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Monitoring of plasma concentrations of dabrafenib and trametinib in advanced *BRAFV600^{mut}* melanoma patients

M. Raynal^{1,2}, J.-C. Alvarez³, P. Saiag^{1,2}, A. Beauchet⁴, C. Funck-Brentano⁵, E. Funck-Brentano^{1,2} *

1 – Department of General and Oncologic Dermatology, Ambroise-Paré hospital, AP-HP, 9 avenue Charles de Gaulle, 92100 Boulogne-Billancourt, France

2 – Research Unit EA4340 ‘Biomarkers and clinical trials in oncology and onco-hematology’, Versailles-Saint-Quentin-en-Yvelines University, Paris - Saclay University, 9 avenue Charles de Gaulle, 92100 Boulogne-Billancourt, France

3 –Department of Pharmacology and Toxicology, Versailles Saint-Quentin-en-Yvelines University, Paris –Saclay University, Inserm U-1173, Raymond Poincaré hospital, AP-HP, 104 boulevard Raymond Poincaré, 92380 Garches, France

4 – Department of Bioinformatics, Ambroise Paré Hospital, AP-HP, 9 avenue Charles de Gaulle, 92100 Boulogne-Billancourt, France

5 – Sorbonne Université, INSERM CIC Paris-Est (CIC-1901), AP-HP. Sorbonne Université, ICAN, Pitié-Salpêtrière Hospital, Department of Pharmacology, 47-83 boulevard de l'Hôpital, 75013 Paris, France

*** Corresponding author**

E-mail address: elisa.funck-brentano@aphp.fr (Elisa Funck-Brentano)

Department of Dermatology, Ambroise Paré Hospital (AP-HP), 9 Avenue Charles De Gaulle, 92100 Boulogne-Billancourt, France

List of abbreviations:

AE: adverse events

AUC: area under the curve

CTCAE: Common Terminology Criteria for Adverse Events

CT-scans: computerized tomography scans

D: dabrafenib

PFS: progression-free survival

OS: overall survival

PCV: plasma concentrations of vemurafenib

PCD: plasma concentrations of dabrafenib

PCT: plasma concentrations of trametinib

ROC: Receiver operating characteristic

T: trametinib

Abstract

Background: Dabrafenib (D) and trametinib (T) improved survival in patients with BRAFV600^{mut} melanoma. High plasma concentration of D (PCD) is weakly associated with adverse events (AE). We investigated the relationship between PCD/T and tumour control or AE.

Methods: We analysed PCD/T in patients treated with D+T for metastatic melanoma. We collected data of tumour response (RECIST 1.1) and AE (CTCAE 4.0) blinded to PCD/T results.

Results: We analysed 71 D and 58 T assays from 34 patients. High inter-individual variability of PCD (median: 65.0 ng/mL; interquartile range (IQR) [4-945]) and of PCT (median: 8.6 ng/mL; IQR [5-39]) was observed. We found a weak relationship between PCD and progression-free survival, taking follow-up time into account (hazard ratio 0.991; 95%CI, 0.981 to 1.000; $P=0.06$). However, no difference was observed between mean PCD/T of progressing patients ($N=21$; 125 ± 183 ng/mL and 9.3 ± 3.6 ng/mL, respectively) and responders (complete, partial or stable response) ($N=13$; 159 ± 225 ng/mL, $P=0.58$ and 10.6 ± 24.4 ng/mL, $P=0.29$, respectively). No significant relationship was found between PCD/T and most common AEs (fever, lymphopenia, CPK increase, and hepatic cytolysis), body mass index, or age. Mean CPT ($N=16$) was significantly higher for female subjects ($N=18$; 11.5 ± 4.8 ng/mL) than for male subjects (8.8 ng/mL ± 2.9 , $P=0.01$), but no difference was observed between sex and CPD ($P=0.32$).

Conclusion: Our study showed a weak relationship between PCD and progression-free survival, but no relationship between PCD/T and AE was found. Monitoring PCD and PCT alone is unlikely to be useful in assessing response to treatment.

Keywords: melanoma, dabrafenib, trametinib, drug monitoring, molecular targeted therapies

1. Introduction

Targeted therapies and immune checkpoint inhibitors have improved survival of patients with unresectable or metastatic melanoma. Three combinations of BRAF and MEK inhibitors (dabrafenib and trametinib, vemurafenib and cobimetinib, and encorafenib and binimetinib) have demonstrated significant progression-free survival and overall survival benefit compared to BRAF inhibitor monotherapy in patients with *BRAF*V600 mutant advanced unresectable melanoma [1–4]. Unlike other targeted therapies such as EGFR inhibitors, the occurrence and severity of adverse events (AE) in patients with melanoma treated with BRAF plus MEK inhibitors is not correlated to tumour control. Predictor biomarkers of tumour response to these combined treatments are still lacking. In a pooled analysis of dabrafenib plus trametinib combination therapy trials, baseline LDH and number of affected organ sites have been shown to be associated with shorter progression-free survival (PFS) and overall survival (OS) in patients with metastases treated with this combination therapy [2-5]. Brain metastases have also been shown to be associated with a poor outcome in patients treated with dabrafenib [6,7]. Several studies have identified a relationship between plasma concentrations of vemurafenib (PCV) and tumour response to treatment, but also with some AE. We showed that at the time of evaluation of tumour response, progression was significantly associated with two parameters: lower mean steady-state PCV and presence of brain metastasis before vemurafenib treatment [8]. This study, done in a limited number of patients, did not show that higher PCV were significantly associated with a greater risk of experiencing several AE. Few studies have been conducted with dabrafenib. Rousset *et al.* showed a relationship between plasma concentrations of dabrafenib (PCD) and the occurrence of AE, with a threshold PCD of 48 ng/mL [9]. They also found that patients older than 60 years had higher PCD. This result was confirmed in another study in patients older than 70 years [10].

Balakitouchenane *et al.*, showed that greater age and female sex were associated with reduced clearance of dabrafenib and its metabolite hydroxy-dabrafenib [11]. Using pharmacokinetic-pharmacodynamic modeling in a population approach, they showed a relationship between the area under the curve (AUC) of dabrafenib and drug limiting toxicity. However, assessing AUC is impractical in the clinical setting and to our knowledge, no study has investigated the relationship between single PCD or plasma concentration of trametinib (PCT) determination and tumour response. Our aim was to investigate a potential relationship between plasma PCD/T at steady state and antitumor response or occurrence of AE.

2. Patients and Methods

Data were collected from a prospective database in our referral skin cancer centre between 04.10.2012 and 31.12.2017, in unresectable stage IIIC or IV mutant BRAFV600 melanoma patients treated with dabrafenib plus trametinib combination (D+T). Initial dabrafenib and trametinib doses were 300 mg/day and 2 mg/day, respectively, for all patients.

Patients were followed and monitored in our department according to our routine procedure, which required examination by a dermato-oncologist 1 and 2 months after treatment initiation, then every two months until progression. Additional visits could be scheduled in case of AE. During these visits, a blood sample was taken for standard laboratory monitoring (blood cell count, renal and liver function tests). Treatment efficacy was assessed every 2 months, by thoraco-abdomino-pelvic computerized tomography scans (CT-scans), brain CT-scans or magnetic resonance imaging, performed by experienced radiologists. All images were collectively re-analysed during weekly pluridisciplinary meetings that included oncologists, surgeons, dermatologists and radiologists. Tumour response was classified according to response evaluation criteria in solid tumours version 1.1 as complete response, partial response, stability or disease progression, in comparison with imaging done just before

starting dabrafenib plus trametinib therapy [12]. Treatment could be continued if a patient had a progression of one or few lesions that could be treated locally by surgery or radiotherapy (targeted therapy was stopped solely during the period of radiotherapy to decrease any risk of toxicity). All tumour evaluations were performed without knowledge of PCD/T.

AE were also recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, without knowledge of PCD/T. A receiver operating characteristic (ROC) curve was generated to determine the area under the curve (AUC) and the sensitivity and specificity for each value of PCD. The calculation of a PCD threshold predictive of AE used the highest Youden index value with the best sensitivity and specificity. We prospectively took a 10 mL blood sample in lithium heparin tubes during patient visits for regular follow-up and additional visits in case of AE. Blood samples were centrifuged and the plasma frozen and stored at -20°C pending assay. The following information was prospectively collected at the time of collection: dabrafenib and trametinib doses, day and time of last dose, day and time of blood collection, weight, treatment adherence and drug co-prescriptions. PCD/T was assessed by a validated high-performance liquid chromatography method coupled to mass spectrometry detection, derived from that previously published for vemurafenib [13].

For this study, we selected patients who had at least one PCD or PCT assay performed at steady-state and distant from peak plasma concentration (trough concentration). Steady state was defined as no discontinuation or modification of drug doses following treatment initiation after at least 5 half-lives of dabrafenib and trametinib, *i.e.* after 2 and 24 days, respectively. Plasma samples were considered to be at trough concentration if drawn between 8 and 14:30 hours after last drug intake for dabrafenib and between 20 and 28 hours for trametinib [14-15].

To study the relationship between PCD/T and tumour response, for each PCD/T assay, we used the result of the nearest tumour response assessment. Only assays carried out before the first progression were used to study the relationship between antitumor response and PCD/T. To study the relationship between PCD/T and safety, we analysed the last concentration of PCD/T closest to the onset of each AE. In the absence of AE, the highest PCD/T was considered.

Quantitative data were expressed as mean \pm standard deviation (SD) or median and interquartile range (IQR), and qualitative data as frequency and percentage, n (%).

Comparisons of means were performed using Student's t-test and the Wilcoxon Rank Sum test was performed for the AE analysis. The Pearson Correlation Coefficient was used to measure the strength of the association between two quantitative variables. A joint model was used to assess the relationship between PC and progression-free survival, taking follow-up time into account. These models are used for simultaneously analysing longitudinal measurement outcomes (repeated measurement data) and time-to-event outcomes (survival data) [16]. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using R software version 3.4.3. PCD/T were not dose-normalized.

This study was approved by the ethics committee (CPP Ile-de-France XI; N° 2013-A1591-44; ref 14005) and considered to be standard of care. The study was performed in accordance with French regulations on non-interventional observational studies, which do not require patient's consent when analysing data obtained from routine care. The study was conducted according to the principles of the Declaration of Helsinki [17].

3. Results

We obtained a total of 139 PCD and 126 PCT samples. Assays without information on the time of the last drug intake ($N=28$ for each drug), or not performed at steady-state, or

performed at the time of peak plasma concentration ($N=40$ for each drug) were excluded from our analyses (Fig. 1).

We analysed 71 PCD and 58 PCT assays from 34 patients (18M/16F) with *BRAFV600* (*BRAFV600E*: $N= 27$; *BRAFV600K*: $N=7$) mutated melanoma treated with combined dabrafenib plus trametinib (administered as first line in 29 patients, 85.3 %). All patients had American Joint Committee on Cancer (AJCC; 8th edition) stage IV melanoma, including 9 (26.5%) patients with brain metastases: 8 were treated as first-line while 7 received concomitant stereotactic cerebral radiotherapy. Patient characteristics and previous treatments are summarized in Table 1.

Drug doses were reduced due to CTCAE AE grade ≥ 2 in 10 patients (29.4%): dose reduction of dabrafenib only in 2 patients, dose reduction of trametinib only in 1, and dose reduction of both dabrafenib and trametinib in 7 patients. The dose reduction of dabrafenib was 33% in 8 patients and 67% in 1 patient; the dose reduction of trametinib was of 25% in all patients having a trametinib dose reduction ($N=8$). AEs resulting in dose reductions were neutropenia ($N=4$), fever ($N=3$), decreased cardiac ejection fraction ($N=2$), and hepatic cytolysis ($N=1$).

There was a high inter-individual variability of PCD (range: 4-945 ng/mL, median 65.0) and PCT (range: 5-39 ng/mL, median 8.6). This high inter-individual variability of PCD (range: 6-945 ng/mL, median 73.9) and PCT (range: 5.7-25.0 ng/mL, median 9.0) was still observed in patients on full-dose dabrafenib and trametinib and for whom only one sample was analysed (Fig. 2). We also observed high intra-subject variability in patients undergoing several measurements of PCD/T under the same regimen. During a median follow-up of 20.7 months (range: 2.1-63.4 months), 21 patients (62%) experienced tumour progression, after a mean duration of 10.4 months of dabrafenib treatment and 8.7 months of trametinib treatment, including 2 exhibiting primary resistance (progression in the first 2 months).

The relationship between PCD and progression-free survival (median: 9.3 months [1.9-18.7]), taking follow-up time into account, almost reached statistical significance: hazard ratio 0.991 (95% confidence interval (CI), 0.981 to 1.000; $P=0.06$); *i.e.* each 1 ng/mL increase in PCD was associated with a 0.9% decrease in the risk of disease progression. PCD/T did not significantly differ between patients with disease progression (125 ± 183 ng/mL and 9.3 ± 3.6 ng/mL, respectively) and those with complete ($N=11$), partial response ($N=1$) or stable disease ($N=1$) (159 ± 225 ng/mL, $P=0.58$ and 10.6 ± 24.4 ng/mL, $P=0.29$, respectively). After exclusion of patients with cerebral progression without extra-cerebral progression ($N=8$), no significant difference was observed between PCD/T in patients with disease progression and those with complete, partial or stable disease (146 ± 233 ng/mL and 9.4 ± 3.9 ng/mL) and responders (180 ± 246 ng/mL and 9.7 ± 3.8 ng/mL, $P=0.71$).

All patients had at least one AE; the most common laboratory and clinical AEs ($N \geq 10$) were increased levels of creatine kinase ($N=18$), aspartate ($N=18$) or alanine aminotransferase ($N=14$), lymphopenia ($N=11$) and fever ($N=10$). No significant relationship was found between these AE and PCD/T (Fig. 3). There was no association between PCD/T and decreased cardiac ejection fraction ($r=0.09$ and 0.11 for dabrafenib and trametinib, respectively). We assessed the occurrence of severe AE (grade ≥ 2 ; $N=16$) in relation to the previously reported PCD threshold of 48 ng/mL [9]. Sensitivity was 0.59 (95%CI, 0.41 to 0.76) and specificity was 0.57 (95% CI, 0.40 to 0.74). The area under the ROC curve for PCD closest to the AE was 0.62 (95%CI, 0.42 to 0.82), with sensitivity of 75% and specificity of 47%, and there was no manifest PCD threshold predictive of AE. Similar results were obtained when using the highest PCD in the absence of AE.

There was no significant relationship between PCD/T and body mass index ($r=0.22$ and -0.32), age ($P=0.19$ and 0.26), PCD/T and dabrafenib ($P=0.10$) or trametinib doses ($P=0.26$), PCD/T and any co-medications (Table 2), or between PCD and PCT ($r=0.11$). PCT

were significantly higher for female subjects (11.5 ± 4.8 ng/mL) than for male subjects (8.8 ± 2.9 ng/mL; $P=0.01$), but no significant relationship between PCD and sex was found ($P=0.32$).

4. Discussion

Despite a high inter- and intra-individual variability of PCD, we found a relationship between PCD and progression-free survival, taking follow-up time into account, which was close to statistical significance. However, no difference was observed between mean PCD/T of progressing patients and responders, in contrast to what was shown with vemurafenib monotherapy [8]. No relationship between PCD/T and the most common AEs was found. We noticed a tendency for lower concentrations of dabrafenib in case of fever (which may just reflect a dose reduction of dabrafenib in case of fever, as the closest concentration to the onset of each AE was considered), and higher concentrations of dabrafenib in case of lymphopenia. Although these results are not significant, this could be an interesting finding that may require more cases in order to be significant, especially lymphopenia.

Balakitrouchenane *et al.* have shown that melanoma patients experiencing dose-limiting-toxicity were overexposed to dabrafenib compared to patients without dose-limiting-toxicity, but as in our study, trametinib plasma exposure was associated with neither toxicity nor efficacy [11]. Rousset *et al.* found a high inter-individual variability, of the same order of magnitude as our results for trametinib (4.1-23.8 ng/mL vs. 5-25 ng/mL), but we observed wider inter-individual variability of PCD (4-945 ng/mL vs. 15.4-279.6 ng/mL) [9]. The high inter-individual variability of dabrafenib concentrations is consistent with variable expression of CYP3A4 and CYP2C8, the main enzymes of dabrafenib metabolism [18]. Patient compliance and co-medications might also play a role. In contrast with the results of Rousset *et al.* obtained in 27 patients, we did not find a threshold of PCD predictive of the occurrence

of AE although we studied 34 patients [9]. As already reported by Puszkiel *et al.*, our study confirms that age, sex and bodyweight do not have any clinically significant influence on plasma exposure to dabrafenib [18]. Recently Balakirouchenane *et al.* found a contribution of sex on CPD, confirming prior results of Ouellet *et al.*, but not of bodyweight [11,19]. On the other hand, as already shown in the population pharmacokinetic study of trametinib, we found a significant relationship between PCT and sex, with higher CPT in female subjects, but no relationship with bodyweight was found [2].

One limitation of our study is the small number of patients. A large number of assayed samples were not interpretable due to inappropriate sampling time relative to the minimal concentration. This reflects different treatment schedules of dabrafenib, which has to be taken at least 1 hour before or at least 2 hours after a meal, leaving an interval of approximately 12 hours between doses. Our patients were asked to withhold their last dose of dabrafenib and trametinib before their visit to the clinic in order to obtain residual PCD and PCT. However, several patients did not change their treatment schedules for fear of forgetting the next dose. We cannot exclude the possibility that some very high PCD/T observed in this study are related to patients providing misleading information about their last intake. We may have lacked power to detect a stronger relationship between PCD/T and therapeutic response. Each patient received a therapeutic education session at the start of treatment, and they were told not to consume grapefruit or herbal medicine during their treatment with dabrafenib and trametinib. They were regularly reminded of these recommendations, but the question was not specifically asked each time plasma concentrations were taken. We cannot formally rule out modification of PCD or PCT by some food-drug interaction.

A further limitation of this study is the lack of measurement of plasma concentration of dabrafenib metabolites, which may contribute to the therapeutic activity of the parent compound. Dabrafenib primarily undergoes CYP2C8 and CYP3A4-mediated metabolism to

hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib, excreted in bile and urine [19]. Carboxy-dabrafenib can be decarboxylated to form desmethyl-dabrafenib, which is reabsorbed and undergoes enterohepatic recirculation. Dabrafenib is also a substrate for intestinal uptake and P-gp-mediated hepatic and intestinal efflux. Hydroxy-dabrafenib terminal half-life parallels that of the parent compound with a half-life of 10 hours while the carboxy- and desmethyl-metabolites exhibit longer half-lives (21-22 hours). Based on exposure, relative potency, and pharmacokinetic properties, both hydroxyl- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib, while the activity of carboxy-dabrafenib is not likely to be significant. The relationship between plasma concentrations of all active moieties derived from dabrafenib administration may be better associated with tumour response than the concentration of the parent compound alone. Indeed, PK-population analyses have shown complex relationships between the AUC of hydroxy-dabrafenib evaluated over 3 months and survival, but this approach is not usable in current practice for individual patients [11].

Trametinib is a P-gp efflux pump inhibitor, and dabrafenib is also one of its substrates [20]. To investigate the potential influence of trametinib on PCD, we analysed the relationship between PCD and PCT but did not find any relationship in our study.

Rowland A *et al.* conducted a physiologically based pharmacokinetic modelling to evaluate the physiological and molecular characteristics driving between-subject variability in dabrafenib exposure [21]. Retaining the threshold of 48 ng/mL for PCD, they found that multivariable consideration of baseline weight, body mass index, and CYP2C8, CYP3A4, and P-gp abundance strongly predicts steady-state dabrafenib trough concentration above 48 ng/mL. Determination of a threshold concentration of dabrafenib associated with therapeutic response could be of value for the conduct of similar studies.

In conclusion, our study, the first to assess the relationship between single PCD/T and tumour response, showed a weak relationship between PCD and progression-free survival. It is, however, unlikely that PCD and PCT alone will be useful for monitoring treatment response. Other studies including dabrafenib metabolite assay in a larger sample size are required to assess the potential utility of therapeutic drug monitoring of dabrafenib in melanoma.

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Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions: CFB, PS and EFB designed the study. MR collected data and participated in analyses. JCA performed the measurements of plasma concentration of dabrafenib and trametinib. AB made statistical analysis and figures. All authors critically revised the draft version of the manuscript and approved the final version.

Ethics approval and consent to participate: The study was performed in accordance with French regulations on non-interventional observational studies, which do not require patient consent for analysis of data obtained from routine care. The study was conducted according to the principles of the Declaration of Helsinki.

Patient consent for publication: The study was performed in accordance with French regulations, which do not require patient consent for publication.

Competing interest:

EFB has received personal fees from Pierre Fabre, Novartis, Bristol-Myers Squibb and MSD.

PS has received personal fees from Amgen, Bristol-Myers Squibb, MSD, Merck-Serono, Pfizer, Roche-Genentech, Pierre Fabre, and Novartis, and has also received nonfinancial support from Bristol-Myers Squibb, MSD, Roche-Genentech, and Novartis.

The other authors declare that they have no conflicts of interest with this study.

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molecular characteristics driving variability in drug exposure. *Clin Pharmacol Ther* 2018; 104:1219–28.

Figure 1. Flow chart.

Figure 2. Plasma concentrations of dabrafenib (A) and of trametinib (B) in each patient.

Each datapoint represents one sample; at dotted line is placed at the median concentrations of 65.0 (A) and 8.6 ng/mL (B).

Figure 3. Box/whisker plots of plasma concentrations of dabrafenib (A) and trametinib (B) for each adverse event.

The horizontal line of the box shows the median; The diamond shows the mean of each group.

The width of the box is proportional to the size of the group. ASAT: Aspartate-aminotransferase; ALAT: Alanine-aminotransferase

Table 1. Clinical characteristics of patients with metastatic melanoma treated with dabrafenib and trametinib (n=34). *Data are mean \pm standard deviation

Mean age, years*	59.2 \pm 12.2
Sex, number of females/number of males	16/18
Body Mass Index, kg/m²	25.4 \pm 4.7
AJCC stage (n, %)	
IV	34 (100)
M1a	4 (11.8)
M1b	6 (17.6)
M1c	15 (44.1)
M1d	9 (26.5)
Treatment lines (n, %)	
First line	29 (85.3)
Second line	4 (11.8)
Third line or more	1 (2.9)
Subcutaneous metastasis (n, %)	17 (50.0)
Nodal metastasis (n, %)	28 (82.4)
Visceral metastasis (n, %)	28 (82.4)
Brain metastasis (n, %)	9 (26.5)
LDH > upper limit of normal (n, %)	6 (17.6)
ECOG status (n, %)	
1	24 (70.6)
2	8 (23.5)
3 or more	2 (5.9)
Histologic subtype (n, %)	
SSM	20 (58.8)
Nodular	8 (23.5)
Unknown primitive	4 (11.8)
Unknown	2 (5.9)
Breslow (mm)	4.09 (\pm 4.35)
Mutational BRAF status (n, %)	
V600E	27 (79.4)
V600K	7 (20.6)

Table 2. Patient comedication (N=34 patients)

Comedication	Number of patients	Percentage of patients
Prednisone	6	17.6%
Omeprazole	5	14.7%
Levetiracetam	5	14.7%
Amlodipine	4	11.8%
Paroxetine	3	8.8%
Bisoprolol	4	11.8%
Rosuvastatin	4	11.8%
Metformin Hydrochloride	4	11.8%
Rilmenidine	3	8.8%
Fluindione	2	5.9%
Atorvastatin	2	5.9%
Doxycycline	2	5.9%
Clobazam	2	5.9%
Irbesartan	2	5.9%
Ramipril	2	5.9%
Hydrocortisone	2	5.9%
Sodium valproate	1	2.9%
Lercanidipine	1	2.9%
Spirolactone	1	2.9%
Sotalol	1	2.9%
Acebutolol	1	2.9%
Nebivolol	1	2.9%
Valsartan	1	2.9%
Simvastatin	1	2.9%
Fenofibrate	1	2.9%
L-thyroxine	1	2.9%
Nevirapine	1	2.9%
Raltegravir	1	2.9%
Abacavir	1	2.9%
Amiodarone	1	2.9%
Furosemide	1	2.9%
Tamsulosin	1	2.9%
Prednisolone	1	2.9%

Plasma concentration of dabrafenib
N=139

Missing data
N=28

Assays not performed at
steady state or at the time of
the peak of plasma
concentration
N=40

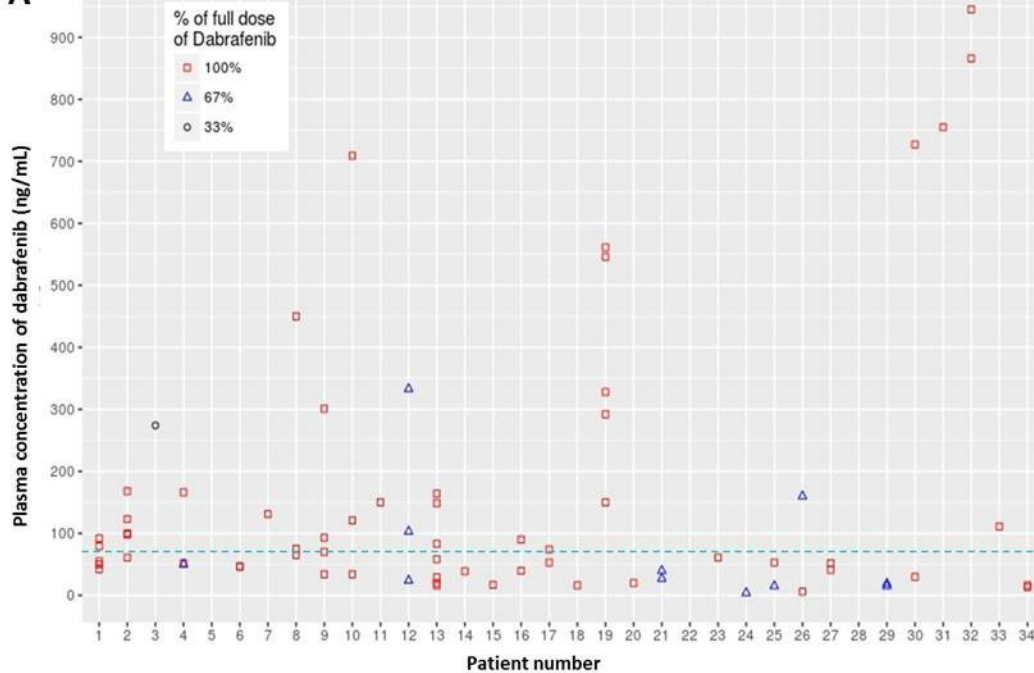
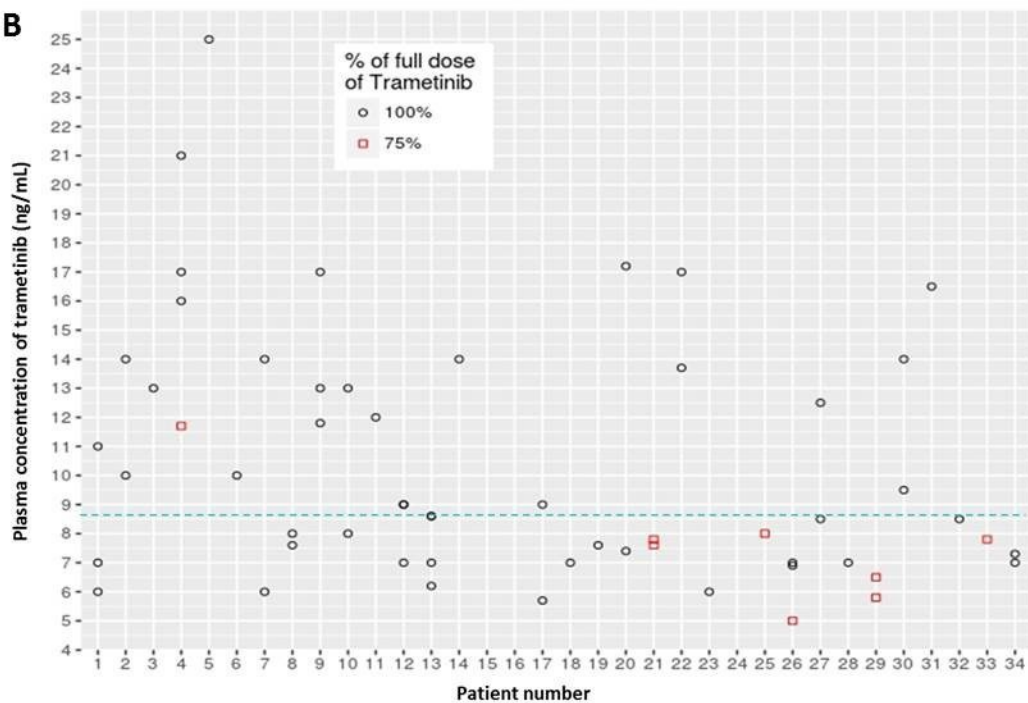
Assays performed at steady state and at
distance of the peak of plasma concentration
N=71

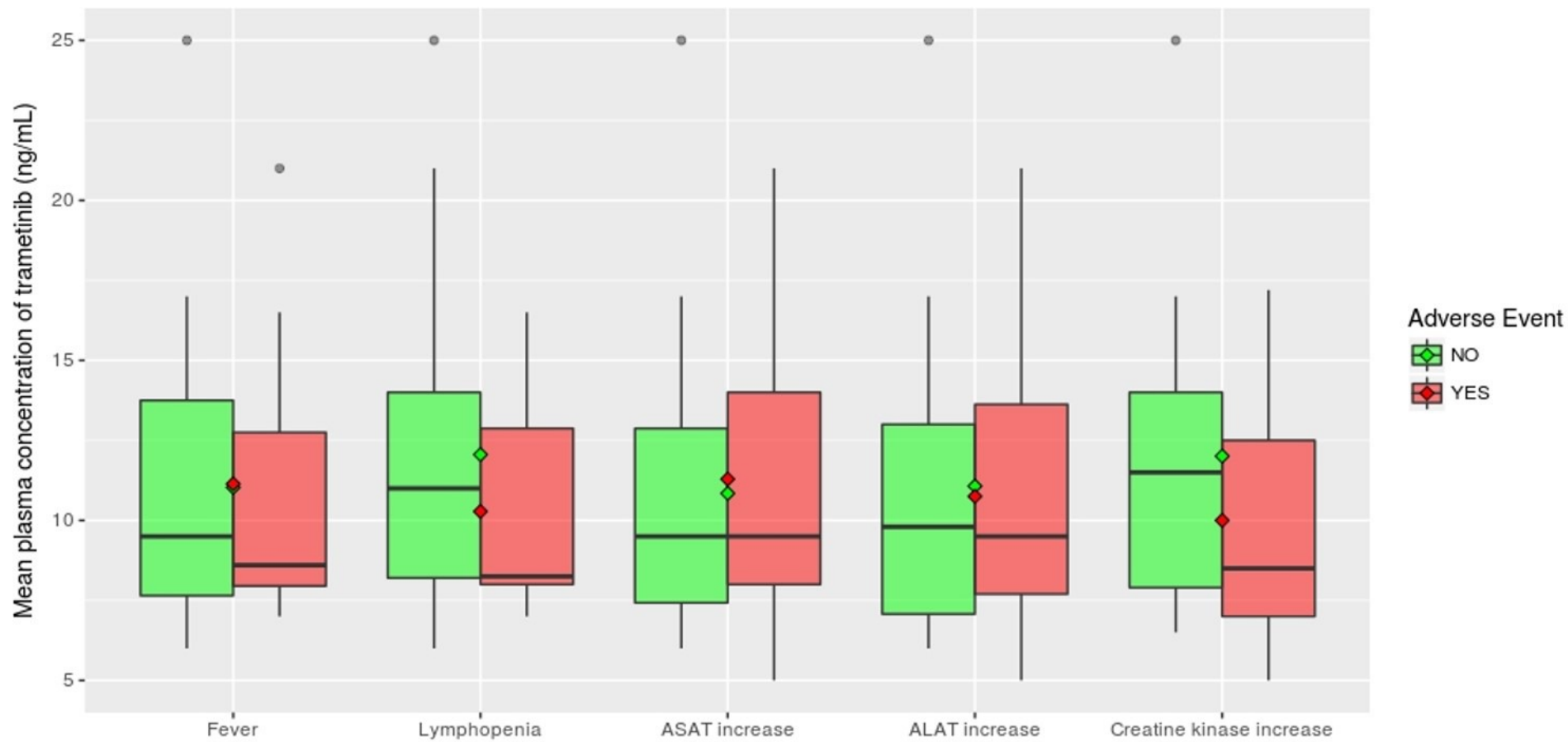
Plasma concentration of trametinib
N=126

Missing data
N=28

Assays not performed at
steady state or at the time of
the peak of plasma
concentration
N=40

Assays performed at steady state and at
distance of the peak of plasma concentration
N=58

A**B**

A**B**