undergone panel-based next-generation sequencing (NGS). NGS-panels used in the Netherlands differ per institution. However, all centers performing diagnostics on patients with CNS-tumors include BRAF in their NGS-panel [31]. All reported (likely) pathogenic gene variants extracted from the pathology reports submitted during enrollment are summarized in Figure 4. No *IDH* mutations or *EGFR* alterations were detected in this cohort, even though all assays included *IDH* testing and all but one included *EGFR*. This observation aligns with existing evidence that alterations in *IDH*, *EGFR,* and *BRAF* are generally mutually exclusive [32,33]. *MGMT* promoter methylation was observed solely in patients with CB, whereas the combination of *TERT* promoter activation and absence of *MGMT* promoter methylation occurred only in patients without CB. These findings are consistent with known prognostic associations of *TERT* and *MGMT* promoter status [7, 34]. Notably, all but one patient with *CDKN2A* loss showed CB, despite literature describing *CDKN2A* homozygous deletion as a poor prognostic feature [35,36]. One patient without CB harbored both a mutation and deletion in *NF1*, which may contribute to the lack of benefit, as *NF1* loss is a known mechanism of resistance to *BRAF* inhibition [37]. A complete overview of the reported gene variants per patient can be found in Supplementary Table S2.

4. Discussion

In this study, treatment with dabrafenib plus trametinib in patients with *BRAF*^{V600E}-mutant CNS-tumors proved to be highly effective and safe, with an ORR of 44% (95% CI, 24.4%–65.1%) and a median DoR of 27.8 months (95% CI, 23.6 months–not reached). Considering that these patients have limited standard of care options and these had already been exhausted, our observed median PFS of 18.1 months (95% CI, 8.4 months–not reached), and OS of 32.3 months (95% CI, 22.0 months–not

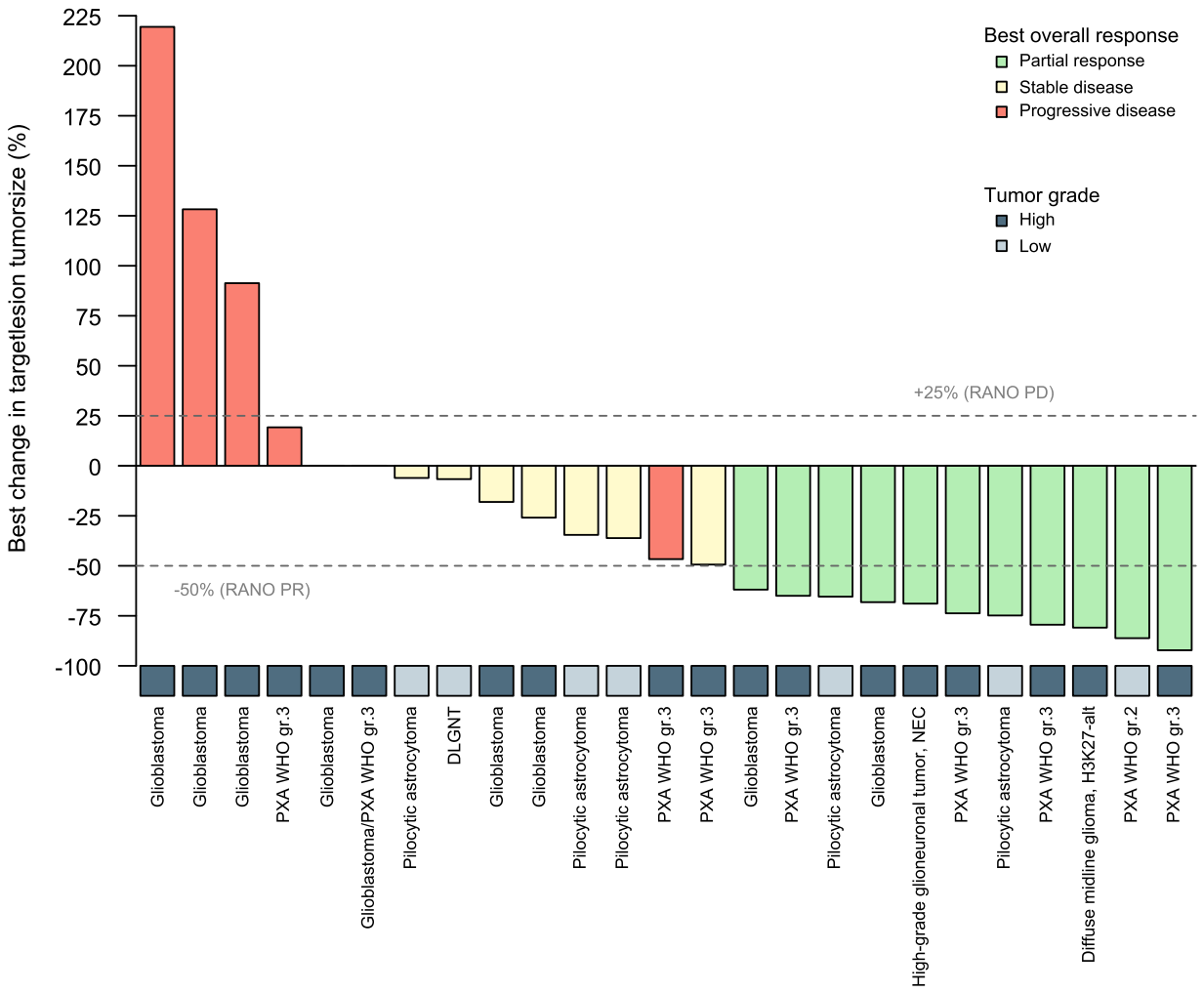

Fig. 2. Waterfall plot. **Figure legend**: Waterfall plot showing the best change in the sum of target lesions for all patients included in the efficacy analysis. The plot is annotated with the tumor grade and type. The patient with DLGNT had response evaluations according to RECIST v1.1, since the tumor was located in the spinal cord. **Abbreviations**: alt, altered; DLGNT, diffuse leptomeningeal glioneuronal tumor; gr, grade; NEC, not elsewhere classified; RANO, Response Assessment in Neuro-Oncology; PD, progressive disease; PR, partial response; PXA, pleomorphic xanthoastrocytoma; WHO, World Health Organization.

reached) become particularly meaningful given that the median overall survival after diagnosis is approximately 10 months for glioblastoma [7], and 53 and 33 months for PXA WHO grade 2 and 3 [38], respectively.

Our findings are comparable to previously performed studies. The low-grade glioma cohort from the ROAR-trial with 13 patients demonstrated a higher ORR of 69% compared to our ORR of 43%. On the other hand, our reported ORR of 44% exceeded the ORR of 33% in the high-grade glioma cohort of 45 patients in the ROAR-trial [19]. In sub-protocol H of the NCI-MATCH trial, 29 patients with *BRAF*^{V600E}-mutated cancers, including five with a CNS-tumor, were treated with dabrafenib plus trametinib and showed an overall ORR of 38% [21]. Another study investigating the efficacy of BRAF inhibitor encorafenib in combination with MEK inhibitor binimetinib in five patients with recurrent *BRAF*-^{V600E}-mutant high-grade gliomas reported an ORR of 60% [39]. Considering that both dabrafenib and trametinib are better at penetrating the BBB than vemurafenib, another BRAF inhibitor, and dual MAPK pathway blockade is more effective, it is not surprising that our results outperform those of the VE-BASKET study, that reported an ORR of 25% in 24 glioma patients treated with vemurafenib [24,25,40].

Within DRUP, pre-treatment biopsies are routinely performed prior to study enrollment to facilitate biomarker analyses by means of WGS for identification of potential predictors of response or resistance. However, due to the anatomical location of the patients' tumors in our cohort, obtaining a new biopsy was deemed a significant burden. Consequently, our biomarker analysis for this cohort relied on the available pathology reports at time of enrollment. Given the heterogeneity in reporting detail and version, certain molecular alterations may have been missed [31]. Nonetheless, our biomarker analysis yielded several observations consistent with previously published data, including the absence of *IDH* mutations or *EGFR* alterations in the presence of a *BRAF* mutation [32,33], the prognostic relevance of *TERT* and *MGMT* promotor status [7,34], and the role of *NF1* alterations as a known resistance mechanism [37]. Interestingly, although *CDKN2A* homozygous deletion has been described as an unfavorable prognostic marker in various CNS-tumors treated with standard therapeutic regimens [35,36], and its presence in *BRAF*^{V600E}-mutant low-grade gliomas has been linked to an increased risk of progression to high-grade disease [41], our findings, albeit in a very small subgroup, did not demonstrate such a negative prognostic association. In contrast, all but one patient harboring a *CDKN2A* deletion showed CB. A comparable finding was reported in a study of pediatric high-grade glioma patients [42], suggesting that the unfavorable prognostic implications of *CDKN2A/B* may be mitigated in the context of targeted therapy.

The absence of a control group is a limitation that warrants consideration when interpreting our results. However, studies have shown no significant difference in 2- and 5-year overall survival between PXA patients with and without a *BRAF*^{V600E} mutation when treated with

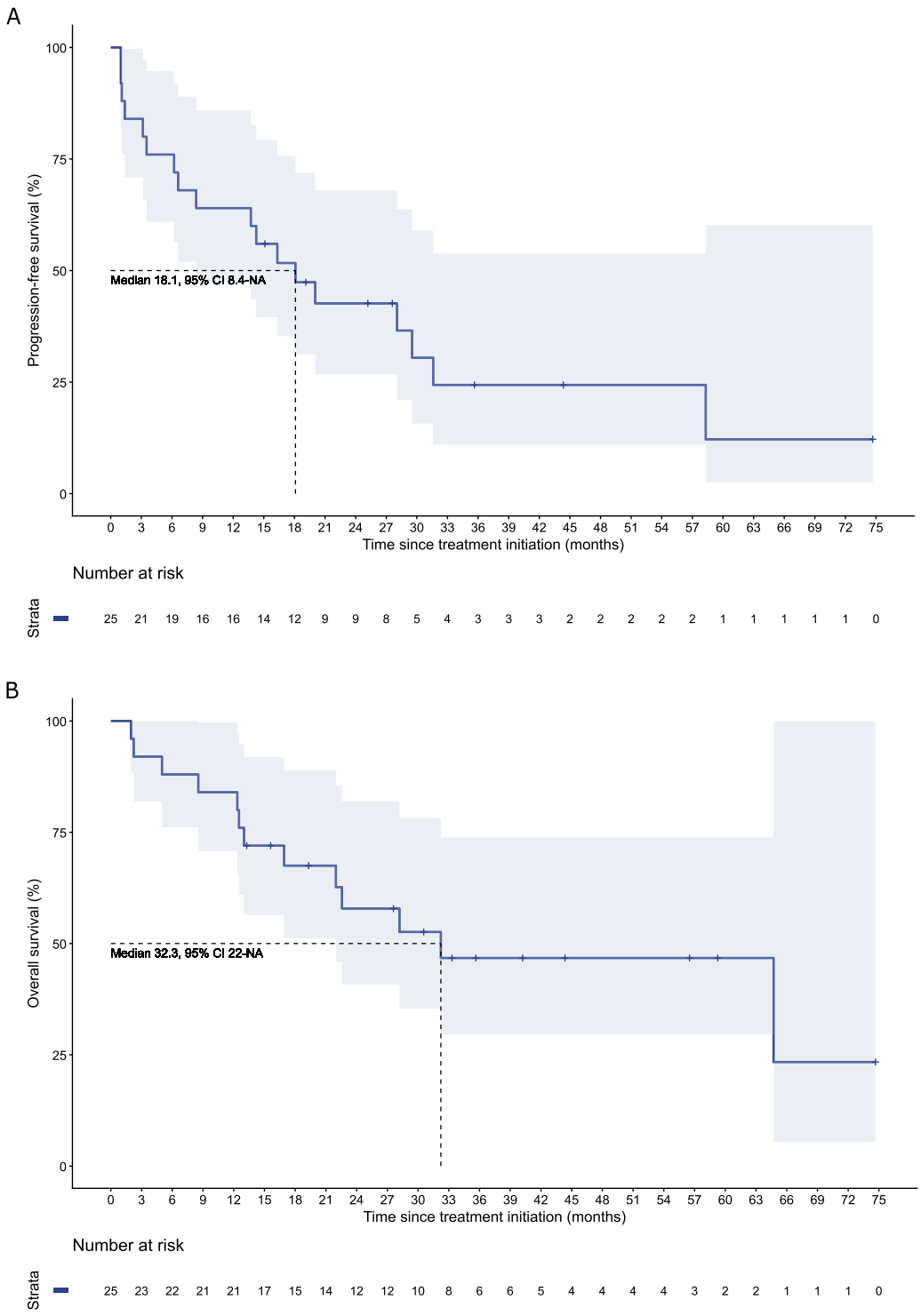

Fig. 3. Kaplan-Meier curves for progression-free survival (A) and overall survival (B). **Figure legend**: The median progression-free survival and overall survival times with 95% CIs are annotated in plots A and B, respectively. **Abbreviations**: CI, confidence interval; NA, not available.

standard of care therapy, making the outcomes observed in our cohort of particular clinical significance [38]. Furthermore, the Committee for the Evaluation of Oncological Agents (cieBOM) of the Dutch Society of Medical Oncology has established the PASKWIL-criteria to evaluate the added clinical value of oncological treatments, including those assessed in non-randomized or single-arm studies [43]. These criteria served as the foundation for the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) [44]. The PASKWIL criteria rely on the lower bound of the 95% CI for response rate to provide a more reliable measure in small studies. They also account for treatments with low response rates but long response durations by linking lower ORR thresholds to longer required response durations. In November 2025, cieBOM issued a positive recommendation for dabrafenib plus trametinib for Dutch glioma patients, based on the evidence from the ROAR-trial, although the quality of the data was rated as 'moderate' [45]. According to the PASKWIL-criteria, the ORR $>$ 20% and DoR $>$ 12 months observed in our cohort also meet the thresholds for a positive evaluation by cieBOM, underscoring the clinical relevance

Table 2
Treatment-related adverse events CTCAE version 4.03.

CTCAE term	Grade 2	Grade 3
Dehydration	1	-
Fever	-	1
Headache	1	-
Hyperglycemia	-	1
Neutrophil count decreased	-	1

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.

of our findings and strengthening the evidence for this therapeutic combination.

5. Conclusion

In conclusion, dabrafenib plus trametinib demonstrated high efficacy in patients with recurrent or progressive *BRAF*^{V600E}-mutated CNS-tumors, providing meaningful benefit in a population with limited treatment options. Patients with *BRAF*^{V600E}-mutated CNS-tumors, progressive after last line of treatment, should be able to access this combination therapy based on this study, combined with previously generated and published clinical evidence [19,21].

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CRediT authorship contribution statement

Soemeya F. Haj Mohammad: Writing – original draft, Resources, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Ilse A.C. Spiekman:** Writing – review & editing, Resources, Project administration, Investigation, Data curation. **Karlijn Verkerk:** Writing – review & editing, Resources, Project administration, Investigation, Data curation. **Florentine A.J. Verbeek:** Writing – review & editing, Resources, Project administration, Investigation, Data curation. **Hans Timmer:** Writing – review & editing, Resources, Project administration, Investigation, Data curation. **Maud A. van Maren:** Writing – review & editing, Resources, Project administration, Investigation, Data curation. **Laurien J. Zeverijn:** Writing – review & editing, Resources, Project administration, Investigation, Data curation. **Birgit S. Geurts:** Writing – review & editing, Resources, Project

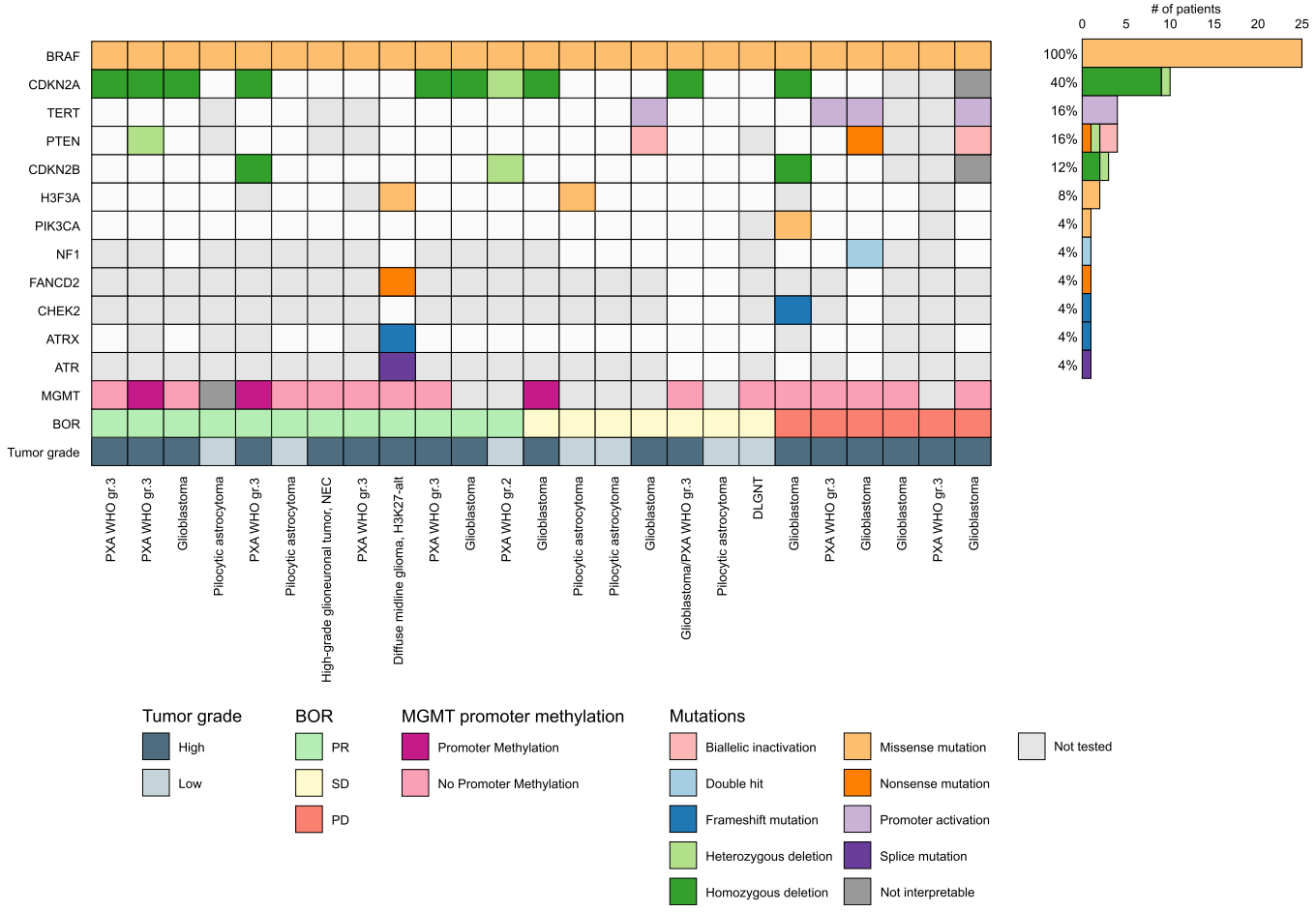

Fig. 4. Oncoplot. **Figure legend**: Oncoplot displaying all (likely) pathogenic molecular alterations by molecular testing prior to participation in DRUP. The bar plot shows the percentage of patients harboring each genetic alteration. Biallelic inactivation includes two mutations or a mutation in combination with loss of heterozygosity. **Abbreviations**: alt, altered; BOR, best overall response; DLGNT, diffuse leptomeningeal glioneuronal tumor; gr, grade; MGMT, O6-methylguanine-DNA methyl-transferase; NEC, not elsewhere classified; PD, progressive disease; PR, partial response; PXA, pleomorphic xanthoastrocytoma; SD, stable disease; WHO, World Health Organization.

administration, Investigation, Data curation. **Antonios Daletzakis:** Writing – review & editing, Formal analysis. **Paul Roepman:** Writing – review & editing, Investigation. **Anne M.L. Jansen:** Writing – review & editing, Investigation. **Wendy W.J. de Leng:** Writing – review & editing, Investigation. **Sybren L.N. Maas:** Writing – review & editing, Resources, Investigation. **Filip Y.F.L. de Vos:** Writing – review & editing, Resources, Investigation. **Henk M.W. Verheul:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition, Conceptualization. **Emile E. Voest:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition, Conceptualization. **Hans Gelderblom:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Emile E. Voest reports financial support was provided by Dutch Cancer Society. Emile E. Voest reports financial support was provided by Stelvio for Life Foundation. Hans Gelderblom reports financial support was provided by Horizon Europe. Hans Gelderblom reports financial support was provided by European Commission. Emile E. Voest reports financial support and equipment, drugs, or supplies were provided by Novartis Pharmaceuticals. Emile E. Voest reports a relationship with Sanofi that includes: board membership. Emile E. Voest reports a relationship with Mosaic Therapeutics that includes: board membership. Emile E. Voest reports a relationship with Amgen Europe GmbH that includes: funding grants. Emile E. Voest reports a relationship with AstraZeneca Pharmaceuticals LP that includes: funding grants. Emile E. Voest reports a relationship with Boehringer Ingelheim GmbH that includes: funding grants. Emile E. Voest reports a relationship with Clovis Oncology Inc that includes: funding grants. Emile E. Voest reports a relationship with Eli Lilly and Company that includes: funding grants. Emile E. Voest reports a relationship with GlaxoSmithKline Inc that includes: funding grants. Emile E. Voest reports a relationship with Ipsen that includes: funding grants. Emile E. Voest reports a relationship with Merck Sharp & Dohme Corp that includes: funding grants. Emile E. Voest reports a relationship with Roche Pharma AG that includes: funding grants. Emile E. Voest reports a relationship with Novartis that includes: funding grants. Sybren L.N. Maas reports a relationship with Servier Monde that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Declaration

The author Hans Gelderblom is an Editor of the EJC and was not involved in the editorial review or the decision to publish this article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116674.

Data availability

The per-patient clinical data presented in this study are available for academic use and can be obtained through a request directed to the corresponding author.

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