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Continuous versus intermittent BRAF and MEK inhibition in patients with BRAF mutated melanoma: a randomized phase 2 trial

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Author Contributions:

A.P.A. served as principal investigator for the study. A.R. served as the cooperative group leader for the study. A.P.A., A.R., J.M., and M.O. designed the study. A.P.A., A.R., and M.O. wrote the manuscript. R.S.L. participated in study design and also made significant contributions to manuscript revisions. M.O. and J.M. were primarily responsible for data analysis. A.I.D., J.M.M., T.-G.T., R.C., K.K., G.C.D., J.I.C., M.J.M, D.F.M., C.L., B.A.F., R.G., A.H.-M., L.D., and K.F.G. accrued patients, contributed to data collection, and participated in manuscript development.

Abstract

Preclinical modeling suggests that intermittent BRAF inhibitor therapy may delay acquired resistance when blocking oncogenic *BRAF*^{V600} in melanoma[1,2]. We conducted S1320, a randomized, open-label, phase 2 clinical trial (NCT02196181) evaluating whether intermittent dosing of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib improves progression-free survival in patients with metastatic and unresectable *BRAF*^{V600} melanoma. Patients were enrolled at 68 academic and community sites nationally. All patients received continuous dabrafenib and trametinib during an 8-week lead-in period, after which patients with non-progressing tumors were randomized to either continuous or intermittent dosing of both drugs on a 3-week-off, 5-week-on schedule. The trial has completed accrual and 206 patients with similar baseline characteristics were randomized 1:1 to the two study arms (105 to continuous dosing, 101 to intermittent dosing). Continuous dosing yielded a statistically significant improvement in post-randomization progression-free survival compared with intermittent dosing (median 9.0 months vs. 5.5 months, p = 0.064, pre-specified 2-sided α=0.2). Therefore, contrary to the initial hypothesis, intermittent dosing did not improve progression-free survival in patients. There were no differences in the secondary outcomes, overall survival and the overall incidence of treatment associated toxicity, between the two groups.

Combination treatments with BRAF and MEK inhibitors yield objective response rates of up to 70% in patients with advanced *BRAF*^{V600} melanoma[3–5]. Yet, acquired resistance, often driven by MAPK pathway reactivation[2], remains common. Preclinical modeling by Das Thakur and colleagues demonstrated that *BRAF*^{V600E} cells that had become resistant to the BRAF inhibitor vemurafenib *in vitro* grew poorly in the absence of the drug[1], and intermittent dosing of vemurafenib according to 4-weeks on, 2-weeks off schedule prolonged drug sensitivity and increased progression-free survival in a mouse model. The drug withdrawal effect is even more profound in *BRAF*^{V600} mutant cells with acquired resistance to BRAF and MEK inhibitor combinations[2]. Based on these findings, we prospectively tested whether intermittent therapy with BRAF and MEK inhibitors in combination improved progression-free survival compared to the standard daily continuous dosing of these agents.

The randomized phase II, cooperative group trial S1320 focuses on the effect of dosing schedule on acquired resistance, randomizing only patients benefiting from therapy after an 8-week lead-in period, during which all patients received continuous treatment. For those patients randomized to intermittent dosing, the off-treatment interval was extended to 3 weeks based on pharmacokinetic modeling taking into account the longer plasma half-life of the combination of dabrafenib and trametinib in patients (Extended Data Figure 1) compared to the shorter plasma half-life of vemurafenib in the mouse[6], and the treatment cycle was extended to a total of 8 weeks to allow clinical imaging response assessments at standard 8-week intervals. Detailed experimental methods are provide in the Methods section and in the Life Sciences Reporting Summary associated with this manuscript.

Between September 19, 2014 and April 16, 2019, 249 patients were registered to the first, lead-in dosing cycle of the study. Of these 249 patients, 242 were found eligible to enroll and received study therapy, and 206 non-progressing patients were randomized (105 to

continuous and 101 to intermittent dosing, CONSORT diagram, Figure 1). A single interim analysis was performed on a data lock with follow-up as of August 25, 2017 after 74 events (progressions and deaths) had occurred. Using a stratified Cox regression model, the hazard ratio (using continuous dosing as the reference) was 1.10 with a one-sided 95% confidence interval (0.75, infinity) and one-sided p-value = 0.33. The protocol called for early termination if the p-value was less than 0.05, so the protocol met the criteria to continue. At the final analysis, the randomized arms were well-balanced (Extended Data Figure 2). 30% of patients on each arm had received prior immune checkpoint inhibitor therapy, including ipilimumab alone (12.4 vs. 7.9%), anti-PD-1 antibodies alone (8.6 vs. 12.9%), sequential ipilimumab and PD-1 antibody therapy (2.9 vs. 3.0%), and concurrent ipilimumab and PD-1 antibody therapy (2.9 vs. 5.0%) in patients randomized to continuous versus intermittent dosing respectively (p = 0.62, Fishers exact test). Details of checkpoint inhibitor exposure were not available for 3 patients assigned to continuous dosing and for 1 patient assigned to intermittent dosing. Fifty-two percent of patients on the continuous therapy arm and 46% on the intermittent therapy arm had melanoma with visceral metastases or elevated lactate dehydrogenase. There was no significant difference in distribution of $BRAF^{V600E}$ and $BRAF^{V600K}$ mutations across the arms (p=0.23).

Progression-free survival (PFS) was significantly longer with continuous therapy versus intermittent therapy (HR=1.36 intermittent:continuous, 80% CI 1.10, 1.66, p=0.063, two-sided α=0.2, Figure 2A). Although S1320 was not powered to detect differences in overall survival, these data were collected as a secondary endpoint, and there was no significant difference in overall survival between the two arms (median = 29.2 months in both arms, HR=1.02, 80% CI 0.78–1.33, p=0.93, Figure 3A) at a median follow up of 2 years. Survival after progression was longer with intermittent therapy (HR=0.76, 80% CI 0.78–1.00, p=0.20, Extended Data Figure 3). Post-progression treatment in continuous versus intermittent dosing arms reported in 50% and 49% of patients and included anti-PD-1 antibodies in 37% versus 42% (p = 0.66), and ipilimumab in 32% versus 26% (p = 0.63). The effects of treatment on PFS and OS were similar across subgroups (Figure 2B, Figure 3B, Extended Data Figure 4). The initial treatment response patterns were similar between the continuous versus intermittent arms: 3 vs. 2% unconfirmed complete response, 73 vs. 71% unconfirmed partial response, 24 vs. 28% stable disease by RECIST v1.1 respectively (p=0.61). Per protocol design, imaging response assessments were scheduled during on-treatment intervals, when patients were taking the combined targeted therapy in both study arms. Despite this, out of window treatment assessments occurred in both arms, with 26 out-of-window assessments in the intermittent dosing arm and 17 in the continuous dosing arm. In the intermittent arm, 12 patients came off of protocol therapy due to progression identified through off-schedule assessments during treatment breaks, without protocol-recommended confirmatory scans during on-treatment intervals.

Treatment-related adverse events are described in Extended Data Figure 5. On the continuous therapy arm, 38 patients (36%) experienced grade 3 adverse events, and 7 (7%) experienced grade 4 events, while on the intermittent therapy arm, 31 patients (31%) experienced grade 3 adverse events, and 3 (3%) experienced grade 4 events (p=0.46 for grade 3, p=0.33 for grade 4). The most common grade 3–4 adverse event across both arms

was fatigue. There was a significant difference in the incidence of grade 3 and 4 pyrexia, (6 patients on continuous dosing vs 1 patient on intermittent dosing, p<0.001).

Optional pretreatment circulating tumor DNA data were available for a subset of patients on S1320 enrolled on or after 1/3/2017 for exploratory analyses. Detection of ctDNA prior to therapy was associated with worse PFS (median $BRAF^{V600}$ ctDNA positive = 5.8; 95% CI: 4.2–9.6 months, $BRAF^{V600}$ ctDNA negative = 21.4 mos; 95% CI 10.4-NA; measured from start of treatment on study, p=0.001). The sample size for the analysis the effect of ctDNA on PFS by randomized arm was limited, but there was some evidence that the favorable prognostic association of undetectable $BRAF^{V600}$ ctDNA was stronger among patients randomized to the continuous therapy arm (interaction p-value = 0.12, Figure 4).

Contrary to pre-clinical studies[1,2,7], this large, randomized phase II clinical trial finds that continuous dosing of dabrafenib and trametinib yields superior PFS compared to intermittent dosing. This was observed despite that fact that, like the murine model[1], the dosing schedule ensured an extended period during which patients were exposed to subtherapeutic drug levels. Although there are preclinical and clinical data suggesting that intermittent dosing could be superior[1,2,8,9], several other pre-clinical and smaller clinical studies of small molecule kinase inhibitors also failed to demonstrate an advantage of intermittent dosing[10–12]. Furthermore, a recent preclinical study modeling *BRAF* mutated melanoma failed to demonstrate an advantage of intermittent dosing, with a trend towards more rapid tumor growth in mice treated intermittently with BRAF and MEK inhibitor combinations[13]. In general, murine models may underrepresent the tumor heterogeneity and disparate mechanisms of acquired resistance seen in humans[2,14–18] and this heterogeneity also makes it difficult to predict which acquired resistance mechanisms will emerge in individual patients *a priori*. The rationale for intermittent therapy is to avoid adaptation by drug-persisting melanoma cells that allows them to survive inhibition of their driver oncogene. By repeatedly interrupting the therapy, the hypothesis is this adaptation process would be less effective and the melanoma cells would not be able to develop acquired resistance events such as *BRAF* amplification. Unfortunately, this approach did not lead to improved PFS in patients. It is possible that treatment discontinuations during off treatment intervals in the intermittent dosing arm may have influenced the study outcome, but this may also reflect the challengs of applying intermittent dosing to patient care, since it is difficult to prevent unscheduled assessements in clinical practice.

The mechanisms underlying the superiority of continuous dosing in S1320 could not be assessed in this clinical trial, and need to be considered in the context of related studies. The rapid regression of accessible tumors in the majority of patients who went onto be randomized to this trial precluded paired biopsy analysis in S1320. However, a recently published animal model shows no differences in the expression of markers associated with apoptosis or cell cycling in animals treated with intermittent versus continuous BRAF and MEK inhibitor combinations[13]. It is certain that overall drug exposure in the intermittent dosing arm of S1320 was lower, but drug exposure was also decreased with intermittent dosing in the murine model using vemurafenib[1]. It is also possible that the relatively long half-life of the MEK inhibitor, trametinib, may have precluded a rapid systemic decrement of drug levels, thereby diminishing the pharmacodynamic effect of drug withdrawal that

might otherwise select against resistant clones[2]. Although the half-life of vemurafenib, the BRAF inhibitor used by Das Thakur et al, is 2–3 days in patients, the half-life of vemurafenib is far shorter in the mouse[19]. It could also take longer than 8-weeks for a significant drug-addicted, resistant tumor clone to develop. Proliferating drug-resistant clones are derived temporally from slowly-dividing drug-tolerant 'persister' clones[20]. These drug-resistant tumor cells lose fitness in response to MAPK inhibitor withdrawal, whereas drug-tolerant persister tumor cells gain fitness. Thus, at a tumor-cell population level, it is possible that proliferative, drug-resistant tumor clones with features of MAPK-reactivation need to be enriched in a given patient across a majority of tumor sites for drug withdrawal or intermittent dosing to have a significant clinical impact on tumor control[8,9].

In summary, S1320 demonstrates that continuous dosing of dabrafenib and trametinib yields superior PFS compared to intermittent dosing in patients with $BRAF^{V600E}$ and $BRAF^{V600K}$ melanoma with similar toxicity in the two dosing arms despite decreased drug exposure in the intermittent arm. This represents a large-scale, real-world test of the intermittent dosing hypotheses with patients drawn from 68 academic and community medical practices over 5 years using a commonly prescribed BRAF and MEK inhibitor combination regimen. Based on these results, continuous dosing of dabrafenib and trametinib remains the optimal therapeutic approach in patients pending additional clinical data using different dosing schedule or agents.

METHODS

Study Design

This was an open-label randomized Phase 2 study. The trial was sponsored by the SWOG Cancer Research Network and enrolled patients from 68 academic and community sites in the United States. The initial protocol and all amendments were reviewed and approved by SWOG, the National Cancer Institute (NCI), the NCI Central Institutional Review Board (CIRB), and the participating institutions' regulatory committees. Each study subject provided a voluntary, written, informed consent document approved by the human subject protection committee of each participating institution. The protocol may be found in the Supplementary Materials.

Patients

Eligible patients had histologically or cytologically confirmed Stage IV or unresectable Stage III melanoma that was *BRAF* mutation positive (V600E or V600K). Patients were required to have measurable disease by RECIST v1.1. Patients with a history of brain metastases were eligible if the patients were asymptomatic with no residual neurological dysfunction. Patients could not have received prior BRAF or MEK inhibitor therapy; prior surgery, radiotherapy, immunotherapy, and chemotherapy were allowed. Patients were required to have Zubrod performance status of 0–2 and adequate hematologic, hepatic, cardiac, and renal function. Patients with hepatitis B and C were not eligible. Patients with HIV were eligible under specific conditions (see protocol in Supplementary Materials).

Randomization and masking

Patients were randomized 1:1, randomization stratification was by dynamic balancing with stratification factors: LDH (elevated > institutional upper limit of normal) versus normal, measured before lead-in dosing at initial study registration) and known prior exposure to immune checkpoint inhibitors (yes versus no). Randomization was completed by sites through the SWOG rando-node dynamic balancing algorithm implemented through the NCI's OPEN registration platform.

Procedures

Patients were registered to lead-in therapy and received 8 weeks of continuous therapy with dabrafenib 150 mg orally twice daily and trametinib 2 mg orally daily. Patients with unequivocal disease progression after the first 8 weeks were not eligible for randomization. All other patients were eligible to be randomized 1:1 between continuous and intermittent dosing arms. The continuous dosing arm continued the lead-in regimen. The intermittent dosing arm used the same doses during weeks 1 and 5–8 of each 8-week cycle (5 weeks on). No therapy was given during weeks 2–4 on the intermittent therapy arm (3 weeks off).The off-treatment interval was extended from the 2-week interval used by Das Thakur et al to 3 weeks to allow an extended period of subclinical exposure to trametinib (Extended Data Figure 1), which has a half-life of 4 days. The treatment cycle was extended from 6 weeks to a total of 8 weeks to allow imaging response assessments at standard 8-week intervals. Toxicities were assessed according to the Common Terminology Criteria for Adverse Events version 4.0 and doses could be adjusted for toxicity according to pre-specified protocol guidelines. Because the primary objective of the study was to compare continuous versus intermittent dosing, unscheduled treatment interruptions beyond what was required for patient safety as specified in the protocol were not permitted. Patients requiring gaps in the dosing of both drugs for greater than 14 consecutive days for any reason were required to be removed from protocol therapy (the drug holiday on the intermittent arm was not counted as a treatment delay). Scans were completed every 56 days (+/− 5 days) on both arms for the first two years from registration; and then every 84 days thereafter. The schedule was selected so that scans were completed 4 weeks into the 5-week treatment period on the intermittent arm. Tumor progression documented outside this window ("unscheduled assessment") was confirmed at the next "scheduled" assessment within the treatment window. There was no cross-over between arms after confirmed disease progression.

Outcomes

The primary objective of the study was to compare progression-free survival with continuous versus intermittent dabrafenib and trametinib combination therapy. Secondary objectives were comparison of treatment response, overall survival, survival after progression, toxicities, and rates of fever between the two arms. RECIST v1.1 criteria were used for tumor response assessment. Progression-free survival was measured from the date of randomization to the first date of tumor progression or death from any cause, with patients last known to be alive without progression censored at the date of last contact. Overall survival was measured from the date of randomization to the date of death from any cause, with patients last known to be alive censored at the date of last contact. Survival after

progression was measured from the date of progression to the date of death from any cause, with patients last known to be alive censored at the date of last contact.

Statistical analysis

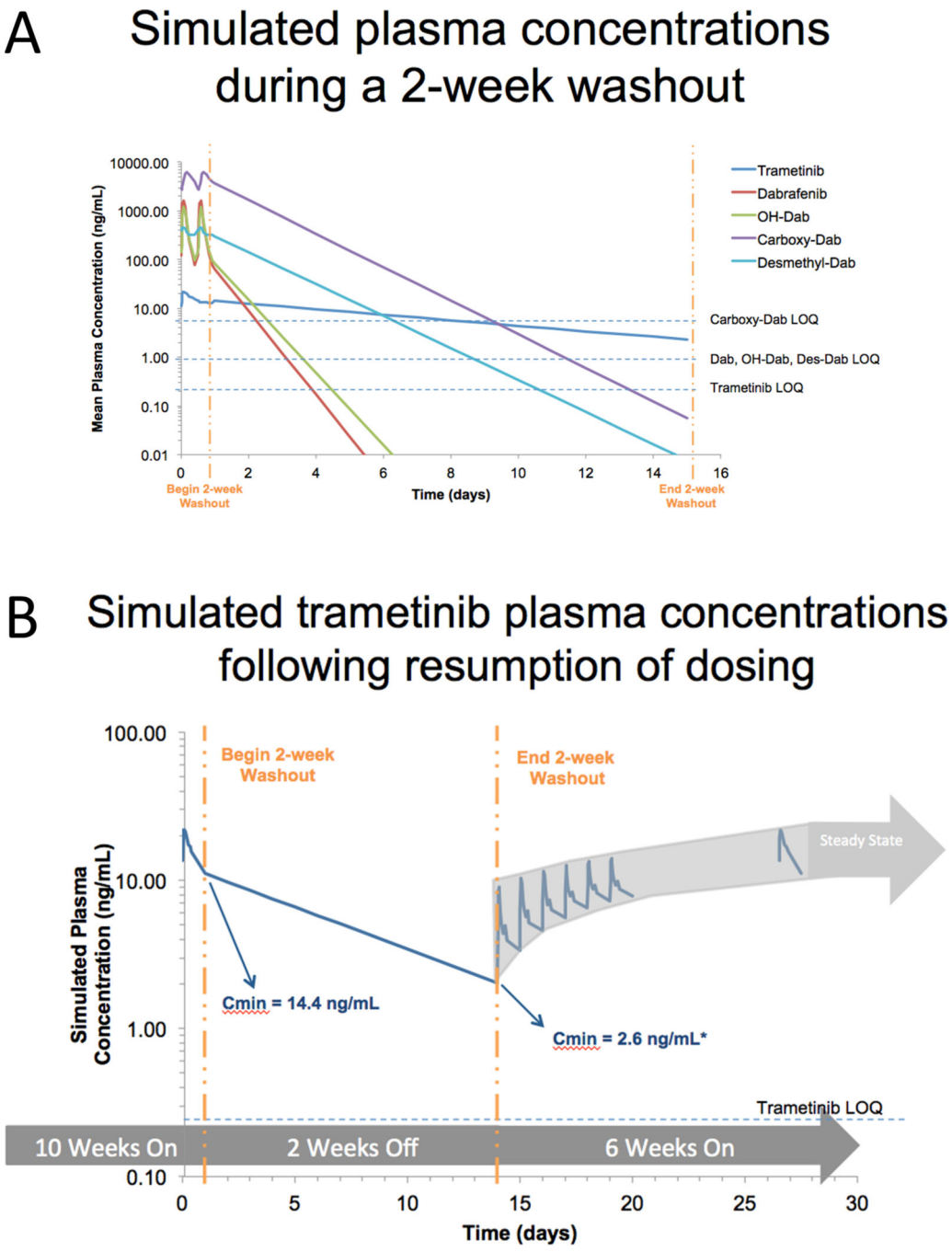
The full details of the design are provided in Section 11 of the protocol document. The design assumed exponential progression-free survival with a median of 9.4 months on the continuous therapy arm (null hypothesis). We powered the study to detect a change in progression-free survival to a median of 14.1 months (alternative hypothesis, corresponding to a hazard ratio of 0.67). 206 eligible randomized patients with 156 progression-free survival events (across both arms) would provide 90% power for a two-sided alpha of 20%. Cox regression models, stratified by randomized stratification factors, were pre-specified for a single interim futility analysis as well as for the final analysis. The interim futility analysis was scheduled at 78 events with a plan to stop early for futility if a one-sided test of the null hypothesis at the 5% level was rejected favoring continuous dosing.

All analyses were completed by co-authors Megan Othus and James Moon at the SWOG statistical center and are intent-to-treat among all randomized patients. The Kaplan-Meier method was used to estimate survival outcomes and log-rank tests and Cox regression models were used to evaluate associations with the outcomes. Fisher's exact test and the Wilcoxon rank sum test were used to assess differences in categorical and quantitative variables across the arms. Analyses were completed in R version 3.6.1 using data provided to SWOG to from individual sites through iMedidata Rave, then imported from Rave into the SWOG SQL database, and then exported from the SQL database using SAS version 9.4 for analysis in R. The study is registered on ClinicalTrials.gov, NCT02196181.

Data Availability Statement

All data (to replicate every analysis in the manuscript and any supplementary materials) will be posted to the NCI NCTN Data Archive per NCTN policy (https://nctn-data-archive.nci.nih.gov). Patient-level data, including a data dictionary, will be available within 6 months of publication through the United States NCTN/NCORP Data Sharing Archive (https://nctn-data-archive.nci.nih.gov) following the Data Sharing Archive policies. De-identified patient-level data that can the numbers, tables, and figures in the manuscript will be made available. The protocol (including statistical analysis plan in Section 11 of the protocol) and informed consent are Supplementary Materials.

Extended Data



Extended Data Fig. 1. Pharmacokinetic modeling.

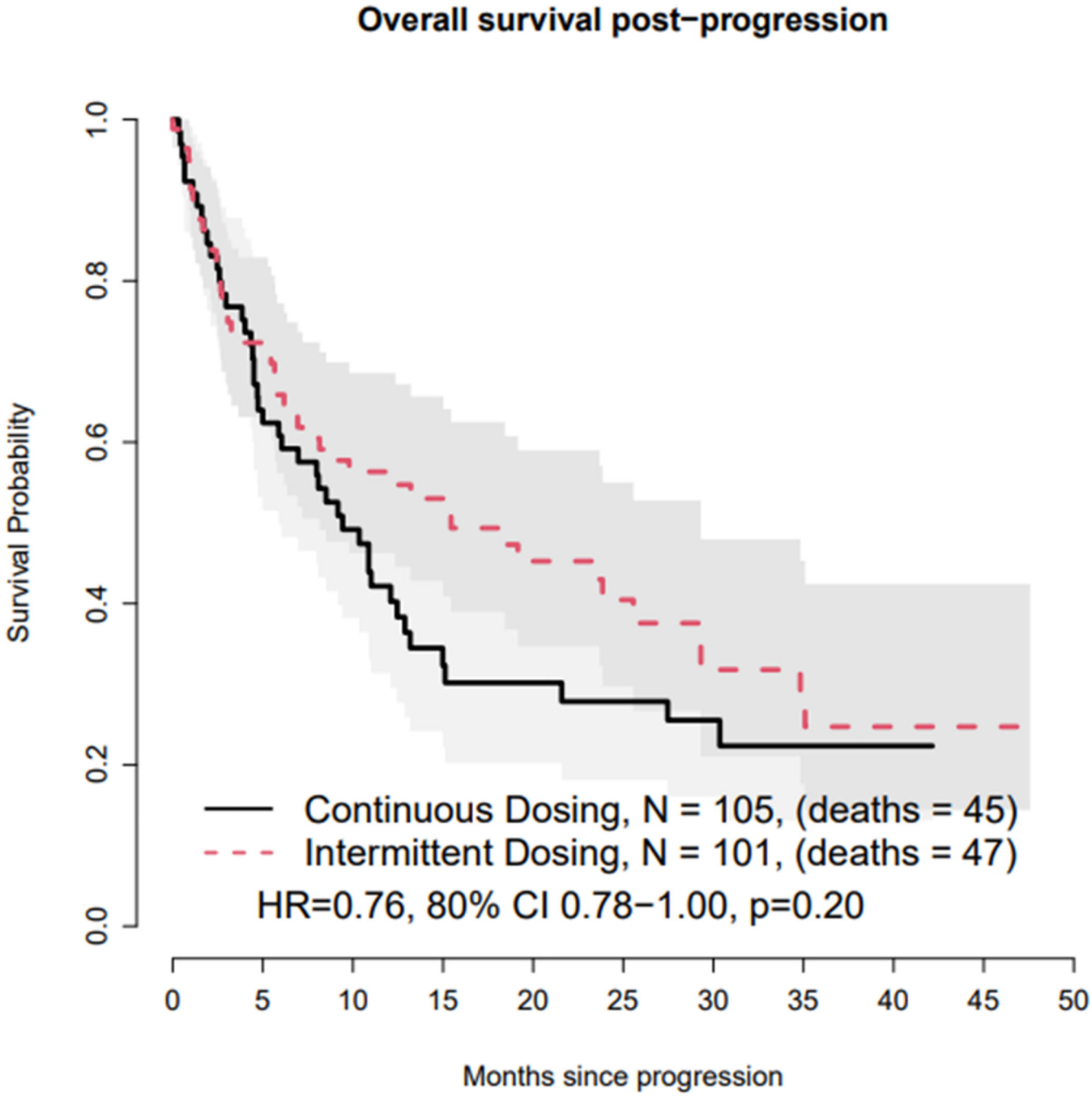
a. Model of plasma concentrations of trametinib, dabrafenib, and dabrafenib metabolites during a 2-week washout period (preceded by steady-state dosing) and after resumption of treatment. b. Trametinib levels are predicted to remain higher than the level of quantification, but they are predicted to fall below the target effective concentration. A 3-week washout was selected for S1320 to ensure an adequate time period with subtherapeutic

exposure to trametinib. Trametinib levels are predicted to reach steady-state within 4 weeks of resuming the medication.

Factor	Continuous Dosing (N = 105)	Intermittent Dosing (N = 101)	P-value
Age at randomization (years)	58 (50, 67)	62 (52, 70)	0.13
Age at randomization (years)			
Younger than 45	21 (20)	18 (18)	0.72
45 and older	84 (80)	83 (82)	
Gender			
Female	43 (41)	31 (31)	0.15
Male	62 (59)	70 (69)	
Race			
White	103 (98)	98 (97)	0.61
Asian and white	0 (0)	1 (1)	
Native American	1 (1)	0 (0)	
Unknown race	1 (1)	2 (2)	
Ethnicity			
Hispanic	2 (2)	4 (4)	0.44
Not hispanic	103 (98)	97 (96)	
PS			
0	59 (57)	58 (57)	0.96
1	43 (42)	41 (41)	
2	1 (1)	2 (2)	
LDH at randomization			
Elevated LDH	39 (37)	38 (38)	1
Normal LDH	66 (63)	63 (62)	
Prior checkpoint inhibitor			
No prior exposure	74 (70)	71 (70)	1
Prior checkpoint therapy	31 (30)	30 (30)	
Primary			
Cutaneous primary	88 (85)	76 (76)	0.11
Unknown primary	15 (15)	24 (24)	
Stage			
M0	13 (12)	12 (12)	0.51
M1A	19 (18)	17 (17)	
M1B	18 (17)	26 (26)	
M1C	55 (52)	46 (46)	
V600			
V600-E	82 (79)	69 (68)	0.22
V600-K	13 (12)	21 (21)	
E/K not distinguished	9 (9)	11 (11)	
Response			
CR	12 (12)	10 (10)	0.13
Unconfirmed CR	2 (2)	1 (1)	
PR	62 (62)	52 (52)	
Unconfirmed PR	13 (13)	15 (15)	
Stable	7 (7)	20 (20)	
Increasing disease	1 (1)	1 (1)	
Inadequate assessment	3 (3)	1 (1)	

Extended Data Fig. 2. Patient characteristics.

Patient characteristics among randomized patients. Median (interquartile range) and N (%) reported. Two-sided p-values from Wilcoxon (quantitative covariates) and Fisher exact (categorical covariates) reported.



Extended Data Fig. 3. Survival after disease progression.

Survival after disease progression in patients randomized to the continuous and intermittent dosing arms. Hazard ratio (HR), 80% confidence interval (shaded regions), and two-sided Wald-test p-values (p) from Cox regression model stratified by randomization stratification factors reported.

Covariate	HR	80% CI	P-value
Intermittent Dosing (ref = Continuous Dosing)	1.78	(1.24, 2.54)	0.039
Age at randomization (years)	0.99	(0.98, 1)	0.16
Male (ref = Female)	1.03	(0.74, 1.43)	0.92
PS 1 (ref = PS 0)	1.29	(1.03, 1.61)	0.14
PS 2 (ref = PS 0)	3.32	(1.27, 8.71)	0.11
Normal LDH (ref = Elevated LDH)	0.61	(0.48, 0.78)	0.0088
Prior checkpoint therapy (ref = No prior exposure)	0.6	(0.47, 0.77)	0.0095
Unknown primary (ref = Cutaneous primary)	0.72	(0.54, 0.96)	0.14
M1A (ref = M0)	1.23	(0.78, 1.92)	0.56
M1B (ref = M0)	1.58	(1.03, 2.43)	0.17
M1C (ref = M0)	1.86	(1.25, 2.78)	0.046
Arm*Gender interaction (ref = continuous dosing, male)	0.82	(0.52, 1.3)	0.59

Extended Data Fig. 4. Baseline characteristics and progression-free survival.
Multivariable Cox regression model of the association of baseline characteristics with progression-free survival; two-sided Wald p-values reported.

Number of Patients with a Given Type and Grade of Adverse Event
Adverse events Unlikely or Not Related to Treatment Excluded
Adverse Events with No Entries for Grade 3 to 5 Have Been Suppressed
Data as of October 23, 2019

		Continuous Dosing (n=104) Grade					Intermittent Dosing (n=101) Grade				
DISORDER CATEGORY	ADVERSE EVENTS	1	2	3	4	5	1	2	3	4	5
Blood and lymphatic	Anemia	20	6	2	1	-	21	2	2	-	-
Cardiac	LV systolic dysfunction	-	-	1	-	-	-	-	1	-	-
Endocrine	Hypothyroidism	-	-	1	-	-	-	1	-	-	-
Eye	Retinal detachment	-	-	-	-	-	-	-	2	-	
	NOS	2	-	-	-	-	2	-	1	-	-
Gastrointestinal	Diarrhea	14	4	2	-	-	13	3	1	-	-
	Gastric hemorrhage	-	-	1	-	-	-	-	-	-	-
	Oral mucositis	3	-	1	-	-	3	1	-	-	-
	Nausea	24	7	-	-	-	28	6	1	-	-
	Pancreatitis	-	-	1	-	-	-	1	-	-	-
General	Chills	20	10	1	-	-	20	12	1	-	-
	Fatigue	31	19	8	-	-	33	17	3	-	-
	Fever	18	19	6	-	-	17	14	-	1	-
	Flu like symptoms	5	4	2	-	-	3	1	-	-	-
	Localized edema	-	1	1	-	-	3	-	-	-	-
Infections	Lung infection	-	-	1	-	-	-	-	-	-	-
	Sepsis	-	-	-	2	-	-	-	-	-	-
	Urinary tract infection	-	-	-	-	-	-	-	1	-	-
	NOS	1	-	-	-	-	-	1	1	-	-
Investigations	AST increased	19	1	1	1	-	11	1	1	-	-
	ALT increased	21	1	4	1	-	19	1	2	-	-
	Alkaline phosphatase increased	19	6	1	-	-	13	3	3	-	-
	Blood bilirubin increased	-	-	1	-	-	2	1	-	-	-
	Creatinine increased	5	1		1	-	5	2	-	-	-
	ECG QTc int prolonged	1	1	1	-	-	1	1	1	-	-
	Ejection fraction decreased	-	9	4	-	-	-	3	4	-	-
	Lipase increased	8	2	2	2	-	5	3	2	1	-
	Lymphocyte count decreased	3	5	4	-	-	6	8	1	-	-
	Neutrophil count decreased	6	6	3	-	-	6	8	-	-	-
	Platelet count decreased	12	-	1	-	-	7	4	-	-	-
	Serum amylase increased	4	1	-	1	-	1	3	2	-	-
	White blood cell decreased	9	8	3	-	-	16	6	1	-	-
	NOS	6	-	-	-	-	8	-	1	-	-
Metabolism and nutrition	Anorexia	10	7	-	-	-	5	7	1	-	-
	Dehydration	4	3	1	-	-	1	1	-	-	-
	Glucose intolerance	1	-	1	-	-	-	-	-	-	-
	Hypercalcemia	1	-	-	-	-	2	-	1	-	-
	Hyperglycemia	5	1	3	-	-	4	4	2	-	-
	Hypoalbuminemia	9	7	1	-	-	10	3	-	-	-
	Hyponatremia	16	-	4	-	-	11	-	2	-	-
	Hypophosphatemia	2	1	-	-	-	-	2	1	-	-
Musculosk./connective tissue	Arthralgia	7	4	2	-	-	8	4	1	-	-
	Back pain	2	1	1	-	-	-	-	-	-	-
	Generalized muscle weakness	2	1	2	-	-	3	1	2	-	-
	Myalgia	8	2	-	-	-	5	5	1	-	-
	Pain in extremity	4	-	1	-	-	1	-	-	-	-
Neoplasms	Second malignancies	-	-	-	-	-	-	-	2	-	-
Nervous system	Syncope	-	-	1	-	-	-	-	-	-	-
Psychiatric	Confusion	-	1	-	-	-	-	1	1	-	-
Renal and urinary	Acute kidney injury	-	-	-	-	-	-	-	-	1	-
	Urinary tract obstruction	-	-	1	-	-	-	-	-	-	-
Intrathoracic	Dyspnea	4	1	-	1	-	2	1	-	-	-
	NOS	-	-	1	-	-	-	1	-	-	-
Skin and subcutaneous tissue	Dry skin	3	1	1	-	-	6		-	-	-
	Hand-foot syndrome	-	-	1	-	-	4	-	-	-	-
	Rash acneiform	12	7	2	-	-	10	2	-	-	-
	Rash maculo-papular	17	4	2	-	-	12	2	1	-	-
	NOS	8	3	1	-	-	9	3	-	-	-
Vascular disorders	Hypertension	1	11	7	-	-	1	8	3	-	-
	Hypotension	1	2	2	-	-	1	3	1	-	-
	Thromboembolic event	-	2	2	1	-	-	-	-	-	-
MAX. GRADE ANY ADVERSE EVENT		**10**	**41**	**38**	**7**	**-**	**13**	**49**	**31**	**3**	**-**

Extended Data Fig. 5. Adverse events.

All adverse events assessed as possibly, probably, and definitely related to study treatment. On the continuous therapy arm, 38 patients (36%) experienced grade 3 adverse events, and 7 (7%) experienced grade 4 events, while on the intermittent therapy arm, 31 patients (31%) experienced grade 3 adverse events, and 3 (3%) experienced grade 4 events (p=0.46 for grade 3, p=0.33 for grade 4). The most common grade 3–4 adverse event across both arms was fatigue. There was a significant difference in the incidence of grade 3 and 4 pyrexia, (6 patients on continuous dosing vs 1 patient on intermittent dosing, p<0.001).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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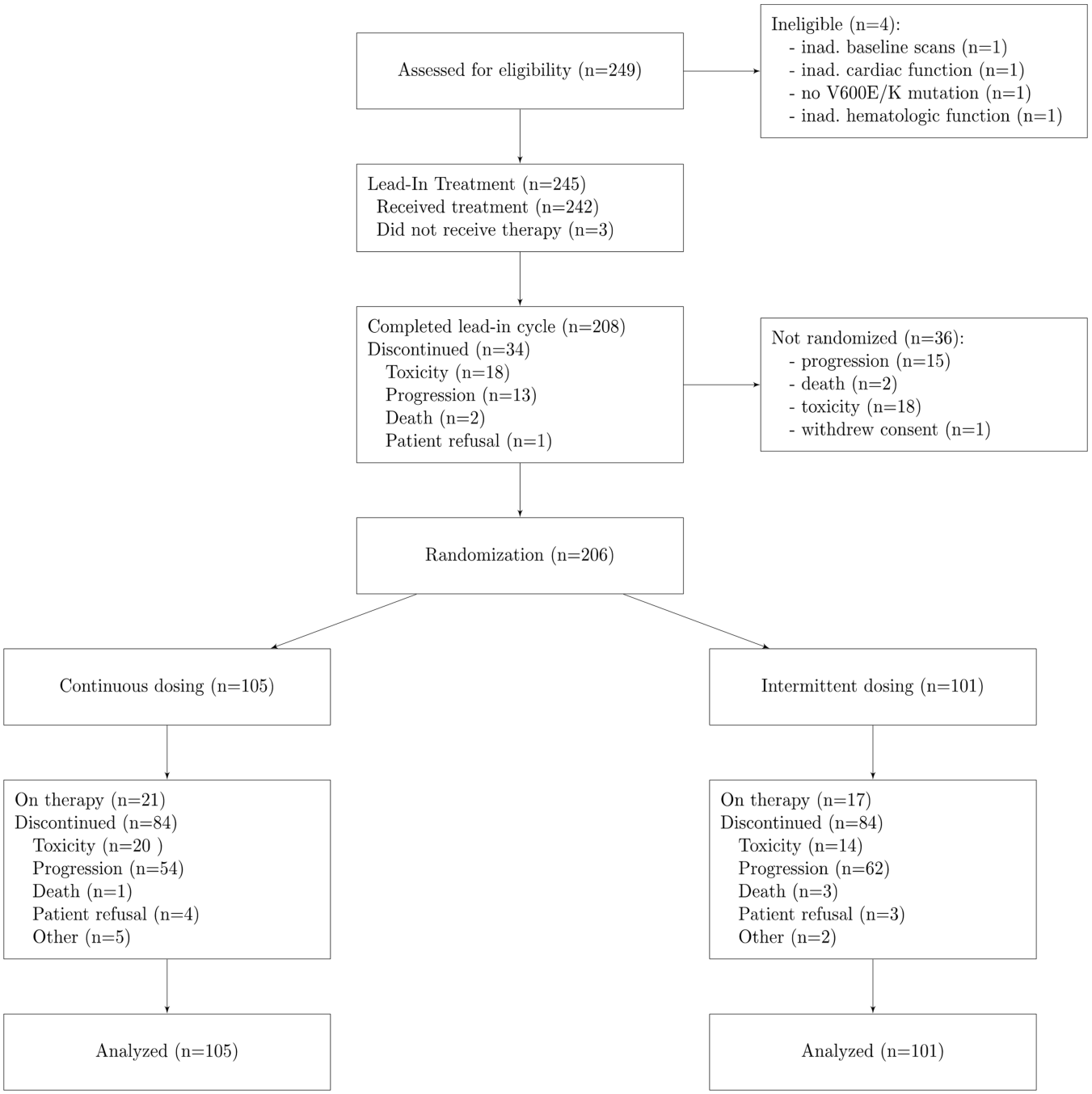
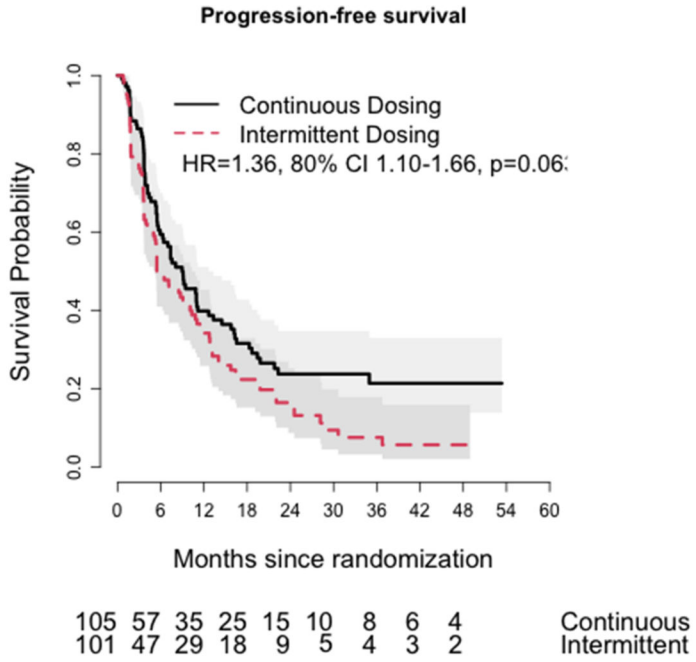


Figure 1.
CONSORT diagram.

A



B

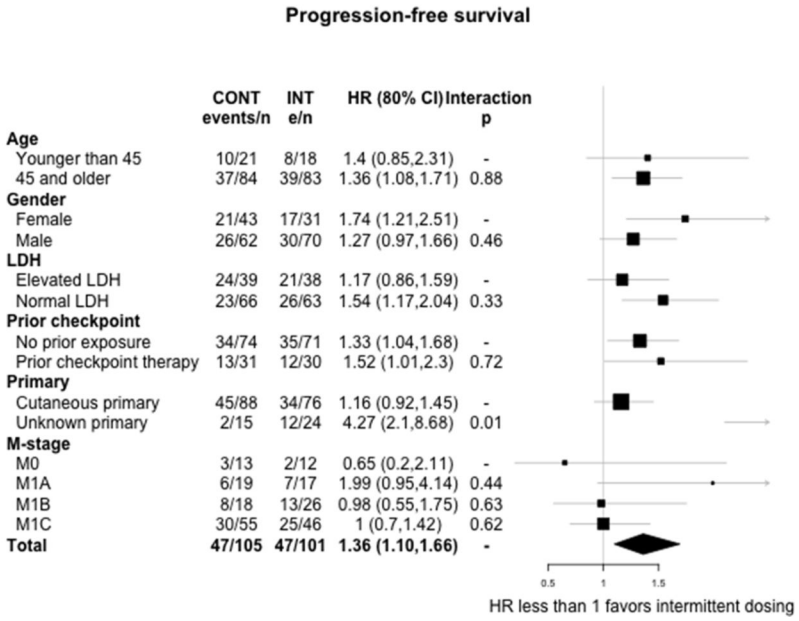
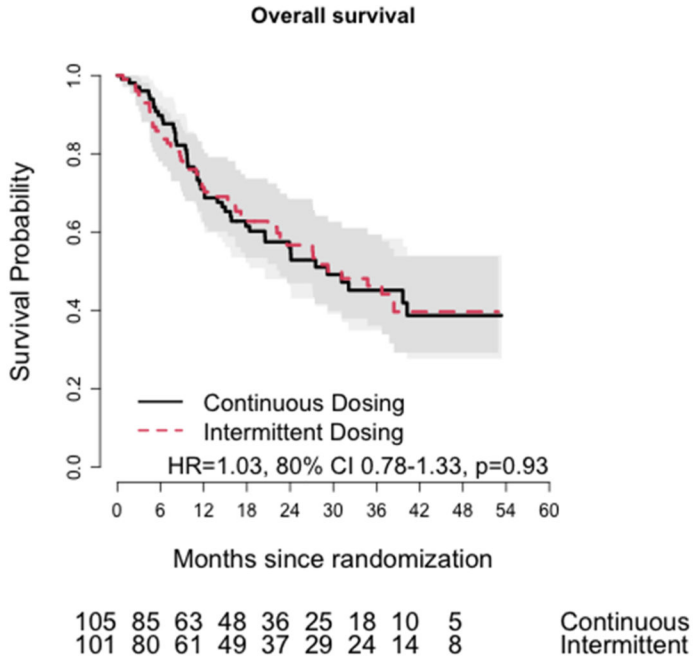


Figure 2:

A. Progression-free survival. The median PFS after randomization (8 weeks after the start of treatment) was 9.0 months in the continuous dosing arm and 5.5 months in the intermittent dosing arm.. Hazard ratio (HR), 80% confidence interval (shaded regions), and two-sided Wald-test p-values (p) from Cox regression model stratified by randomization stratification factors reported. B. Progression-free survival by subgroup; hazard ratio (HR), 80% confidence interval (CI), and two-sided Wald-test p-values (p) from Cox regression model; no adjustment was made for multiple comparisons.

A



B

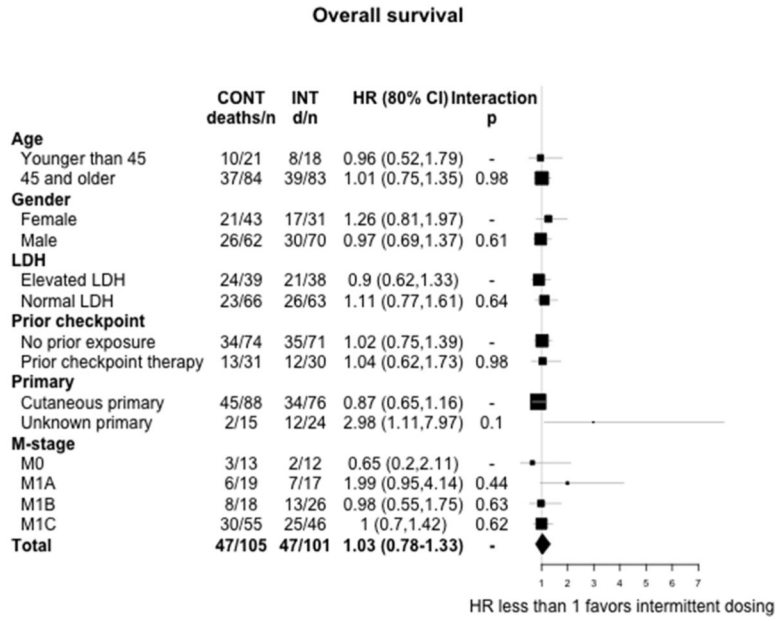


Figure 3.

A. Overall survival. The median OS after randomization (8 weeks after the start of treatment) was 29.2 months in the continuous dosing arm and 29.2 months in the intermittent dosing arm. Hazard ratio (HR), 80% confidence interval (shaded regions), and two-sided Wald-test p-values (p) from Cox regression model stratified by randomization stratification factors reported. B. Overall survival by subgroup; hazard ratio (HR), 80% confidence interval (CI), and two-sided Wald-test p-values (p) from Cox regression model; no adjustment was made for multiple comparisons.

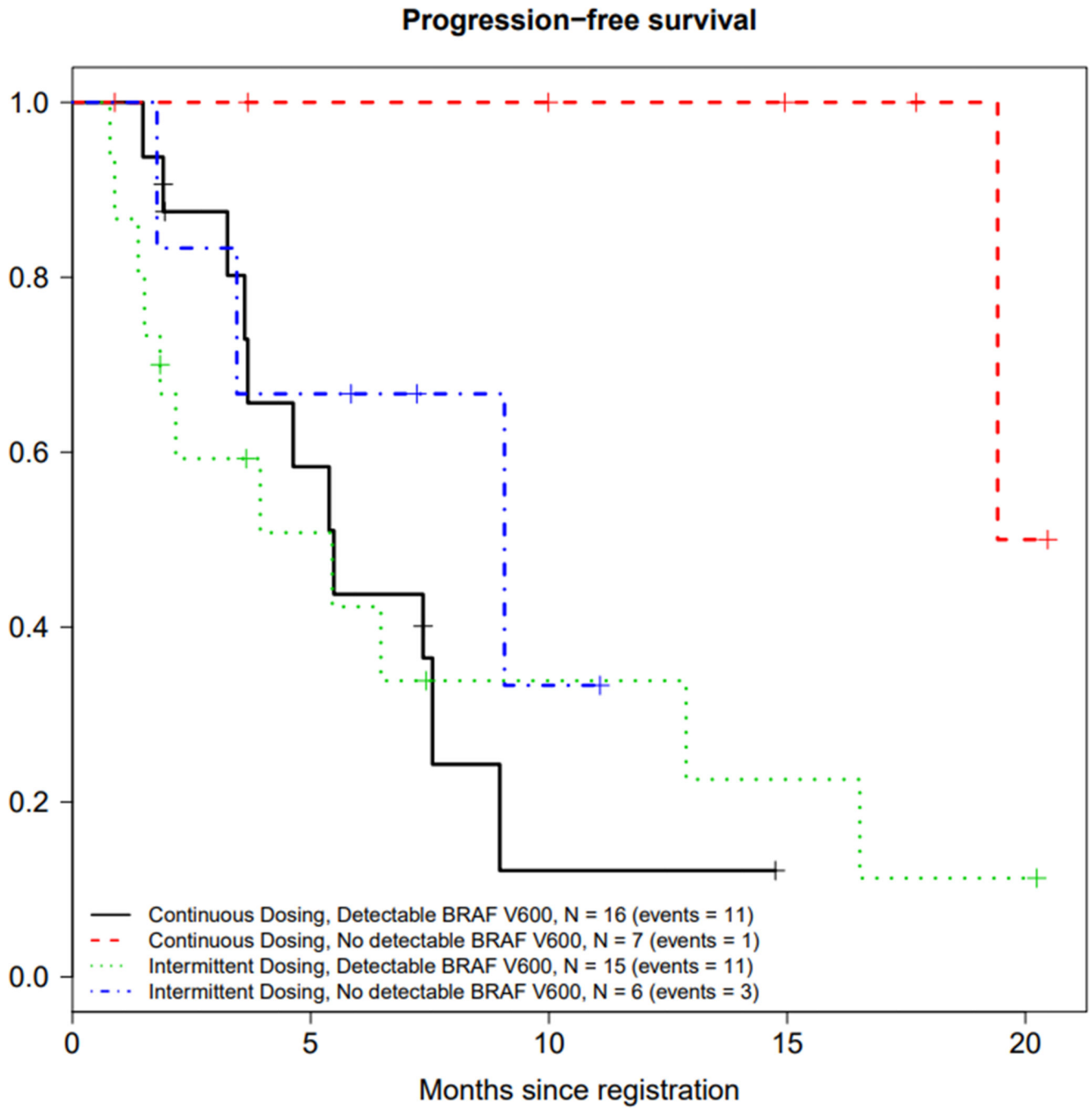


Figure 4.

Progression-free survival in patients with detectable and undetectable circulating $BRAF^{V600}$ tumor DNA (ctDNA) at baseline in patients assigned to continuous intermittent dosing. Detection of ctDNA prior to therapy was associated with worse PFS (median $BRAF^{V600}$ ctDNA positive = 5.8; 95% CI: 4.2–9.6 months, $BRAF^{V600}$ ctDNA negative = 21.4 mos; 95% CI 10.4-NA; measured from start of treatment on study, p=0.001), two-sided p-value from Cox regression model Wald-test).