Supplementary Appendix

Supplement to: Bouffet E, Hansford JR, Garrè ML, et al. Dabrafenib plus trametinib in pediatric glioma with *BRAF* V600 mutations. N Engl J Med 2023;389:1108-20. DOI: 10.1056/NEJMoa2303815

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Dabrafenib Plus Trametinib in *BRAF* V600–Mutant Pediatric Low-Grade Glioma

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Supplementary Methods

Blinded independent assessment

Scans were conducted at screening (within 28 days before initiation of study treatment), every 8 weeks for the first 56 weeks, every 16 weeks thereafter while on treatment and during post-treatment follow-up, and at any time there was suspicion of clinical progression. All scans were submitted to a central imaging vendor and read by an expert pediatric oncology neuroradiologist blinded to treatment; response determinations per Response Assessment in Neuro-Oncology (RANO)-LGG criteria were based primarily on T2 FLAIR changes.[1,2] Partial and complete responses were confirmed by repeat assessments performed ≥4 weeks after the criteria for response were first met. Scans meeting the criteria for minor response were categorized as stable disease for this trial. Clinical data necessary for RANO response determination (ie, steroid usage, clinical/neurological status) were provided to the vendor after the initial response by radiological criteria only had been determined for incorporation into the RANO response determination. Progressive disease was evaluated on best response (nadir). Response determinations based on independent assessment were not made available to investigators except by request to allow crossover from chemotherapy to dabrafenib plus trametinib. All patient management decisions, other than crossover, were solely managed by investigators without regard to the independent assessment.

Patient-reported outcomes (PROMIS Parent Proxy Global Health 7+2)

The 7+2 item parent proxy global health measure includes independent global health (7 items), pain (1 item), and fatigue (1 item) scores.[3] Scoring and handling of missing data were according to the user guide; no imputation was applied for missing data and results for each scheduled

assessment for each treatment group were summarized descriptively. The assessment was administered at weeks 1, 5, 8, 16, 24, 32, 40, 48, 56, and every 16 weeks thereafter.

Biomarker assessment

Molecular data were available from patients with baseline tumor samples for which there was sufficient material for biomarker testing (after central *BRAF* confirmation) that yielded results that passed quality control measures. DNA methylation profiling was performed using the Illumina EPIC/850k DNA methylation array kit (Illumina; San Diego, CA). Evaluation of genomic aberrations of potential clinical relevance in the *CDKN2A/B* and *TP53* genes was defined post hoc. Copy number aberrations were inferred from methylation array data using the R/Bioconductor package conumee.[4] Tumor sample collection at progression was optional per investigator discretion and no such samples were available for analysis.

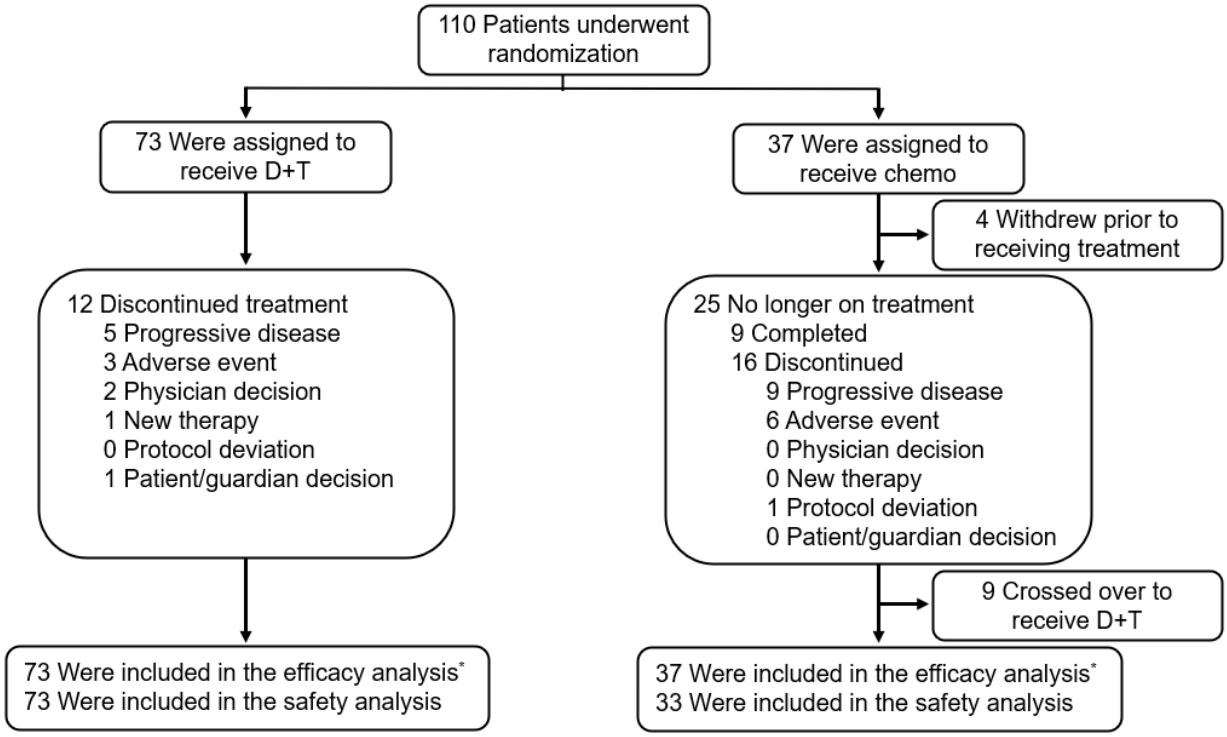
Visual acuity

Visual acuity was assessed by ophthalmic examination via local standard procedures at screening; week 5, week 16, and every 16 weeks thereafter; and at investigator discretion in the event of suspected visual changes. Post hoc analysis involved transformation of Snellen scale data into the logMAR (Minimum Angle of Resolution) scale for each eye at baseline and over time on treatment and was conducted for patients with tumors located near the optic chiasm; improved, stable, or worsened acuity was defined per Table S7.

Trial oversight

A Steering Committee comprised of trial investigators and sponsor personnel was established to ensure transparent management of the study in accordance with the protocol. This committee also reviewed protocol amendments as appropriate. A Data Monitoring Committee, comprised of individuals not otherwise involved in study conduct or affiliated with trial investigators, was also established to monitor safety. This committee was convened prior to randomized of the first patient and reviewed safety data approximately every 6 months for the first 2 years of the study and approximately yearly thereafter, providing recommendations to continue, modify, or halt the study as needed.

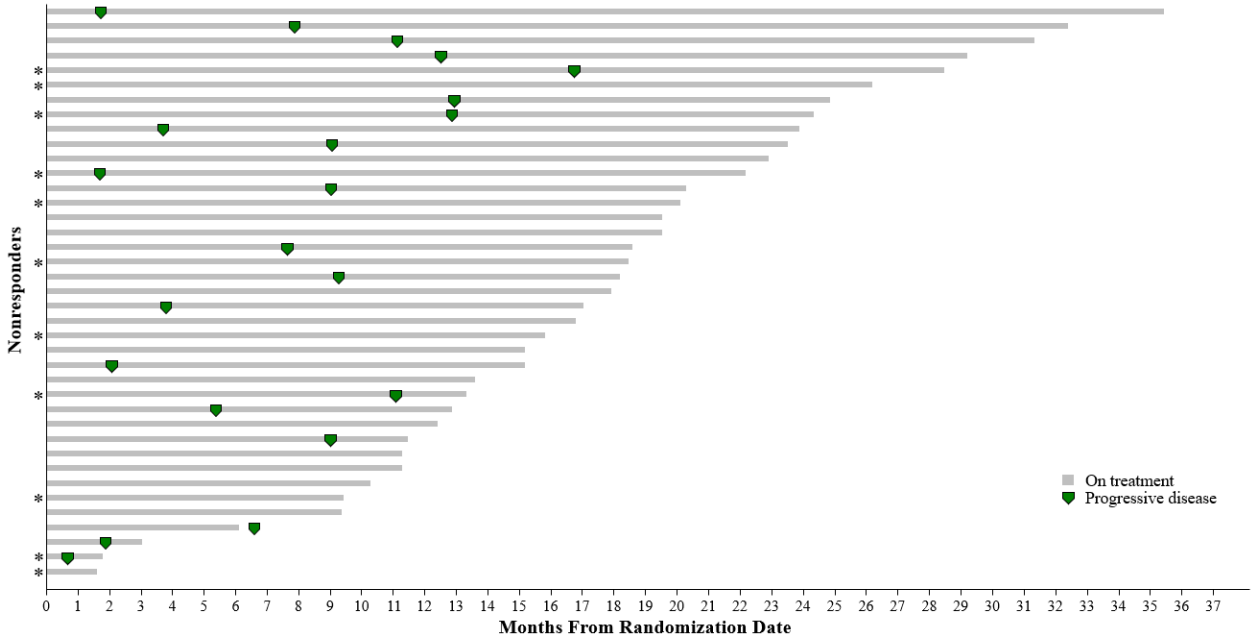
Figure S1. Consort Diagram



chemo, chemotherapy; D+T, dabrafenib plus trametinib.

* Efficacy analysis was performed on the intent-to-treat population, which includes all patients who were assigned by randomization regardless of whether they received treatment.

Figure S2. Duration of Treatment for Nonresponders Who Were Randomized to Receive Dabrafenib Plus Trametinib

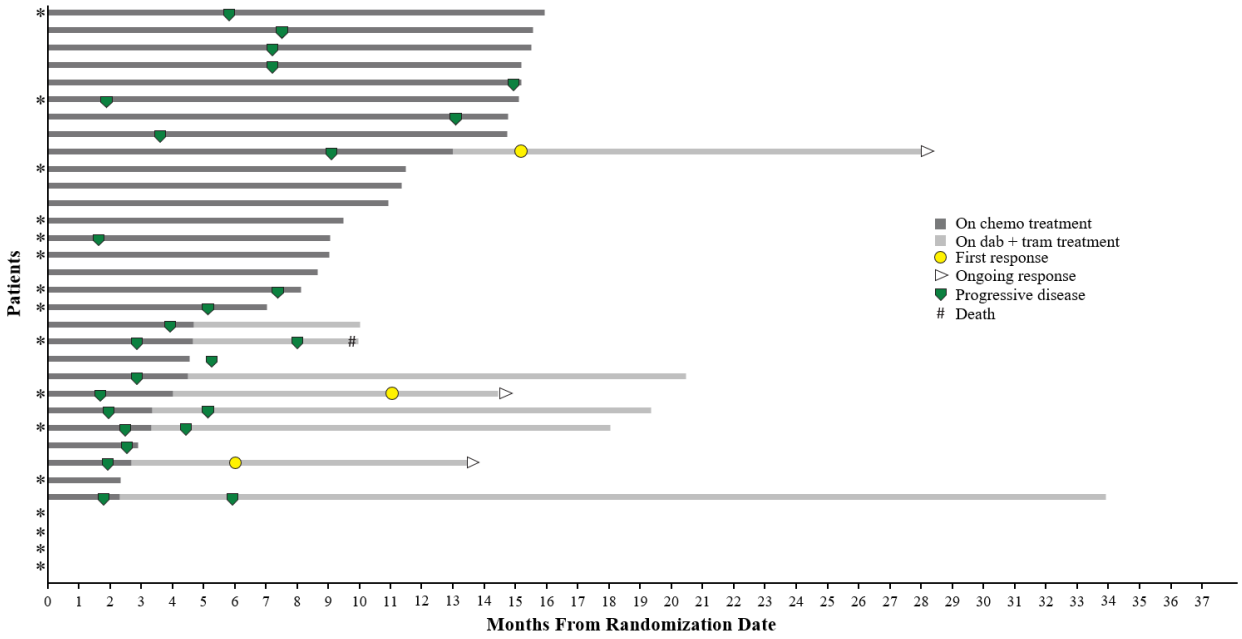


Only first occurrence of each response (CR, PR) and/or PD are displayed.

CR, complete response; PD, progressive disease; PR, partial response.

* Not in the evaluable set.

Figure S3. Duration of Treatment for Nonresponders Who were Randomized to Receive Chemotherapy, Including Nine Patients Who Crossed Over to Receive Dabrafenib Plus Trametinib

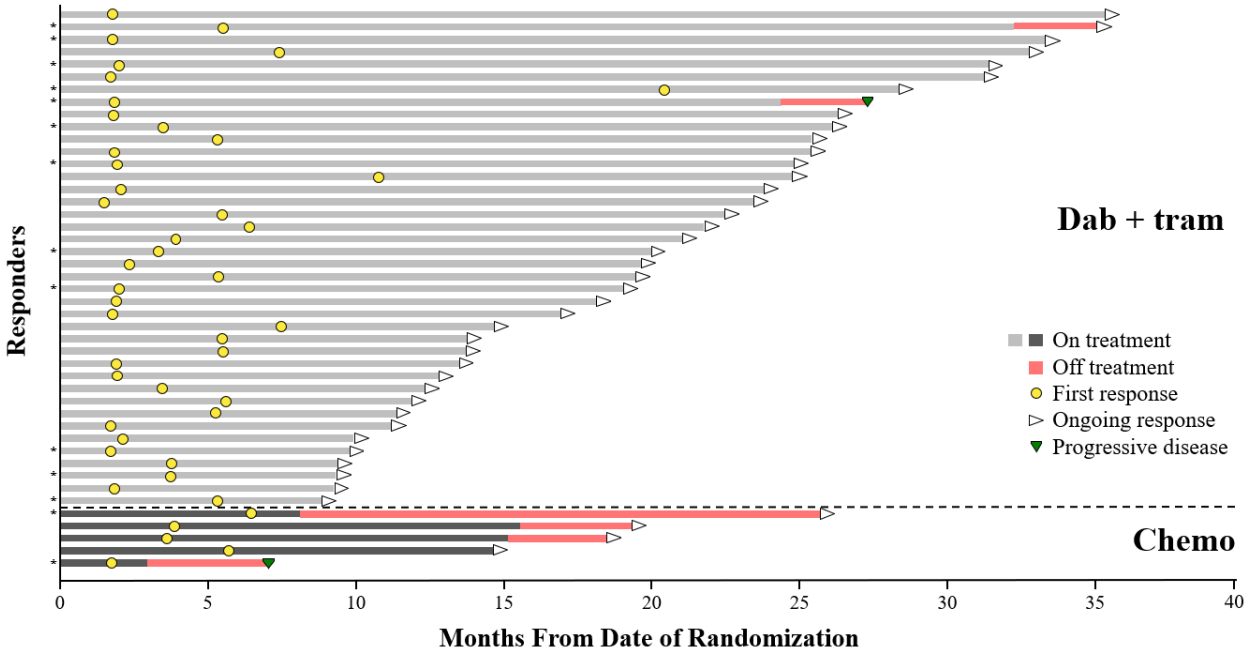


Only first occurrence of each response (CR, PR) and/or PD are displayed.

chemo, chemotherapy; CR, complete response; dab, dabrafenib; PD, progressive disease; PR, partial response; tram, trametinib.

* Not in the evaluable set.

Figure S4. Duration of Response (Investigator Assessment)



Only first occurrence of each response (CR, PR) and/or PD are displayed.

chemo, chemotherapy; CR, complete response; dab, dabrafenib; PD, progressive disease; PR, partial response; tram, trametinib.

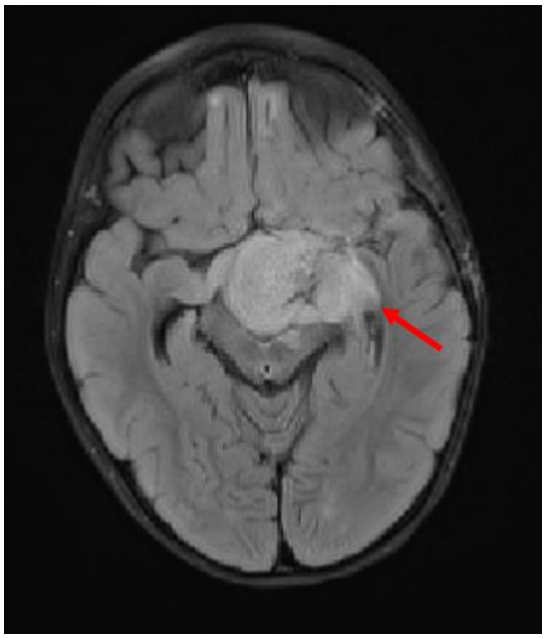
* Not in the evaluable set.

Figure S5. Representative Scans of a Patient With Tumor Shrinkage After Treatment With Dabrafenib Plus Trametinib Using T2-FLAIR (A) and T1 Post Contrast (B)

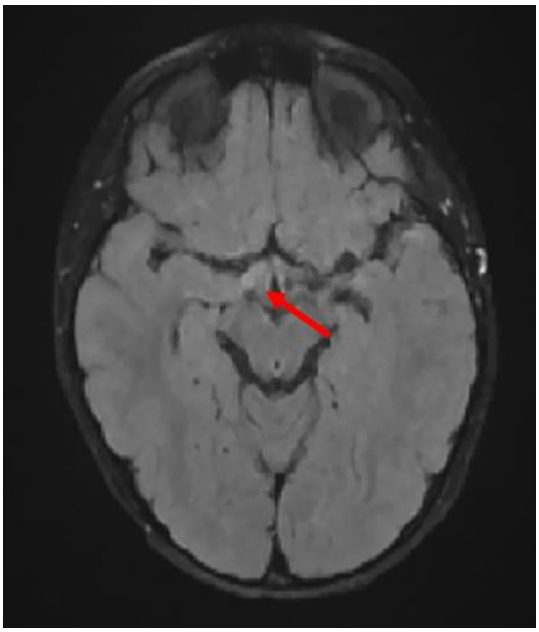
This patient with grade 1 pilocytic astrocytoma treated with dabrafenib plus trametinib (performance status 90 at baseline, 100 during treatment) experienced tumor shrinkage consistent with a partial response in the brain at first on-treatment scan (week 8) and ongoing at week 137.

(A)

Screening: 59 mm × 47 mm

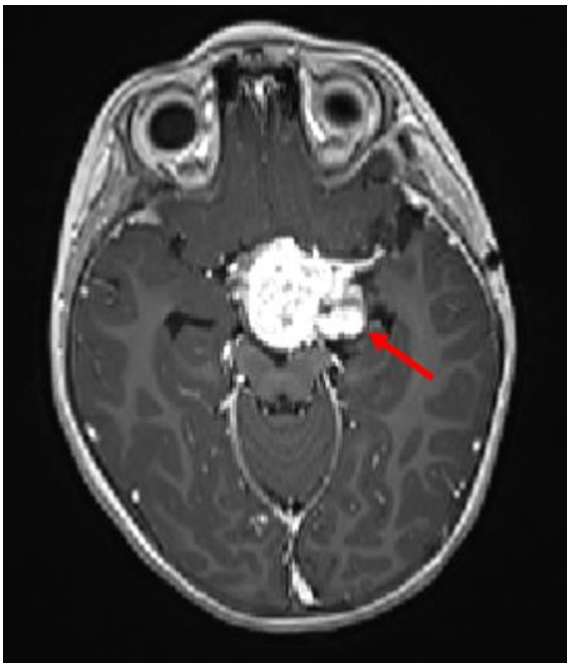


Week 104: 9 mm × 5 mm



(B)

Screening: 59 mm × 47 mm



Week 104: 9 mm × 5 mm

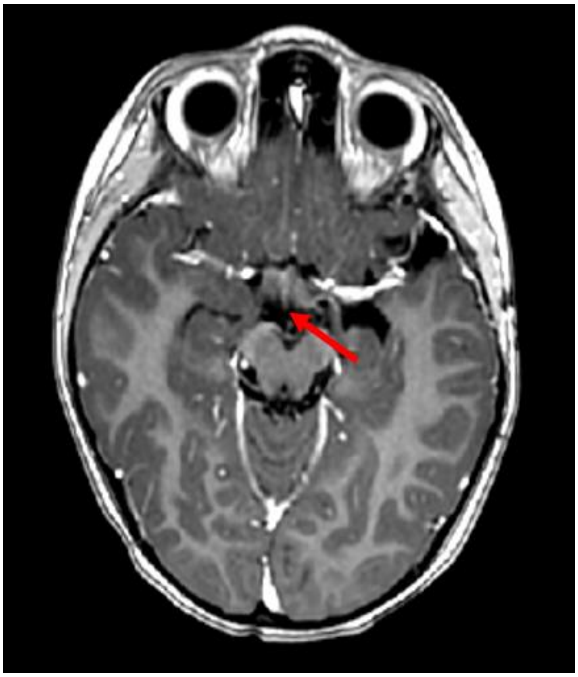
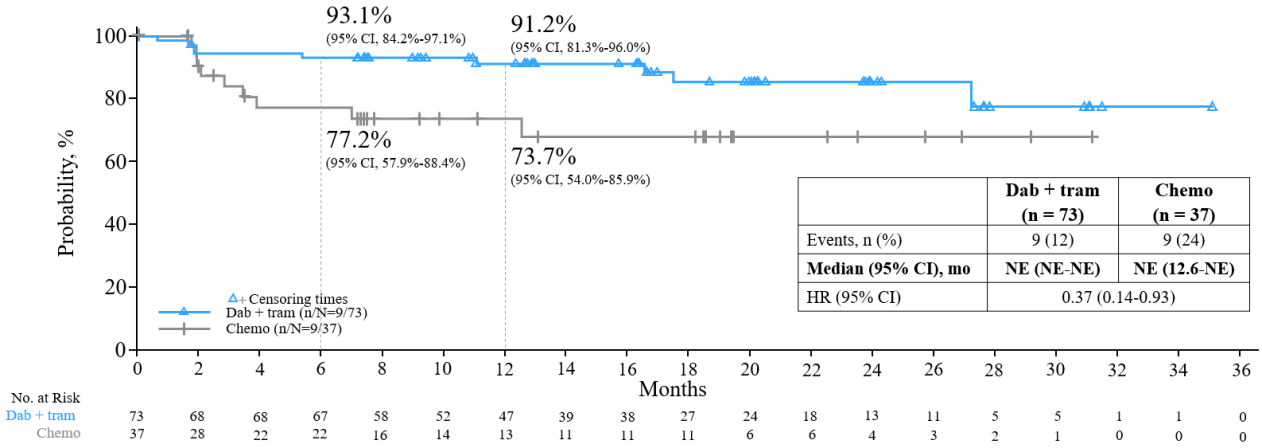


Figure S6. Progression-Free Survival (Investigator Assessment per RANO Criteria)

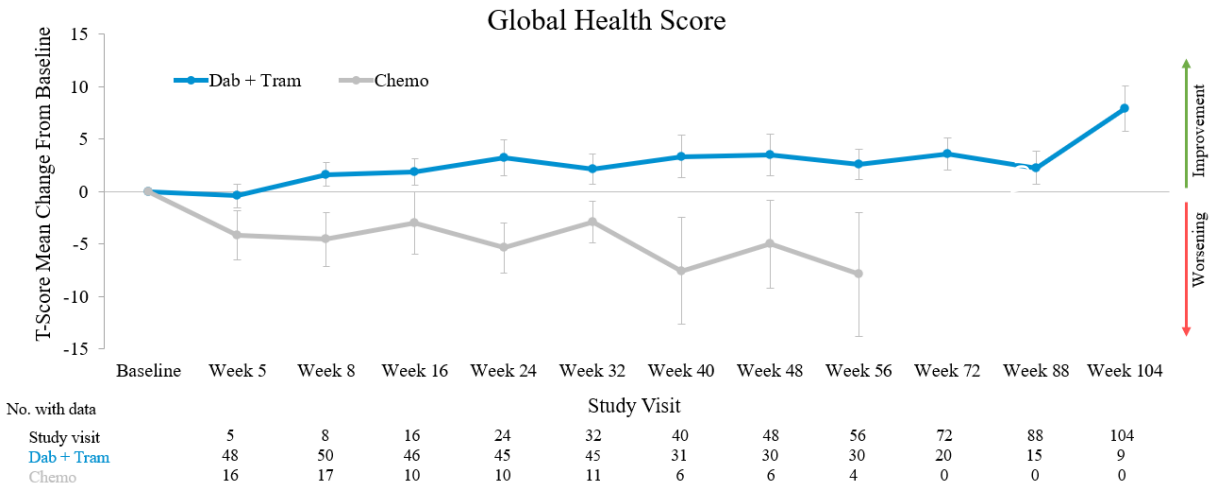


	Dab + tram (n = 73)	Chemo (n = 37)
Events, n (%)	9 (12)	9 (24)
Median (95% CI), mo	**NE (NE-NE)**	**NE (12.6-NE)**
HR (95% CI)	0.37 (0.14-0.93)	

chemo, chemotherapy; dab, dabrafenib; HR, hazard ratio; NE, not evaluable; RANO, Response Assessment in Neuro-Oncology; tram, trametinib.

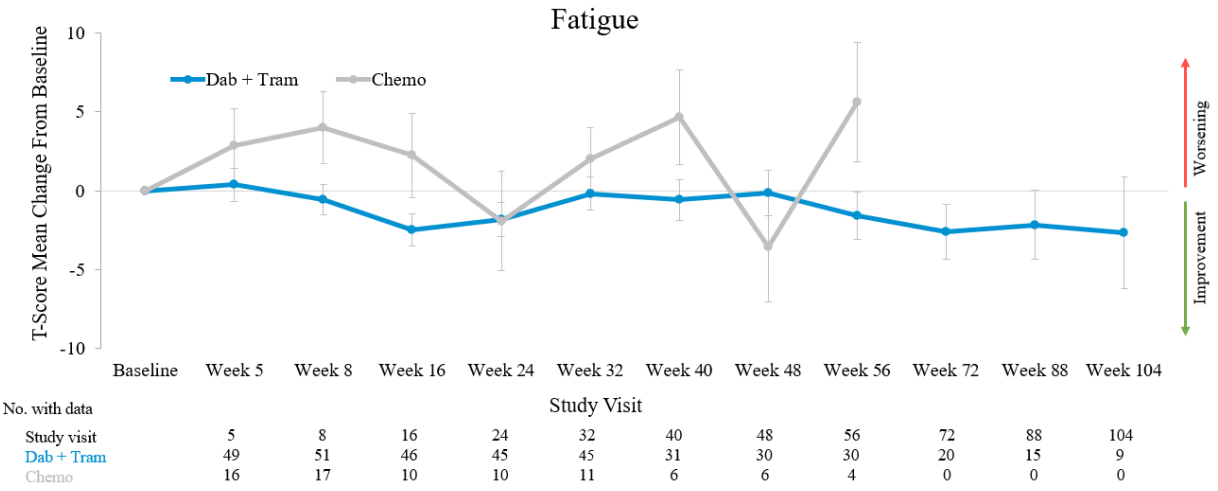
Figure S7. Change From Baseline in PROMIS Global Health 7+2–Parent Proxy Questionnaire Scores: Global Health Score (A), Fatigue (B), and Pain (C)*

(A)



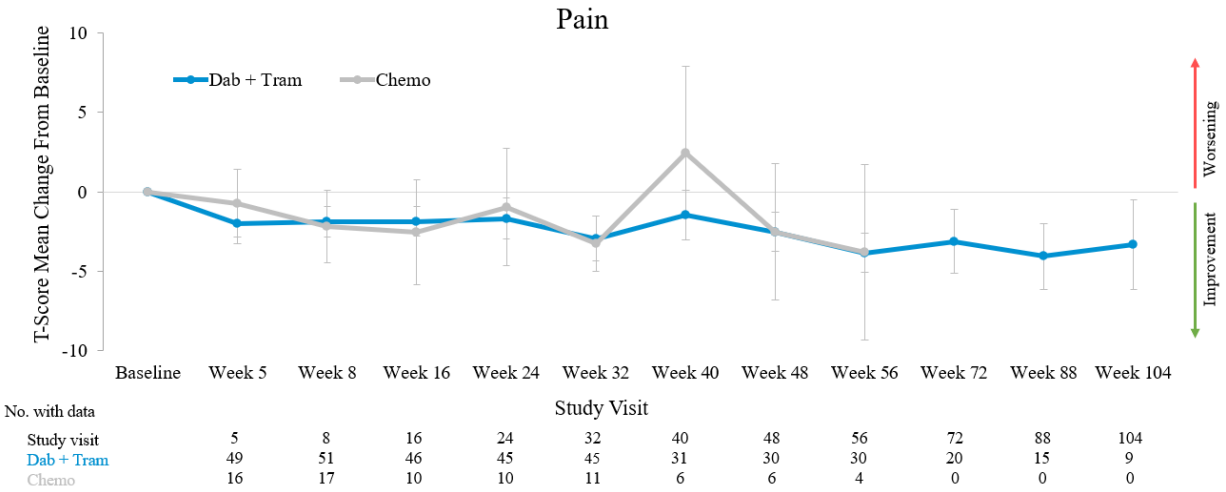
No. with data											
Study visit	5	8	16	24	32	40	48	56	72	88	104
Dab + Tram	48	50	46	45	45	31	30	30	20	15	9
Chemo	16	17	10	10	11	6	6	4	0	0	0

(B)



No. with data											
Study visit	5	8	16	24	32	40	48	56	72	88	104
Dab + Tram	49	51	46	45	45	31	30	30	20	15	9
Chemo	16	17	10	10	11	6	6	4	0	0	0

(C)



chemo, chemotherapy; dab, dabrafenib; tram, trametinib.

* Not statistically tested. Clinically relevant differences between dabrafenib + trametinib and chemotherapy were those ≥5 points.

Table S1. Expanded Demographics and Baseline Characteristics

Category	Dabrafenib + Trametinib (n=73)	Chemotherapy (n=37)
Age, median (range), years	**10.0 (1-17)**	**8.0 (1-17)**
12 months to <6	20 (27.4)	14 (37.8)
6 to <12	25 (34.2)	11 (29.7)
12 to <18	28 (38.4)	12 (32.4)
Male, n (%)	29 (39.7)	15 (40.5)
Race, n (%)		
White	55 (75.3)	25 (67.6)
Asian	5 (6.8)	3 (8.1)
Black or African American	2 (2.7)	3 (8.1)
Not reported	2 (2.7)	1 (2.7)
Unknown	6 (8.2)	4 (10.8)
Other	3 (4.1)	1 (2.7)
Ethnicity, n (%)		
Not Hispanic or Latino	48 (65.8)	17 (45.9)
Hispanic or Latino	8 (11.0)	4 (10.8)
Not reported	12 (16.4)	11 (29.7)
Unknown	5 (6.8)	5 (13.5)
Weight, median (range), kg	36.5 (7.8-115.0)	38.2 (9.0-110.3)
Height, median (range), cm	140.1 (54.0-187.2)	141.0 (76.1-177.3)
Body mass index, median (range), kg/m^2	19.4 (13.1-97.7)	20.1 (15.5-40.9)
Body surface area, median (range), m^2	1.22 (0.4-2.4)	1.26 (0.5-2.3)
Karnofsky/Lansky performance status, n (%)*		
100	40 (54.8)	18 (48.6)
90	20 (27.4)	9 (24.3)
80	5 (6.8)	2 (5.4)
70	3 (4.1)	3 (8.1)
<70	2 (2.7)	0
Missing	3 (4.1)	5 (13.5)
Prior antineoplastic therapy, n (%)		
Any therapy		
No	11 (15.1)	5 (13.5)
Yes	62 (84.9)	29 (78.4)
Missing	0	3 (8.1)
Surgery		
No	11 (15.1)	5 (13.5)
Yes	62 (84.9)	29 (78.4)
Missing	0	3 (8.1)
Radiotherapy		
No	73 (100)	34 (91.9)
Yes	0	0

Missing	0	3 (8.1)
Systemic treatment		
No	72 (98.6)	34 (91.9)
Yes	1 (1.4)†	0
Missing	0	3 (8.1)
Ongoing medical conditions, n (%)‡		
Precocious puberty	3 (4.1)	3 (8.1)
Optic atrophy	5 (6.8)	2 (5.4)
Vision blurred	4 (5.5)	2 (5.4)
Myopia	2 (2.7)	3 (8.1)
Constipation	6 (8.2)	2 (5.4)
Headache	12 (6.4)	7 (18.9)
Nystagmus	5 (6.8)	1 (2.7)
Hydrocephalus	4 (5.5)	1 (2.7)
Seizure	4 (5.5)	4 (10.8)
Hemiparesis	3 (4.1)	2 (5.4)
Acne	7 (9.6)	2 (5.4)
Reason to treat, n (%)§		
Blindness in 1 eye and low vision in the other eye	2 (2.7)	2 (5.4)
Clinical progression	21 (28.8)	7 (18.9)
Deterioration of visual acuity	19 (26.0)	11 (29.7)
Diencephalic syndrome of infancy	1 (1.4)	0
Neurological symptoms	31 (42.5)	19 (51.4)
Nystagmus	9 (12.3)	5 (13.5)
Pressure effect of tumor mass	17 (23.3)	10 (27.0)
Radiological progression	44 (60.3)	15 (40.5)
Vision abnormalities	22 (30.1)	19 (51.4)
Time since diagnosis, median (range), months	4.9 (0.9-199.9)	2.4 (0.7-62.2)
Histological grade at initial diagnosis, n (%)‖		
1	60 (82.2)	28 (75.7)
2	12 (16.4)	8 (21.6)
3	0	0
4	0	0
Missing	1 (1.4)¶	1 (2.7)¶
Histology at initial diagnosis, n (%)‖		
Astrocytoma	1 (1.4)	1 (2.7)
Desmoplastic astrocytoma (not otherwise specified)	0	1 (2.7)
Desmoplastic infantile astrocytoma	2 (2.7)	1 (2.7)
Diffuse astrocytoma	1 (1.4)	1 (2.7)
Diffuse glioma (not otherwise specified)	2 (2.7)	0
Ganglioglioma	21 (28.8)	9 (24.3)
Glioneuronal (not otherwise specified)	2 (2.7)	1 (2.7)

Infantile desmoplastic ganglioglioma	1 (1.4)	0
LGG (not otherwise specified)	14 (19.2)	6 (16.2)
Pilocytic astrocytoma	22 (30.1)	12 (32.4)
Pleomorphic xanthoastrocytoma	6 (8.2)	5 (10.8)
Missing	1 (1.4)	0
Primary site of cancer, n (%)		
Optic/hypothalamic	25 (34.2)	12 (32.4)
Brainstem	16 (21.9)	1 (2.7)
Hemispheric	16 (21.9)	8 (21.6)
Thalamus	5 (6.8)	6 (16.2)
Cerebellum	6 (8.2)	5 (13.5)
Other	4 (5.5)	5 (13.5)
Missing	1 (1.4)	0
BRAF* mutation status, n (%)*		
V600E	70 (95.9)	35 (94.6)
Nonmutant	0	1 (2.7)††
Other	3 (4.1)‡‡	0
Missing	0	1 (2.7)§§

LGG, low-grade glioma; pLGG, pediatric low-grade glioma.

* Karnofsky performance status and Lansky performance status apply to patients aged ≥16 years and <16 years, respectively.

† Patient received steroids for symptom control >4 weeks prior to study entry; patient met eligibility criteria.

‡ Conditions reported in ≥5 patients in both treatment arms combined are listed.

§ Patients may have had >1 reason to treat and may be counted in multiple categories.

‖ Histological data were investigator determined at initial diagnosis and may not necessarily reflect histology at study entry.

¶ Data were not reported by the institution.

** Local *BRAF* status is presented when available; 4 patients were enrolled based on central *BRAF* status.

†† One patient discontinued from the study upon confirmation of non-*BRAF* V600−mutant pLGG.

‡‡ Three patients had local *BRAF* status of "other" that were V600E centrally.

§§ One patient withdrew consent prior to treatment with no local result entered and prior to central result analysis.

Table S2. Representativeness of Patients

Category	Example
Disease under investigation	pLGG
Special considerations related to:	
Sex	Male sex is a risk factor for poor cognitive outcomes in patients with pLGG.[5]
Age	Younger age is an unfavorable prognostic factor in patients with pLGG.[5,6]
Race or ethnic group	Black race and Hispanic ethnicity are associated with decreased overall survival.[7,8]
Overall representativeness of this trial	The proportion of male patients was similar between the dabrafenib plus trametinib arm (39.7%) and the chemotherapy arm (40.5%). The median age of patients was higher in the dabrafenib plus trametinib arm vs the chemotherapy arm (10 vs 8 years, respectively). The proportions of patients based on race and ethnicity were generally consistent between treatment arms; however, the proportion of White patients was slightly higher, and the proportion of Black patients was slightly lower in the dabrafenib plus trametinib arm vs the chemotherapy arm.

pLGG, pediatric low-grade glioma.

Table S3. Disposition and Duration of Exposure

Category, n (%)	Dabrafenib + Trametinib (n=73)	Chemotherapy (n=37)
Treated	**73 (100)**	**33 (89.2)***
Treatment ongoing	**61 (83.6)**	**8 (21.6)**
Discontinued	**12 (16.4)**	**25 (67.6)**
Completed	0	9 (24.3)
Progressive disease	5 (6.8)	9 (24.3)
Adverse event	3 (4.1)	6 (16.2)
Physician decision	2 (2.7)	0
New therapy	1 (1.4)	0
Protocol deviation	0	1 (2.7)
Patient/guardian decision	1 (1.4)	0
Post-treatment follow-up for those who discontinued		
Crossed over to dabrafenib + trametinib	–	9 (24.3)
Did not enter	6 (8.2)	9 (24.3)
Entered†	6 (8.2)	16 (43.2)
Ongoing	5 (6.8)	13 (35.1)
Discontinued	1 (1.4)	3 (8.1)
Completed	0	1 (2.7)
Physician decision	0	1 (2.7)
Progressive disease	0	1 (2.7)
Patient/guardian decision	1 (1.4)	0
Survival follow-up		
Did not enter	1 (1.4)	11 (29.7)
Entered	6 (8.2)	1 (2.7)
Alive	4 (5.5)	0
Unknown	2 (2.7)	1 (2.7)
	Dabrafenib (n=73)	**Carboplatin (n=33)**
Duration of exposure, median (range), months‡	17.4 (0.6-34.4)	7.8 (2.8-16.1)
Duration of exposure categories		
<8 weeks	2 (2.7)	0
8 to <24 weeks	2 (2.7)	13 (39.4)
24 to <56 weeks	22 (30.1)	10 (30.3)
56 to <112 weeks	36 (49.3)	10 (30.3)
≥112 weeks	11 (15.1)	0

C+V, carboplatin plus vincristine.

* Four patients in the C+V arm discontinued prior to receiving treatment.

† Ongoing in randomized phase at data cutoff.

‡ Duration of exposure is number of days from the first date when a nonzero dose of any component of study treatment was administered to the last date when a nonzero dose of any component of study treatment was administered, up to and including the data cutoff. Exposures with trametinib and vincristine were similar to dabrafenib and carboplatin, respectively.

Table S4. Dose Adjustments and Discontinuations

n (%)	Dabrafenib (n=73)	Trametinib (n=73)	Carboplatin (n=33)	Vincristine (n=33)
Patients with dose reduction/interruption				
No dose reduction/ interruption	14 (19.2)	18 (24.7)	6 (18.2)	8 (24.2)
≥1 dose reduction/ interruption	59 (80.8)	55 (75.3)	27 (81.8)	25 (75.8)
1	14 (19.2)	12 (16.4)	5 (15.2)	5 (15.2)
2	5 (6.8)	14 (19.2)	1 (3.0)	4 (12.1)
>2	40 (54.8)	29 (39.7)	21 (63.6)	16 (48.5)
Patients with dose reduction	45 (61.6)	14 (19.2)	21 (63.6)	11 (33.3)
1	19 (26.0)	11 (15.1)	11 (33.3)	8 (24.2)
2	12 (16.4)	2 (2.7)	5 (15.2)	1 (3.0)
>2	14 (19.2)	1 (1.4)	5 (15.2)	2 (6.1)
Reason for dose reduction*				
Adverse event	35 (47.9)	9 (12.3)	21 (63.6)	7 (21.2)
Per protocol	11 (15.1)	4 (5.5)	0	1 (3.0)
Physician decision	4 (5.5)	3 (4.1)	2 (6.1)	3 (9.1)
Patient/guardian decision	4 (5.5)	0	0	0
Technical problems	1 (1.4)	0	0	0
Patients with dose interruption	56 (76.7)	53 (72.6)	23 (69.7)	22 (66.7)
1	21 (28.8)	16 (21.9)	4 (12.1)	4 (12.1)
2	13 (17.8)	10 (13.7)	7 (21.2)	7 (21.2)
>2	22 (30.1)	27 (37.0)	12 (36.4)	11 (33.3)
Reason for dose interruption*				
Adverse event	53 (72.6)	51 (69.9)	21 (63.6)	19 (57.6)
Per protocol	0	0	3 (9.1)	3 (9.1)
Dosing error	1 (1.4)	3 (4.1)	0	0
Physician decision	5 (6.8)	4 (5.5)	3 (9.1)	5 (15.2)
Patient/guardian decision	2 (2.7)	3 (4.1)	1 (3.0)	1 (3.0)
Technical problems	1 (1.4)	1 (1.4)	0	0
Patients with ≥1 dose re-escalation	41 (56.2)	8 (11.0)	12 (36.4)	9 (27.3)
Patients with permanent discontinuation†	13 (17.8)	13 (17.8)	26 (78.8)	25 (75.8)
Reason for permanent discontinuation				
Adverse event	3 (4.1)	3 (4.1)	6 (18.2)	7 (21.2)
Completed	0	0	10 (30.3)	8 (24.2)
Physician decision	2 (2.7)	2 (2.7)	0	0
Progressive disease	5 (6.8)	5 (6.8)	9 (27.3)	9 (27.3)

Protocol deviation	0	0	1 (3.0)	1 (3.0)
Patient/guardian decision	3 (4.1)	3 (4.1)	0	0

* Patients may be counted under multiple reasons for dose reduction/interruption.

† Permanent discontinuation refers to discontinuing drug component as opposed to discontinuing the study.

Table S5. Summary of Response (Investigator Assessment)

	Dabrafenib + Trametinib (n=73)	**Chemotherapy (n=37)**	**OR* (95% CI)**	**RR* (95% CI)**	***P* value†**
ORR (CR + PR), n (%) [95% CI] CR PR	**40 (54.8) [42.7-66.5]** 3 (4.1) 37 (50.7)	**5 (13.5) [4.5-28.8]** 0 5 (13.5)	**7.76 (2.7-22.2)**	**4.05 (1.8-9.4)**	**<0.001**
SD‡	28 (38.4)	18 (48.6)	–	–	–
PD	4 (5.5)	7 (18.9)	–	–	–
Unknown	1 (1.4)	7 (18.9)	–	–	–
CBR (CR + PR + SD), n (%)§, [95% CI]	**67 (91.8) [83.0-96.9]**	**22 (59.5) [42.1-75.2]**	**7.61 (2.6-22.0)**	**1.54 (1.2-2.0)**	**<0.001**
DOR Events, n (%) **Median (95% CI), months** 12-month rate (95% CI), % 24-month rate (95% CI), %	 1 (2.5) **NE (25.5-NE)** 100 100	 1 (20.0) **NE (5.3-NE)** 80 (20.4-96.9) NE (NE-NE)	–	–	–

CBR, clinical benefit rate; CR, complete response; dab, dabrafenib; DOR, duration of response; NE, not evaluable; OR, odds ratio; ORR, overall response rate; PD, progressive disease; PR, partial response; RR, risk ratio; tram, trametinib.

* Odds ratio (dabrafenib + trametinib vs chemotherapy) and 2-sided 95% CI are from a logistic regression with treatment as the only covariate. Odds and risk ratios >1 favor dab + tram.

† The *P* value is computed from χ^2 test (Mantel-Haenszel) at a 1-sided 2.5% level of significance.

‡ SD for 16 weeks or longer is recorded at 15 weeks or later (ie, ≥105 days) from treatment start date.

§ SD for 24 weeks or longer is recorded at 23 weeks or later (ie, ≥161 days) from treatment start date.

Table S6. Overall Response Rate by Subgroups (Independent Review per RANO Criteria)

Subgroup, n/N (%)*	Dabrafenib + Trametinib (n=73)		Chemotherapy (n=37)	
Histology at initial diagnosis	**ORR†**	**95% CI‡**	**ORR†**	**95% CI‡**
Astrocytoma	1/1 (100)	(2.5-100)	0/1 (0)	(0-97.5)
Desmoplastic astrocytoma, NOS	—	—	1/1 (100)	(2.5-100)
Desmoplastic infantile astrocytoma	0/2 (0)	(0-84.2)	0/1 (0)	(0-97.5)
Diffuse astrocytoma	1/1 (100)	(2.5-100)	1/1 (100)	(2.5-100)
Diffuse glioma, NOS	0/2 (0)	(0-84.2)	—	—
Ganglioglioma	8/21 (38.1)	(18.1-61.6)	0/9 (0)	(0-33.6)
Glioneuronal, NOS	0/2 (0)	(0-84.2)	0/1 (0)	(0-97.5)
Infantile desmoplastic ganglioglioma	1/1 (100)	(2.5-100)	—	—
LGG, NOS	12/14 (85.7)	(57.2-98.2)	1/6 (16.7)	(0.4-64.1)
Pilocytic astrocytoma	9/22 (40.9)	(20.7-63.6)	1/12 (8.3)	(0.2-38.5)
Pleomorphic xanthoastrocytoma	2/6 (33.3)	(4.3-77.7)	0/5 (0)	—
Missing	0/1 (0)	(0-97.5)	—	—
Central molecular profile				
No *CDKN2A/B* homozygous deletion	4/7 (57.1)	(18.4-90.1)	1/5 (20.0)	(0.5-71.6)
CDKN2A/B homozygous deletion	2/5 (40.0)	(5.3-85.3)	0/1 (0)	(0-97.5)
TP53 balanced	3/7 (42.9)	(9.9-81.6)	0/5 (0)	(0-52.2)
TP53 gain	0/1 (0)	(0-97.5)	—	—
TP53 deletion	3/4 (75.0)	(19.4-99.4)	1/1 (100)	(2.5-100)

CR, complete response; LGG, low-grade glioma; NOS, not otherwise specified; ORR, overall response rate; PR, partial response; RANO, Response Assessment in Neuro-Oncology.

* Percentages are taken out of the n in each subgroup.

† ORR includes patients with a best overall confirmed response of CR or PR per independent

review using RANO criteria.

‡ The exact binomial 2-sided 95% CI (Clopper-Pearson) is presented.

Table S7. Change in Visual Acuity in Patients With Suprasellar, Chiasmatic, or Hypothalamic Tumors in the Safety Analysis Set (logMAR Scale)*†

n (%)	**Dabrafenib + Trametinib (n=25)**	**Chemotherapy (n=11)**
Worst case post baseline, n	41	18
Improved	6 (14.6)	1 (5.6)
Stable	25 (61.0)	9 (50.0)
Worsened	10 (24.4)	8 (44.4)
Best case post baseline, n	41	18
Improved	14 (34.1)	2 (11.1)
Stable	26 (63.4)	14 (77.8)
Worsened	1 (2.4)	2 (11.1)

* Improved = 0.2 logMAR improvement; stable = neither 0.2 logMAR improvement nor worsening; worsening = 0.2 logMAR worsening.

† Percentages are taken from the n at each time point, which corresponds to the number of eyes (left and right), not the number of patients.

Table S8. Treatment-Related Adverse Events Occurring in ≥5% of Patients in Either Arm (Safety Analysis Set)*

Preferred Term, n (%)	Dabrafenib + Trametinib (n=73)		Chemotherapy (n=33)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any	**67 (91.8)**	**19 (26.0)**	**32 (97.0)**	**29 (87.9)**
Pyrexia	31 (42.5)	5 (6.8)	4 (12.1)	1 (3.0)
Dry skin	16 (21.9)	0	1 (3.0)	0
Fatigue	15 (20.5)	0	8 (24.2)	0
Headache	13 (17.8)	0	4 (12.1)	1 (3.0)
Vomiting	10 (13.7)	0	14 (42.4)	1 (3.0)
Nausea	10 (13.7)	0	14 (42.4)	0
Rash	10 (13.7)	0	2 (6.1)	1 (3.0)
Neutrophil count decreased	9 (12.3)	3 (4.1)	14 (42.4)	14 (42.4)
Anemia	8 (11.0)	0	19 (57.6)	7 (21.2)
Diarrhea	8 (11.0)	0	2 (6.1)	1 (3.0)
White blood cell count decreased	8 (11.0)	0	11 (33.3)	5 (15.2)
Maculopapular rash	8 (11.0)	1 (1.4)	0	0
Weight increased	7 (9.6)	4 (5.5)	0	0
Epistaxis	7 (9.6)	0	1 (3.0)	0
Dermatitis acneiform	7 (9.6)	0	0	0
Abdominal pain	6 (8.2)	0	3 (9.1)	0
Paronychia	6 (8.2)	0	0	0
Erythema	6 (8.2)	0	0	0
Panniculitis	6 (8.2)	0	0	0
Eczema	5 (6.8)	0	0	0
Erythema nodosum	5 (6.8)	0	0	0
Pruritis	5 (6.8)	0	2 (6.1)	0
Alanine aminotransferase increased	5 (6.8)	0	7 (21.2)	3 (9.1)
Aspartate aminotransferase increased	5 (6.8)	1 (1.4)	4 (12.1)	0
Chills	4 (5.5)	0	0	0
Constipation	4 (5.5)	0	11 (33.3)	0
Neutropenia	4 (5.5)	4 (5.5)	10 (30.3)	10 (30.3)
Stomatitis	4 (5.5)	0	5 (15.2)	0
Rash pustular	4 (5.5)	0	0	0
Upper abdominal pain	4 (5.5)	0	1 (3.0)	0
Extremity pain	3 (4.1)	0	3 (9.1)	0
Lymphocyte count decreased	3 (4.1)	0	4 (12.1)	2 (6.1)
Platelet count decreased	2 (2.7)	0	10 (30.3)	3 (9.1)

Weight decreased	2 (2.7)	0	3 (9.1)	0
Decreased appetite	2 (2.7)	0	7 (21.2)	0
Alopecia	2 (2.7)	0	8 (24.2)	0
Hypomagnesemia	1 (1.4)	0	2 (6.1)	1 (3.0)
Myalgia	1 (1.4)	0	3 (9.1)	0
Hyponatremia	1 (1.4)	1 (1.4)	2 (6.1)	0
Leukopenia	1 (1.4)	0	2 (6.1)	0
Gastroesophageal	1 (1.4)	0	2 (6.1)	0
Asthenia	1 (1.4)	0	3 (9.1)	0
Thrombocytopenia	0	0	4 (12.1)	3 (9.1)
Hypersensitivity	0	0	4 (12.1)	1 (3.0)
Infusion related	0	0	5 (15.2)	1 (3.0)
Blood bicarbonate decreased	0	0	2 (6.1)	0
Hypokalemia	0	0	2 (6.1)	0
Jaw pain	0	0	6 (18.2)	0
Facial pain	0	0	2 (6.1)	0
Neuralgia	0	0	2 (6.1)	0
Paresthesia	0	0	3 (9.1)	0
Peripheral motor neuropathy	0	0	5 (15.2)	1 (3.0)
Peripheral sensory neuropathy	0	0	6 (18.2)	1 (3.0)

* A patient with multiple severity grades for an adverse event was only counted under the maximum grade.

Table S9. Adverse Events Leading to Dose Adjustment and/or Interruption (Occurring in ≥2% of Patients in Either Arm) and Leading to Discontinuation of Treatment (Safety Analysis Set)*

Preferred Term, n (%)	Dabrafenib + Trametinib (n=73)		Chemotherapy (n=33)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Patients with ≥1 adverse event	**58 (79.5)**	**27 (37.0)**	**26 (78.8)**	**19 (57.6)**
Pyrexia	39 (53.4)	6 (8.2)	0	0
Neutropenia	5 (6.8)	5 (6.8)	7 (21.2)	7 (21.2)
Weight increased	5 (6.8)	2 (2.7)	0	0
Vomiting	4 (5.5)	0	1 (3.0)	0
Alanine aminotransferase increased	4 (5.5)	3 (4.1)	1 (3.0)	1 (3.0)
Chills	3 (4.1)	0	0	0
Headache	3 (4.1)	0	0	0
Seizure	2 (2.7)	1 (1.4)	0	0
Aspartate aminotransferase increased	2 (2.7)	2 (2.7)	0	0
Neutrophil count decreased	2 (2.7)	2 (2.7)	9 (27.3)	9 (27.3)
Diarrhea	2 (2.7)	0	0	0
Procedural complication	2 (2.7)	2 (2.7)	0	0
Paronychia	2 (2.7)	0	0	0
Tonsilitis	2 (2.7)	0	0	0
Rash	2 (2.7)	1 (1.4)	1 (3.0)	1 (3.0)
Maculopapular rash	2 (2.7)	1 (1.4)	0	0
Anemia	1 (1.4)	0	3 (9.1)	3 (9.1)
Device-related infection	1 (1.4)	1 (1.4)	1 (3.0)	1 (3.0)
Nasopharyngitis	1 (1.4)	0	1 (3.0)	0
Skin infection	0	0	1 (3.0)	0
Pain in jaw	0	0	1 (3.0)	0
Thrombocytopenia	0	0	3 (9.1)	1 (3.0)
Ascites	0	0	1 (3.0)	0
Constipation	0	0	2 (6.1)	0
Influenza-like illness	0	0	1 (3.0)	0
Hypersensitivity	0	0	3 (9.1)	0
Infusion-related reaction	0	0	4 (12.1)	1 (3.0)
Blood creatinine increased	0	0	1 (3.0)	0
Platelet count decreased	0	0	6 (18.2)	2 (6.1)
White blood cell count decreased	0	0	1 (3.0)	0
Paresthesia	0	0	2 (6.1)	0

Peripheral motor neuropathy	0	0	2 (6.1)	0
Peripheral sensory neuropathy	0	0	4 (12.1)	1 (3.0)
Cough	0	0	1 (3.0)	0
Flushing	0	0	1 (3.0)	1 (3.0)
Any adverse event leading to discontinuation of treatment	**3 (4.1)**	**2 (2.7)**	**6 (18.2)**	**3 (9.1)**
Chills	1 (1.4)	0	0	0
Fatigue	1 (1.4)	0	0	0
Pyrexia	1 (1.4)	1 (1.4)	0	0
Weight increased	1 (1.4)	1 (1.4)	0	0
Headache	1 (1.4)	0	1 (3.0)	1 (3.0)
Neutropenia	0	0	1 (3.0)	1 (3.0)
Eyelid ptosis	0	0	1 (3.0)	0
Hypersensitivity	0	0	1 (3.0)	0
Infusion-related reaction	0	0	2 (6.1)	0
Dizziness	0	0	1 (3.0)	1 (3.0)
Peripheral motor neuropathy	0	0	1 (3.0)	1 (3.0)
Urticaria	0	0	1 (3.0)	1 (3.0)

* A patient with multiple severity grades for an adverse event was only counted under the maximum grade.

Supplementary References

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