



**HAL**  
open science

## Clinical value of early detection of circulating tumour DNA-BRAFV600mut in patients with metastatic melanoma treated with a BRAF inhibitor

Baptiste Louveau, Jörg Tost, Florence Mauger, Aurélie Sadoux, Marie-Pierre Podgorniak, Alexandre How-Kit, Cécile Pages, Jennifer Roux, Laetitia da Meda, Céleste Lebbe, et al.

### ► To cite this version:

Baptiste Louveau, Jörg Tost, Florence Mauger, Aurélie Sadoux, Marie-Pierre Podgorniak, et al.. Clinical value of early detection of circulating tumour DNA-BRAFV600mut in patients with metastatic melanoma treated with a BRAF inhibitor. *ESMO Open*, 2017, 2 (2), pp.e000173. 10.1136/esmoopen-2017-000173 . cea-04516146

**HAL Id: cea-04516146**

**<https://cea.hal.science/cea-04516146>**

Submitted on 16 May 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



CrossMark

# Clinical value of early detection of circulating tumour DNA-*BRAF*<sup>V600mut</sup> in patients with metastatic melanoma treated with a BRAF inhibitor

Baptiste Louveau,<sup>1</sup> Jörg Tost,<sup>2</sup> Florence Mauger,<sup>2</sup> Aurélie Sadoux,<sup>1</sup> Marie-Pierre Podgorniak,<sup>1</sup> Alexandre How-Kit,<sup>3</sup> Cécile Pages,<sup>4</sup> Jennifer Roux,<sup>4</sup> Laetitia Da Meda,<sup>4</sup> Céleste Lebbe,<sup>4,5,6</sup> Samia Mourah<sup>1,5,6</sup>

**To cite:** Louveau B, Tost J, Mauger F, *et al.* Clinical value of early detection of circulating tumour DNA-*BRAF*<sup>V600mut</sup> in patients with metastatic melanoma treated with a BRAF inhibitor. *ESMO Open* 2017;2:e000173. doi:10.1136/esmoopen-2017-000173

BL and JT are co-first authors. CL and SM are co-last authors.

Received 31 January 2017  
Revised 9 March 2017  
Accepted 11 March 2017

<sup>1</sup>Assistance Publique-Hôpitaux de Paris, Laboratoire de Pharmacogénomique, Hôpital Saint-Louis, Paris, France  
<sup>2</sup>Laboratory for Epigenetics and Environment, Centre National de Génotypage, CEA-Institut de Génétique, Evry, France  
<sup>3</sup>Laboratory for Genomics, Fondation Jean Dausset-CEPH, Paris, France  
<sup>4</sup>Département de Dermatologie, Assistance publique—Hôpitaux de Paris, Paris, France  
<sup>5</sup>Université Paris Diderot, Sorbonne Paris Cité, Paris, France  
<sup>6</sup>UMR-976, INSERM, Hôpital Saint-Louis, Paris, France

## Correspondence to

Professor Samia Mourah, Service de Pharmacogénomique, Hôpital Saint-Louis 24 1 Avenue Claude Vellefaux, 75475, Paris cedex 10, France; samia.mourah@aphp.fr

[Click here to see the linked article](#)

*BRAF*<sup>V600</sup> mutations (*BRAF*<sup>V600mut</sup>) are detected in about 50% of lesions from patients with metastatic melanoma. In the last few years, clinical treatment of melanoma has benefited from the approval of personalised therapies targeting *BRAF*<sup>V600</sup>. These innovative therapies still require molecular biomarkers predicting response duration. Circulating tumour DNA (ctDNA) appears to be a promising tool thanks to its ability to capture tumour heterogeneity. Detection of *BRAF*<sup>V600mut</sup> in ctDNA (ct*BRAF*<sup>V600mut</sup>) could be a hopeful tool to monitor and predict clinical response in melanoma treated with BRAF/MEK inhibitors.

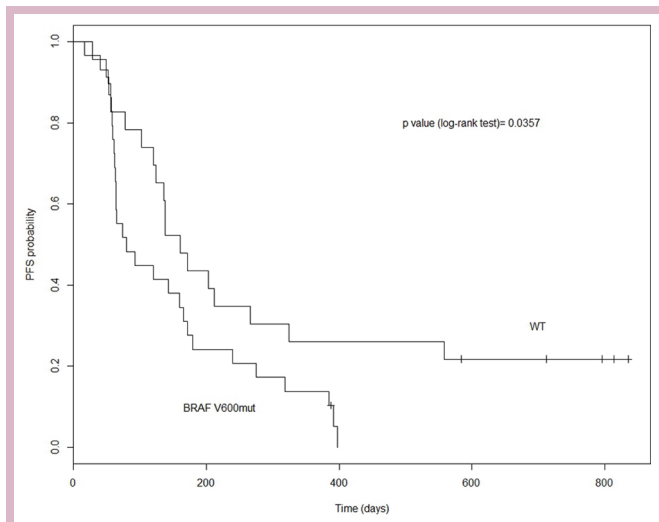
Low baseline levels (pretreatment initiation) of ct*BRAF*<sup>V600mut</sup> have been found to be significantly associated with longer progression-free survival (PFS) and variation in ct*BRAF*<sup>V600mut</sup> levels during treatment was associated with the clinical course.<sup>1,2</sup> Similarly, overall survival (OS) was significantly associated with *BRAF*<sup>V600mut</sup> status in ctDNA prior to any targeted therapy.<sup>3</sup> Furthermore, a significantly higher PFS was found for patients in whom ct*BRAF*<sup>V600mut</sup> became undetectable at some time point after initiation of targeted therapy.<sup>4</sup>

From 2012 to 2014, 85 patients from the onco-dermatology department of the Saint-Louis Hospital (Paris, France) presenting unresectable stage III (n=12) or stage IV (n=73) melanoma with *BRAF*<sup>V600E</sup> mutated lesions at targeted therapy initiation (BRAF inhibitors, vemurafenib or dabrafenib) were included in this retrospective study after signed informed consent. The cohort included 52 (62%) patients presenting a

stage IV m1c melanoma, and 23 (27%) had brain metastasis. Clinical response was evaluated using RECIST (Response Evaluation Criteria in Solid Tumors) V.1.1 criteria. Detection of ct*BRAF*<sup>V600mut</sup> was monitored at baseline and during therapy using the highly sensitive E-ice-COLD-PCR method (0.1% sensitivity threshold).<sup>5</sup> The aim was to study the potential of *BRAF*<sup>V600mut</sup> detection in ctDNA as a predictor of tumour escape at baseline and at early intervals after therapy initiation.

Consistent with previous studies,<sup>1,4</sup> 68% of patients (58/85) presented a ct*BRAF*<sup>V600mut</sup> detection at first visit. Our study focused on the 53 patients with a blood sample within the first 3 months after therapy initiation and categorized them into two groups according to their ct*BRAF*<sup>V600mut</sup> status at this postinitiation visit, regardless of their ct*BRAF*<sup>V600mut</sup> status prior to treatment. Univariate analysis highlighted a significant difference (p=0.036, log-rank test) for PFS (time between therapy initiation and disease progression) with a median of 5.3 months and 2.8 months for wild-type patients and *BRAF*<sup>V600mut</sup> in ctDNA patients, respectively (figure 1). No significant association was found for OS (time between therapy initiation and death). Cox multivariate analysis allowed the estimation of the risk for ct*BRAF*<sup>V600mut</sup> positive status associated with the PFS adjusted on patient's sex and melanoma stage: HR (CI 95%)=2.81 (1.43 to 5.54).

Awaiting confirmation on larger cohorts, our results demonstrate that early detection of ct*BRAF*<sup>V600mut</sup> is associated with PFS, which represents a promising predictive tool in



**Figure 1** Kaplan-Meier plot presenting PFS for patients with *BRAFV600*-mutated ctDNA at first visit (<3 months) after targeted therapy initiation (n=30) compared with patients without *BRAFV600*-mutated ctDNA at the first visit (<3 months) after targeted therapy initiation (n=23). ctDNA, circulating tumour DNA; PFS, progression-free survival.

clinical practice. As the pretreatment ct*BRAF*<sup>V600mut</sup> status and the longitudinal monitoring are rarely performed in daily clinical practice, our results show the clinical value of *BRAF*<sup>V600mut</sup> detection in ctDNA early after initiation of targeted therapy (<3 months). Such tool may allow the anticipation of clinical response and assessment of secondary resistance, hence facilitating earlier management of melanoma patients treated with targeted therapies.

**Contributors** BL analysed and interpreted the data and drafted the manuscript. JT performed the molecular analyses and contributed to data collection, study design and writing of the manuscript. FM and AH-K performed the molecular

analyses and contributed to data collection and assembly. AS and M-PP provided a technical support. CP and JR provided clinical data. LDM performed clinical data management. CL provided her expertise in the melanoma field, designed the study and wrote the manuscript. SM designed the study, interpreted the data and wrote the manuscript.

**Competing interests** CL declares honoraria from Roche, advisory roles at Roche, GSK, Novartis, BMS, MSD and Amgen, and travel accommodation provided by Roche. SM declares a consulting role at Roche and Novartis.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© European Society for Medical Oncology (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

## REFERENCES

- Sanmamed MF, Fernández-Landázuri S, Rodríguez C, *et al.* Quantitative cell-free circulating BRAFV600E mutation analysis by use of droplet digital PCR in the follow-up of patients with melanoma being treated with BRAF inhibitors. *Clin Chem* 2015;61:297–304.
- Gray ES, Rizos H, Reid AL, *et al.* Circulating tumor DNA to monitor treatment response and detect acquired resistance in patients with metastatic melanoma. *Oncotarget* 2015;6:42008–18.
- Knol AC, Vallée A, Herbreteau G, *et al.* Clinical significance of BRAF mutation status in circulating tumor DNA of metastatic melanoma patients at baseline. *Exp Dermatol* 2016;25:783–8.
- Schreuer M, Meersseman G, Van Den Herrewegen S, *et al.* Quantitative assessment of BRAF V600 mutant circulating cell-free tumor DNA as a tool for therapeutic monitoring in metastatic melanoma patients treated with BRAF/MEK inhibitors. *J Transl Med* 2016;14:95.
- How-Kit A, Lebbé C, Bousard A, *et al.* Ultrasensitive detection and identification of *BRAF* V600 mutations in fresh frozen, FFPE, and plasma samples of melanoma patients by E-ice-COLD-PCR. *Anal Bioanal Chem* 2014;406:5513–20.