Materials and Methods

Study Design

We conducted a single-center, retrospective, descriptive analysis of a cohort of 52 patients treated with *BRAF*-V600 and MEK inhibitors for advanced melanoma over a 12-month period.

The aim of this study was to characterize disease progression, defined as metastatic pattern, disease kinetics, and to assess response to subsequent treatments, in melanoma patients treated with *BRAF*-V600 + MEK inhibitors but who then had disease progression.

The secondary objective was to evaluate the efficacy and safety of *BRAF*-V600 + MEK inhibitors within a real-life setting.

Patients

Pro tempore authorization for use (namely *autorisation temporaire d'utilisation*, ATU) of a treatment is a specific French procedure that allows prescription of a treatment that has shown significant efficacy before the health authority approval of the molecule. ATU is conducted under specific conditions, and the drug is given to patients that fulfil pre-established criteria.

All patients with *BRAF*-mutated metastatic melanoma included in the cobimetinib ATU were identified. Patients systematically received cobimetinib associated with the *BRAF*-V600 inhibitor (vemurafenib, except for patients who had severe adverse events and were secondarily switched to dabrafenib). According to the ATU criteria, patients could have received concomitant introduction of both treatments or have a delayed introduction of cobimetinib if there was no disease progression after a previously prescribed *BRAF* inhibitor.

End Points

The primary end point was disease progression, which was defined according to clinical-radiological manifestations of disease progression, time until a relapse, survival time after progression, and response to a subsequent therapy. Assessment of the tumor at the time of disease progression was made using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) adapted through clinician global assessment.

The metastatic sites of disease progression were divided into central nervous system (CNS) metastasis or extra-CNS metastasis. The patients were divided into three groups: group A included patients with exclusively CNS metastasis; group B included those with CNS metastasis + extra-CNS metastasis, and group C included patients with exclusively extra-CNS metastasis. Time until a relapse was calculated for patients who displayed progression and was defined as the time elapsed from the first use of the *BRAF*-V600 inhibitor until the first diagnosis of disease progression or death from any cause. Survival after progression was defined as the time elapsed between the first occurrence of disease progression until death. A therapeutic response to subsequent therapy(ies) included a description of the therapy, response rate, and qualitative evaluation of the therapeutic response (progression, stable disease, partial response, or complete response).

The secondary end point was the efficacy of the association of *BRAF*-V600 + MEK inhibitors in a real-life setting with regard to response rates, PFS, and OS. For descriptive purposes, adverse events (AEs) were recorded and characterized according to the NCBI common terminology criteria for adverse events V4.03 (CTCAE, V4.03), then sorted into two categories: limiting versus nonlimiting AEs. An AE was considered limiting when its occurrence, and/or duration, and/or perception by the

patient lead to temporary and/or definitive discontinuation of treatment, whatever the CTCAE grade.

Data Collection

The following data for all included patients were retrieved from the personal medical and computerized case reports at our institution:

- Demographics: age at diagnosis of melanoma, age at first metastasis, gender ratio
- Description of baseline tumor: Breslow, ulceration, Clark, mitotic rate, stage of disease (AJCC status), type of *BRAF* mutation
- Baseline metastatic description: intracranial metastasis at baseline, co-introduction of dual-inhibition *BRAF*-V600 + MEK, delay between melanoma diagnosis and first metastasis, delay between first metastasis and introduction of the *BRAF* inhibitor
- Disease progression and metastatic pattern, type of subsequent treatment(s) and responses to subsequent treatment(s)

Statistical Analyses

Analyses were performed using GraphPad Prism statistical software, release 6.0 (GraphPad, La Jolla, CA, USA). Quantitative variables are presented as their mean (95% CI) or median (interquartile range), according to their distribution. Qualitative variables are presented as percentages of the analyzed data. Survival was assessed using Kaplan-Meier curves. Comparisons of survival times between the subgroups were made using the log rank test, comparisons between descriptive variables in the subgroups were made using the χ^2 or the Mann-Whitney test, as appropriate, and this was confronted with an α-value of 5%. All *p* values were 2-sided.

Analyses were conducted on an intent-to-treat basis; data from patients who did not have disease progression were censored at the time of analyses. The last observation was carried forward for those patients lost to follow-up.