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

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BRAFV600 mutations (BRAFV600mut) 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 BRAFV600. 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 BRAFV600mut in ctDNA (ctBRAFV600mut) could be a hopeful tool to monitor and predict clinical response in melanoma treated with BRAF/MEK inhibitors.

Low baseline levels (pretreatment initiation) of ctBRAFV600mut have been found to be significantly associated with longer progression-free survival (PFS) and variation in ctBRAFV600mut levels during treatment was associated with the clinical course.12 Similarly, overall survival (OS) was significantly associated with BRAFV600mut status in ctDNA prior to any targeted therapy.3 Furthermore, a significantly higher PFS was found for patients in whom ctBRAFV600mut became undetectable at some time point after initiation of targeted therapy.4 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 BRAFV600mut 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 ctBRAFV600mut was monitored at baseline and during therapy using the highly sensitive E-ice-COLD-PCR method (0.1% sensitivity threshold).5 The aim was to study the potential of ctBRAFV600mut detection in ctDNA as a predictor of tumour escape at baseline and at early intervals after therapy initiation.

Consistent with previous studies,1 4 68% of patients (58/85) presented a ctBRAFV600mut 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 ctBRAFV600mut status at this postinitiation visit, regardless of their ctBRAFV600mut 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 BRAFV600mut positive status, 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 ctBRAFV600mut 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 ctBRAFV600mut is associated with PFS, which represents a promising predictive tool in
clinical practice. As the pretreatment c\textit{t}BRAF\textit{V600mut} status and the longitudinal monitoring are rarely performed in daily clinical practice, our results show the clinical value of c\textit{t}BRAF\textit{V600mut} detection in c\textit{t}DNA 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.

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