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Outcomes after discontinuation of immunotherapy in patients with advanced melanoma with brain metastases following induction of dual immunotherapy with Ipilimumab/Nivolumab

Charlotte Isautier

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UNIVERSITE DE MONTPELLIER
FACULTE DE MEDECINE MONTPELLIER-NIMES

THESE

Pour obtenir le titre de
DOCTEUR EN MEDECINE

Présentée et soutenue publiquement
Par
Charlotte ISAUTIER

Le jeudi 20 avril 2023

Résultats après arrêt de l'immunothérapie chez les patients atteints de mélanome avancé avec métastases cérébrales ayant reçu un protocole initial de double immunothérapie ipilimumab/nivolumab

Outcomes after discontinuation of immunotherapy in patients with advanced melanoma with brain metastases following induction of dual immunotherapy with ipilimumab/nivolumab

Directeurs de thèse : Professeur DEREURE Olivier &
Docteur LAMOUREUX Anouck

JURY

Président : Professeur DEREURE Olivier

Asseseurs : Professeur MEUNIER Laurent

Docteur LAMOUREUX Anouck

Docteur BERGERET Blanche

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Outcomes after discontinuation of immunotherapy in patients with advanced melanoma with brain metastases following induction of dual immunotherapy with ipilimumab/nivolumab

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ABSTRACT

Background and purpose :

Patients who have melanoma brain metastasis are a distinct group in terms of how they respond to treatment and their overall outcome. Combining immunotherapy drugs Nivolumab and Ipilimumab is becoming more common as a first or second line treatment for these patients, as it can provide long-term control and even lead to treatment discontinuation in some cases. However, there is currently limited information available on the outcomes of these patients, particularly in regards to the evolution of subsequent brain metastases, response to second-line treatments in the case of intracranial relapse, and overall survival. We aimed to gather data on this specific subset of patients in a real-world setting using the French nationwide MELBASE database.

Patients and Methods :

This national real-world retrospective study evaluated outcomes of 106 patients from the French MELBASE database with brain metastatic melanoma treated with ipilimumab and nivolumab who discontinued treatment in the absence of disease progression (PD). We describe efficacy outcomes (overall survival [OS], progression-free survival [PFS] and response to re-treatment in the event of intra cranial relapse.

Results:

Median time on treatment was 11.3 months (range 6.4-22.3) with a median best overall response time of 7.3 months (range 2.8-13.4). OS and PFS at 2 years was estimated at 70% and 38.9% respectively for the all cohort.

In the subgroup analysis, median OS in the group 1 (no brain relapse n=62) was not reach while in group 2 (brain relapse, n=44) median OS was 13.1 months (95% CI 4.1-21.8) with a median follow-up of 13.8 months and 10.5 months for each group respectively. After discontinuation of treatment, 76% (n=81) experienced progression, with 22% of cases being intracranial. Of these, 21 patients achieved a response (CR, PR or SD) after retreatment.

Conclusion :

This real-world cohort study offers promising results for patients with melanoma brain metastases who discontinue immunotherapy after induction with combined IT, with a 56% global survival rate after two years without retreatment. Moreover our finding suggest that retreatment is effective in some cases of intracranial relapse.

Keywords : melanoma, MBM, IT, immunotherapy, combined IT, anti PD1, Ipilimumab

INTRODUCTION

Cutaneous melanoma accounts for 10% of all skin cancers and 1.1% of cancer-related deaths across genders (1). This increasingly (2–4) frequent skin malignancy displays a specific tropism to the brain (5) and represents the third most common cause of brain metastases after lung and breast cancer and it has been previously reported that 40-60% of patients with metastatic melanoma will develop brain metastases during follow up (6,7).

The recent development of immune checkpoint inhibitors (IT, mainly anti-PD1 +/- anti-CTLA4 agents) along with targeted therapies (BRAF and MEK inhibitors) (7–11) has considerably improved the outcome of patients with advanced melanoma including brain metastases (12–18) but this latter subset still represents a distinct group regarding therapeutic response and overall outcome. Combination immunotherapy with Nivolumab and Ipilimumab is increasingly used as a first- or second -line treatment in this setting, regardless of BRAF status, allowing long term control that may result in considering treatment discontinuation in some patients. The CheckMate 204 study (an open-label, multicenter, phase 2 study) investigating long-term outcome of patients with melanoma brain metastases (MBM) receiving nivolumab and ipilimumab combination treatment followed by nivolumab for up to 2 years (until disease progression or unacceptable toxicity) indeed showed an overall survival rate of approximately 72% in patients with asymptomatic MBM after a 3-year follow-up period (19).

However, the required duration of IT-induced long-term control before considering treatment discontinuation remains uncertain. Several studies investigating outcome of patients with and without MBM after IT interruption suggested that about 75-80% of patients experienced a sustained response after 1-3 years of anti-PD1 therapy (20–22). Dimitriou et al. reported a 92% survival probability without any additional treatment three years after discontinuing immunotherapy for complete response (23).

To our knowledge, brain metastases and overall outcome following IT treatment discontinuation after long-term MBM control has not been specifically documented to date.

To obtain more insight in this specific and crucial issue a nationwide study aims to describe outcome data in a large cohort of French patients (MELBASE database) achieving MBM control after combination immunotherapy with IPILIMUMAB and NIVOLUMAB and for whom treatment was subsequently discontinued.

MATERIALS AND METHODS

Data

Data were retrospectively collected from MelBase, a French nationwide multicenter clinico-biological database recording prospective follow-up data of adult patients with advanced melanoma (unresectable stage III or IV) receiving a systemic treatment. MelBase was approved by the French ethics committee (CPP Ile-de-France XI n 12027, 2012) and registered in the NIH clinical trials database (NCT02828202). Written informed consent was obtained from all patients. Cut-off date for the analysis was 09/01/2022 based on the database reference date of 12/01/2022.

Patients

Eligible patients were adults (age 18 years or older) with brain metastases who received ipilimumab/nivolumab combination immunotherapy regardless of line and who discontinued immunotherapy after disease control was achieved on extra- and intracerebral targets (complete response (CR), Partial Response (PR) or Stable disease (SD)).

The following data were collected from MelBase medical records: age, gender, Eastern Cooperative Oncology Group (ECOG) status, baseline lactate dehydrogenase (LDH) before the first dose of duals IT, BRAF mutation status, number of metastatic sites and localization(s), number of brain metastases, number and characteristics of local and systemic treatment(s) received prior to combination immunotherapy, use of systemic steroids and follow up duration after treatment discontinuation.

Patients were enrolled up to 3 months before the cut-off date and followed until the data cutoff date or until discontinuation of follow-up. Once control was achieved (CR, PR or SD), discontinuation was considered either by investigator decision or due to toxicity (irAEs).

Patients with uveal melanoma or included in a clinical trial were excluded. CR, PR, SD were defined by the RECIST v1.1 guidelines (24) on imaging (CT or MRI).

Efficacy assessment

The primary endpoint was to assess the outcomes of patients with brain metastases after discontinuation of IT therapy, following long-term control who received a combination of IPILIMUMAB and NIVOLUMAB immunotherapy and their characteristics. Secondary endpoints were the overall survival (OS), progression free survival (PFS), and treatment free survival (TFS). OS is defined as the time (in months) from the first immunotherapy dose to death from any cause

or last report. PFS is defined as the time (in months) between the first administration of immunotherapy to the first identified progression at follow-up or death from any cause. TFS was defined as the time (in months) from last immunotherapy dose to disease progression / initiation of a subsequent treatment or death.

We also performed a subgroup analysis to assess predictive criteria for disease recurrence and non-recurrence: The following subgroups were analyzed: - Group 1: brain metastases recurrence after discontinuation of treatment during follow-up - Group 2: no recurrence of brain metastases after discontinuation of treatment during follow-up. A multivariable analysis using a cox model was performed to explore the relationship between OS, PFS and several variables such as LDH (normal/> ULN), CR, number of sites (>2/≤2), duration of IT (>1 year/≤1 year), number of brain metastases (>3/≤3), and Braf mutation status (mutated or wild type).

Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous and ordinal variables are described using median and range. χ^2 test was used to compare categorical variables. For continuous variables, Fisher's exact test was used. A Cox proportional hazards model was used to perform univariate analysis (HR et IC 95%). PFS, OS and TFS were described using the Kaplan Meier method and were also estimated according to the following landmarks : 6, 12, 24 months. A p value <.05 was considered significant.

RESULTS

Patient characteristics at combination IT implementation

106 patients with advanced melanoma with brain metastases who received at least one perfusion of dual ITs and later discontinued either antiPD1+antiCTLA4 or subsequent anti PD1 monotherapy after a proper disease control including intracranial targets was achieved were included (59 men (56%) and 47 women (44%); median age 58 years, range 25-87). Patients' characteristics at treatment implementation are detailed in **Table 1**. The most common histopathological pattern of the primary tumor was SSM (42%, n=44), and 49 patients (46%) harbored a BRAF mutation. Most patients showed an ECOG performance status <1 (n=100, 94%) and serum lactate dehydrogenase (LDH) rate was initially increased in 36 patients (34%).

63 (59%) of included patients received IPILIMUMAB + NIVOLUMAB as a first-line therapy vs 43 (41%) after at least one prior line of systemic treatment including targeted therapy with anti-

BRAF + anti-MEK (n=22) or anti-BRAF alone (n=2), anti-PD1 monotherapy (n=17), or chemotherapy (n=2). Most patients (57%) discontinued IT owing to significant adverse effects versus mutual patient/physician decision based on disease control (41%).

Regarding brain metastases (BM) pattern, a median of 2 lesions per patient (ranging from 1 to 5) were present at combination IT implementation. Most patients (n=77) presented with less than 3 MBM, 18 between 3 and 10 MBM, and 11 with more than 10 MBM. BM were smaller than 1cm in diameter in 28 patients vs larger than 3cm in 10 patients. Data for 44 patients were not available. Out of the 106 patients, only 8 displayed leptomeningeal involvement and 16 patients experienced clinical neurological symptoms. Approximately 80% received local therapy for one or more central nervous system(CNS) metastases in addition to systemic treatment: neurosurgery (8 patients), radiotherapy (55 patients), or a combination of both (23 patients).

BOR before treatment discontinuation

The median follow-up duration after initiating combination IT was 20.6 months (range 6.7-30.6), with a median time to best overall response (BOR) achievement of 7.3 months (range 2.8-13.4). Regarding BOR pattern, complete, partial response or stable disease was obtained in 27 (25%), 12 (11%) and 67 (63%) respectively (**Table 2**). In this cohort, median duration of IT therapy was 11.3 months, ranging from 6.4 to 22.3 months.

Primary endpoint : intracranial outcome after IT discontinuation

After treatment discontinuation, 41% (n=44) of the 106 patients experienced intracranial relapse upon follow-up. In this subset of patients, subsequent treatment(s) resulted in 22% of response (11% CR,11% PR), 26% of stable disease (n=11) versus 53% of progressive disease (n=23). **Table 3**. All relapsing patients received local treatment by radiotherapy (n=34), surgery (n=3), or a combination of both (n=7), in addition to systemic treatment consisting of anti-PD1 monotherapy for 19 patients, targeted therapy for 14 patients, or chemotherapy for 11 patients.

Results were presented according to the following group analysis: Group 1 included patients who did not experience brain metastases relapse after discontinuing treatment during follow-up, while group 2 included patients who did.

Patients who did not experience intracranial relapse during follow-up (group 1) were slightly older (mean age 60 years, range 53-70) compared to relapsing patients (group 2: 55 years, range 45-65). Most group 1 patients (68%) were treatment-naive whereas patients were almost equally distributed between treatment-naive and receiving a second line or more treatment in group 2 (48% and 52% respectively). Fewer BM were present at treatment implementation in group 1 vs group

2 (mean number 3 and 4,5 respectively) with a lower proportion of patients with more than 10 BM in group 1 (6% vs 16%). Local therapy, including radiotherapy, surgery, or both, was most frequently used in group 1 (83% vs 77%). (**table 1**) Response rate was higher in group 1 than in group 2 (CR/PR 27%/16% vs 23%/5% respectively) whereas an inverse trend was observed for SD (56% vs 73% respectively). (**table 2**)

Secondary endpoints : overall outcome OS, PFS, TFS

After treatment discontinuation, 76% (n=81) of the 106 patients experienced relapse regardless of the site of progression: 22% (n=23) of merely intracranial progression, 35% of extracranial progression only (n=37), and 20% (n=21) of simultaneous progression on both locations. Regarding overall outcome after relapse, a control by subsequent treatment(s) was obtained in 34% of patients (13% CR and 21% PR) versus 28% of stable disease and 38% of progressive disease. **Table 3**

Median OS was 30.9 months (95% CI 21.2–NA) for the entire cohort as shown in **Figure 1**. The overall 6-month survival rate was 75.2% (95% CI: 67.4% to 83.9%), and ongoing survival analyses showed overall 12-month and 24-month survival rates of 70.1% (95% CI: 61.8% to 79.5%), and 56.4% (95% CI :47.3% to 67.3%) respectively. **Table 4**. Median overall survival (OS) was not reached for intracranial non-relapsing patients versus 13.1 months (95% CI:4.1-21.8) for intracranial relapsing patients (**Figure 2**). At 1 and 2 years, OS rate was higher in intracranial non-relapsing patients (83.4%, 95% CI:74.6% to 93.4% and 75.4%, 95% CI: 64.9% to 87.6% respectively) compared to intracranial relapsing patients (51.9%, 95% CI:39.0% to 69.1% and 31.5%, 95% CI:20.0% to 49.6% respectively), with a significant difference between the two groups (p-value <0.05) based on the log-rank test. (**table 4**).

Overall median PFS from first exposure to combination IT was 9.7 months (95% CI:5.6 to 21.8 ; (**figure 3**) with landmark PFS of 57.1% (95% CI:48.3% to 67.4%) and 48.8% (95% CI :40.1% to 59.5%) at 6 and 12 months respectively and an estimated PFS of 38.9% at 2 years (**Table 5**). The Median PFS was not reached in intracranial non-relapsing patients and was approximately 4.4 months (95% CI: 2.9 to 10.8) in intracranial relapsing patients (**figure 4**) with landmark PFS at 6, 12, and 24 months longer in intracranial non-relapsing patients (68.8%, 95% CI: 58.1% to 81.5%; 61.7%, 95% CI: 50.5% to 75.4%; 55.9%, 95% CI: 44.5% to 70.3% respectively), compared to intracranial relapsing patients (40.9%, 95% CI: 28.7% to 58.4%; 31.3%, 95% CI :20.1% to 48.7%; 16.0%, 95% CI: 7.9% to 32.5% respectively) (**table 5**). Additionally, local therapy and line of treatment were significantly associated with PFS (**p <0.001, table 6**).

Overall median TFS was estimated at 10.3 months (95% CI 9.6 to 13) (**figure 5**). The

median TFS for group 1 was 11.3 months (95% CI 9.9 to 16) versus 9.7 months (95% CI 9.2 to 13) in group 2 with no statistically significant difference at 3, 6 and 12 months (log rank test ; p value = 0,2). (figure 6)

A Cox model was used to investigate a possible relationship between outcome (relapse/no relapse) and a number of predefined baseline variables such as LDH rate (normal vs > ULN), percentage of patients achieving CR or not before IT discontinuation, number of metastatic sites (>2 vs ≤2), duration of IT (>1 year vs ≤1 year), , number (>3 vs ≤3) and size of BM (< 3cm versus ≥ 3cm), Braf status (mutated vs wild type), line of treatment (first line vs at least second line), number of dual IT perfusions (≤2 vs >2), times to BOR achievement (≤6months vs >6months), local therapy (performed vs not performed), leptomeningeal involvement (present vs absent), gender (M vs F) and ECOG status (0-1 vs >1). The only significant variable significantly related to intracranial relapse was the size of BM. (TABLE 7).

DISCUSSION

Combination of immune checkpoint inhibitors have emerged as a promising therapeutic approach for the management of metastatic brain melanoma with an intracranial response in 51-56% of MBM patients (14,20). To our knowledge, there are no studies in the literature that have investigated the long-term response of patients with MBM receiving dual immunotherapy after treatment cessation.

Several studies have already demonstrated the long-term efficacy of immunotherapy (without distinguishing between dual ICI and single immunotherapy) after discontinuation due to side effects, disease control, or complete response in patients with metastatic melanoma (with and without brain metastases).

A recent study by Perez et al.(23) evaluated the elective discontinuation of checkpoint inhibitors in patients with metastatic melanoma (extra and intracerebral cofounded) who achieved an overall complete response (two negative scans at three-month intervals were required to stop treatment) with a global relapse rate of only 9% with a median time to relapse of 27.4 months. Other studies have shown relapse rates ranging from 18.5% to 22% (22,26) as reported in the table 11. In a retrospective study investigating the response in patients with metastatic melanoma with and without BM after elective discontinuation of anti-PD1 IT due to complete response, Dimitriou and al. (24) showed a low relapse incidence of only 8% in the overall cohort after a median follow-up of 38 months. Furthermore, a subgroup analysis evaluating the response of MBM patients (n=25) showed that only 12% experienced relapse, either extracranially (n=1) or intracranially (n=2).

Our study revealed a higher relapse rate, with a relapse rate of 76% (n=81/106), including 23 (22%) intracranial, 37 extracranial (35%), and 21 (20%) in both locations. This can be explained by our particular, true-life study population, which included only patients with brain metastases, a population that is known to be more difficult to treat with a poorer prognosis, approximately 60% of our patients discontinued treatment due to side effects, and 63% discontinued treatment with merely stable disease.

According to the above-mentioned studies, the majority of metastatic melanoma patients do not experience relapse after discontinuing immunotherapy, after a median follow-up of 15 to 26 months post-treatment cessation and an unattained median PFS (23,24,26). However, the current study, which only included patients with MBM, revealed a median overall PFS of only 9.7 months for a median follow-up of 20.6 months, which may be explained by the poorer overall prognosis of this population. In contrast, patients who did not experienced brain relapse (group 1) had an unreached PFS and OS compared to those who did (group 2), with a PFS of 4.4 months and OS of 13.1 months in the latter group, suggesting that when patients do not relapse to IC, patients who initially have brain metastases appear to have survival and progression-free survival approaching those with metastatic disease without brain metastases.

However, the 2-year results were less favorable, with an estimated PFS of 56% for group 1 patients, compared to a PFS at 2 years between 71% and unreached in previous studies (22–24,26). This can be explained by the fact that our study targeted MBM patients and that we selected patients with controlled disease (CR, PR, or SD) rather than only patients who achieved a complete response, with a higher percentage of SD, which may lead to a higher likelihood of progression after treatment discontinuation. Indeed our study included more patients with SD and PR (76%) than those in CR (25%). In their study, Perez's an and al.(23) also compared the 46 patients in the study who achieved a complete response (CR) to those who did not achieve a CR (n=86) and continued treatment, showing significantly lower rates in terms of median overall survival and progression-free survival in this population (8.8 months and 5.5 months, respectively), further confirming our hypothesis.

We also determined a TFS rate of 10.3 months. The difference between group 1 and 2 was not significant, with a TFS of 11.3 months and 9.7 months, respectively, which may be explained by the small size of our sample and the proportion of patients with only extracerebral progression (35%). Furthermore, since TFS is defined as the time between the end of treatment and progression, death, or or initiation of new treatment, we can assume that some patients who initially stopped treatment due to adverse events (AE) resumed treatment later after AE resolution despite the absence of disease progression, which could explain the difference with PFS.

All 44 patients experiencing MBM relapse during follow up in our study received local treatment including radiotherapy, surgery, or both, as well as systemic treatment, mainly anti-PD1 or targeted therapy. A response to this further treatment was achieved in 10 (23%) patients (5 CR 5 PR). Dimitriou et al.(24) reported that among the 8% of the overall cohort who experienced disease recurrence, 90% responded to retreatment (dual ICI, anti PD1 monotherapy, local therapy) after a median follow-up of 38 months, but these results should be extrapolated with caution given the small sample size (n=125). In their MBM population, the 2 intracranial relapses received retreatment with anti-PD1 and neurosurgery, which led to renewed disease control. Finally, Jansen and al. (26) reported that 19 out of 40 relapsers (intracranial or extracranial) (48%) were retreated with anti-PD-1, of which 6 (32%) achieved an objective response (complete or partial). Overall, these reports including our study confirm that a response may be achieved in relapsing MBM by a subsequent treatment after first-line therapy, particularly with anti-PD-1. However, larger and specifically designed clinical trials are needed to evaluate the efficacy and safety of these approaches.

The patients in our study display similar characteristics to those reported in the literature (24), including a high rate of local treatment (approximately 80%), limited LDH rates, an overall good general status (ECOG \leq 1) and most of them were treatment-naive (60%). However, the patients were slightly younger on average (58 years vs. 66 years) and had a slightly higher rate of BRAF mutation. Several studies, including a meta-analysis, suggest that the prognosis of patients with MBM may be influenced by several factors, including KPS, LDH rate, MBM number and volume, extracranial tumor burden, and BRAF mutation pattern (27,28). Regarding local intracranial treatments such as surgery, stereotactic radiosurgery, it has been established that their use alone or in combination with immunotherapy improves overall survival in this specific population (29). In our study, only the size of the brain metastases ($>$ 3cm in diameter) was significantly related to intracranial relapse hazard whilst treatment line, leptomeningeal involvement, and number of metastatic sites ($>$ 2) did not appear to statistically IC relapse rate. . Studies assessing potential factors predictive of IC relapse are cruelly lacking. The only ones that have provided information on the subject concern global relapse and not just for intracranial metastases such as Valentin and al.(22) who found no association between relapse and age, sex, elevated LDH, BRAF status, presence of brain metastases, previous treatments, radiotherapy, or duration of anti-PD-1 treatment. In their multivariable analysis, Pokorny and al.(21) found that younger age, a history of brain metastases, and higher post-PD-1 LDH were associated with global recurrence.

A number of methodological limitations have to be acknowledged. First, the retrospective design cannot guarantee the exhaustivity and accuracy of collected data, unlike a randomized

controlled trial. Second, the relatively small sample size might potentially limit the statistical power of the study and its ability to detect significant differences between subgroups especially regarding risk factors of relapse. Additionally, the decision to discontinue anti-PD-1 therapy was based on limiting toxicity or on a shared decision between the physician and patient after a long-term control was obtained, which may introduce selection bias. The lack of a standardized protocol of IC recurrence treatment may have contributed to the variability in outcomes regarding OS analysis. Finally, the median follow-up duration was only 21 months, which may not be sufficient to draw definitive conclusions regarding long-term outcome of these specific patients.

To summarize, this retrospective real-life study provides valuable information regarding the response after discontinuation of IT in melanoma patients with brain metastasis. Dual ITs allow prolonged control of melanoma brain metastases even after IT discontinuation. In case of relapse, second-line treatment, including anti-PD-1, may be effective. Although it is possible to discontinue treatment after achieving a complete response (CR), a prospective, controlled, randomised study evaluating the response after discontinuation of treatment in patients with a complete response to a first-line double ITs is essential to establish clear criteria for discontinuation.

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Table 1: Baseline characteristics of patients at Ipilimumab+Nivolumab treatment initiation

Characteristics	All patients (N=106)	No brain relapse (N=62)	Brain relapse (N=44)
Age, mean (SD) years	58(15)	60(14)	56(15)
—, median (range) years	58(49–68)	60(52–70)	55(45–65)
—, (Min ;Max) ans	(25–87)	(25–87)	(32–77)
Sexe, N (%)			
Female	47(44)	28(42)	19(43)
Male	59(56)	34(58)	25(57)
ECOG, N (%)			
0-1	100(94)	59(95)	41(93)
>=2	6(6)	3(5)	3(7)
LDH>ULN, N (%)			
Yes	36(34)	18(29)	18(41)
No	70(66)	44(71)	26(59)
BRAF mutation, N (%)			
Wild	57(54)	32(52)	25(57)
Mutant	49(46)	30(48)	19(43)
Line of therapy, N (%)			
First-line	63(59)	42(68)	21(48)
2 Second-line or higher	43(41)	20(32)	23(52)
Prior therapy, N (%)			
No prior treatment	63(59)	42(68)	21(48)
APD1 monotherapy	17(16)	8(13)	9(20)
Anti Braf monotherapy	2(2)	2(3)	0(0)
Anti BRaf+Anti MEK	22(21)	9(15)	13(30)
Chemotherapy	2(2)	1(2)	1(2)
Melanoma type, N (%)			
SSM	44(42)	28(45)	16(36)
NM	23(22)	12(19)	11(25)
ALM	3(3)	3(5)	0(0)
Mucosal	2(2)	1(2)	1(2)
Other	34(32)	18(29)	16(36)
Localisation of extracranial metastasis, N (%)			
Nodes	65(61)	34(55)	31(70)
Lung	69(65)	35(56)	34(77)
Skin	39(37)	19(31)	20(45)
Liver	30(28)	15(24)	15(34)
Bones	39(27)	20(32)	19(43)
Digestive system	24(23)	13(21)	11(25)
Muscle	14(13)	9(15)	5(11)
Spleen	7(7)	3(5)	4(9)
Heart	4(4)	2(3)	2(5)
Kidneys	2(2)	2(3)	0(0)
Number of organs affected, N (%)			
0-1	27(25)	20(32)	7(16)
2-3	40(38)	22(35)	18(41)
>=4	39(37)	20(32)	19(43)

Maximum diameter of MBM, N (%)			
<1cm	28(26)	17(27)	11(25)
1-3 cm	24(23)	18(29)	6(14)
>=3 cm	10(9)	10(16)	0(0)
Missing data	44(42)	17(27)	27(61)
Number of MBM, N (%)	3.5(7)	3(6)	4.5(7)
Total, mean (SD) years			
—, median (range) years	2(1–5)	2(1–4)	3(1–9)
0-3	77(73)	47(76)	30(68)
3-10	18(17)	11(18)	7(16)
>=10	11(10)	4(6)	7(16)
Leptomeningeal involvement, N (%)			
yes	8(8)	2(3)	6(14)
Neurological symptoms ,, N (%)			
yes	16(15)	9(15)	7(16)
Local treatment of MBM ,, N (%)			
Radiotherapy	55(52)	29(47)	26(59)
Surgery	8(8)	6(10)	2(5)
Combination	23(22)	17(27)	6(14)
Number Combi IT perfusions, N (%)			
<=2	36(34)	19(31)	17(39)
>2	70(66)	43(69)	27(61)
Reason for discontinuation of IT, N (%)			
Toxicity	60(57)	37(60)	23(52)
Disease control	46(41)	25(40)	21(48)
Median follow up, mean (SD) months	20.8(14.3)	22.6(14.0)	18.7(12.6)
—, median (range) months	20.6(6.7–30.6)	13.8(6.7–32.8)	10.5(7.5–29.4)
Best response time, mean (SD) months	10.6(7.4)	10.0(7.8)	10.0(7.0)
—, median (range) months	7.3(2.8–13.4)	6.5(2.8–15.6)	8.1(2.9–11.2)
Duration of Treatment time, mean (SD) months	15.7(12.3)	16.5(12.6)	14.5(12.1)
— median (range) months	11.3(6.4–22.3)	13.8(6.4–23.6)	10.5(7.1–18.8)

Table 2 : Best response treatment rate

Months	Global Population N (%)	No brain relapse N(%)	Brain relapse N(%)
Best response, N(%) ; CI (95%)			
CR	27(25)	17(27)	10(23)
PR	12(11)	10(16)	2(5)
SD	67(63)	35(56)	32(73)

Table 3 : Characteristics after treatment discontinuation

Characteristics	All patients (N=106)
Relapse after discontinuation, N (%)	
Intracranial	23 (22)
Extra cranial	37 (35)
Both	21 (20)
Local treatment for intracranial progressors, N (%)	
Radiotherapy	34(77)
Surgery	3(7)
Combination	7(16)
Systemic treatment for intracranial progressors, N (%)	
APD1 monotherapy	19(43)
Anti BRAF+Anti MEK	14(32)
Chemotherapy	11(25)
BOR for intracranial progressors, N (%)	
CR	5(11)
PR	5(11)
SD	11(26)
PD	23(53)
ORR	10(22)
OCR	21(48)
BOR global population, N (%)	
CR	14(13)
PR	22(21)
SD	30(28)
PD	40(38)
ORR	36(34)
OCR	66(62)

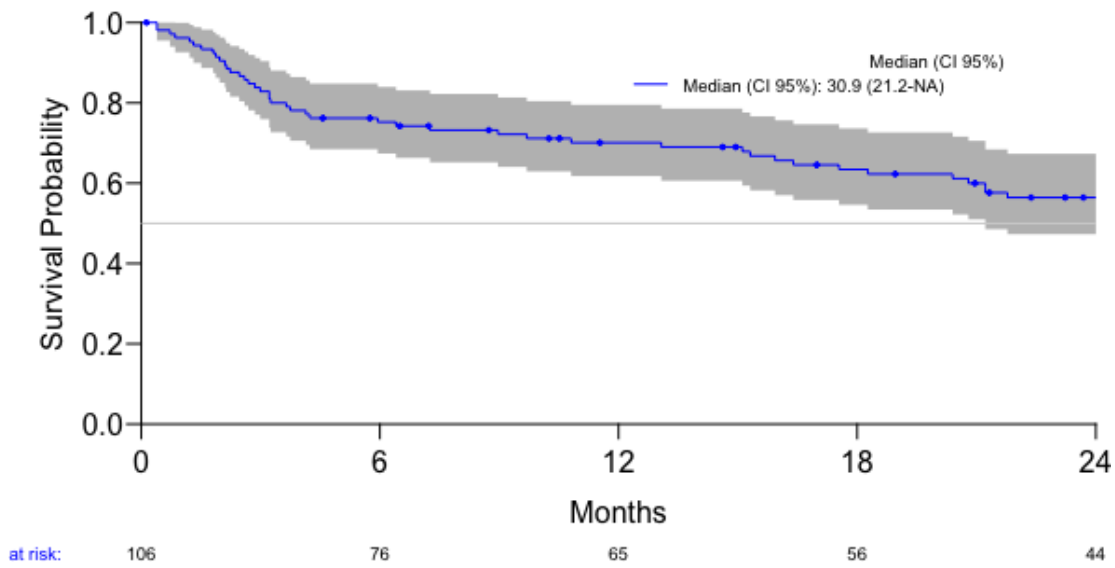


Figure 1 – OS Ipilimumab+Nivolumab

TABLE 4: Ipilimumab+Nivolumab OS estimation

<u>Months</u>	<u>All patients (%) (IC 95%)</u>	<u>Groupe 1(%) (IC 95%)</u>	<u>Groupe 2(%) (IC 95%)</u>
6	75.2(67.4–83.9)	85.2(76.7–94.6)	61.4(48.5–77.6)
12	70.1(61.8–79.5)	83.4(74.6–93.4)	51.9(39.0–69.1)
24	56.4(47.3–67.3)	75.4(64.9–87.6)	31.5(20.0–49.6)

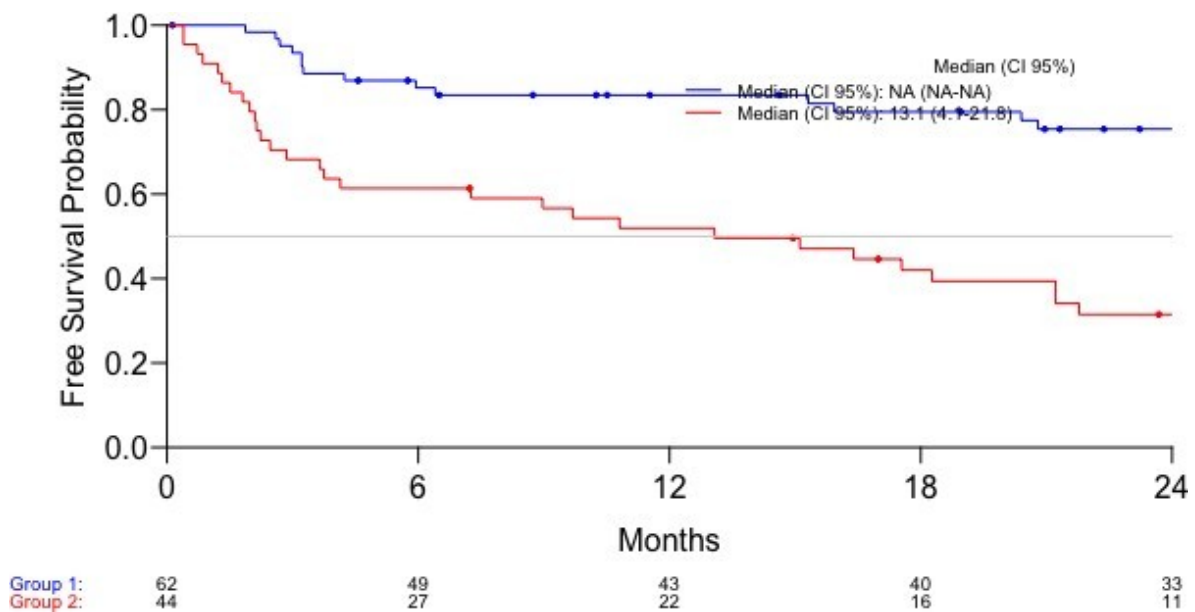


Figure 2 – OS Ipilimumab+Nivolumab/Group

Survival difference between the two groups is calculated according to the log rank test. The p-value is <0.05 . A significant difference in survival between the two groups can therefore be concluded.

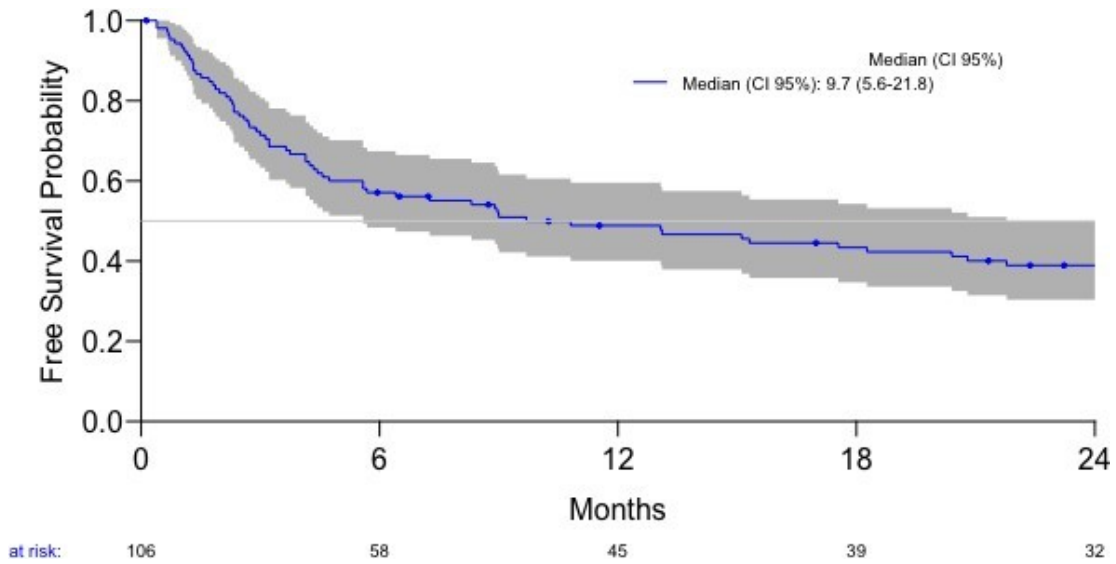


Figure 3 – PFS Ipilimumab+Nivolumab

TABLE 5| **Estimation PFS Ipilimumab+Nivolumab.**

Months	All patients (%) (IC 95%)	Groupe 1(%) (IC 95%)	Groupe 2(%) (IC 95%)
6	57.1(48.3–67.4)	68.8(58.1–81.5)	40.9(28.7–58.4)
12	48.8(40.1–59.5)	61.7(50.5–75.4)	31.3(20.1–48.7)
24	38.9(30.4–49.9)	55.9(44.5–70.3)	16.0(7.9–32.5)

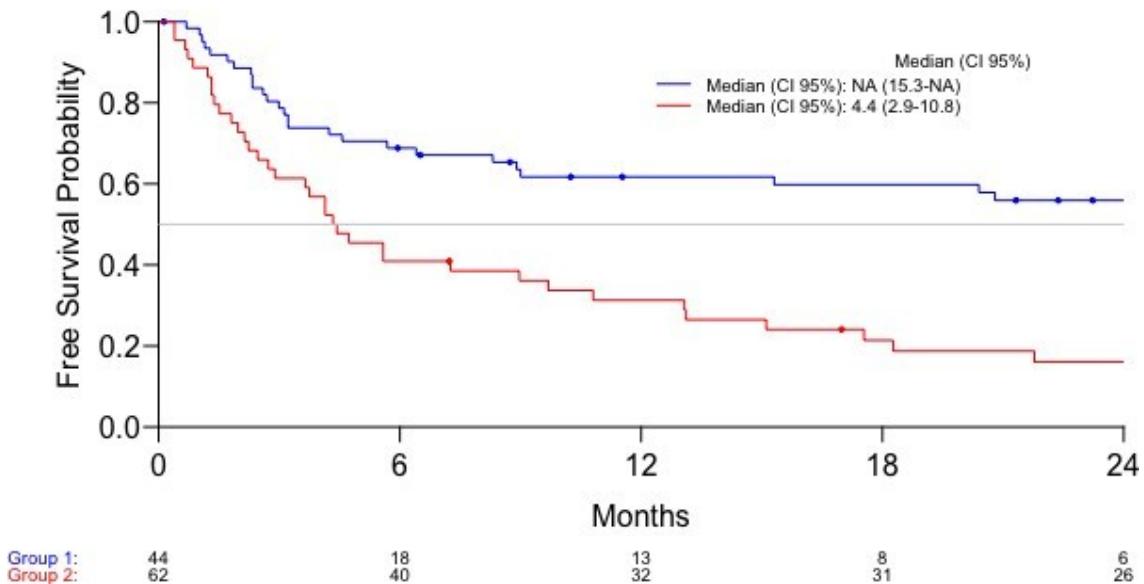


Figure 4 – PFS Ipilimumab+Nivolumab/Group

PFS between the two groups is calculated according to the log rank test. The p-value is <0.05. A significant difference in progression-free survival between the two groups can therefore be concluded.

Table 6 – Cox models specific PFS analyzes

Variables	HR	IC 95(%)	p (effect)
All patients			
<u>Local treatment</u>	2.51	(1.29–4.87)	<0.001
<u>LDH</u>	1.18	(0.75–1.84)	0.48
<u>Number of sites</u>	1.06	(0.98–1.16)	0.15
<u>Duration ICI</u>	1.41	(0.85–2.10)	0.21
<u>Treatment line</u>	2.19	(1.41–3.41)	<0.001
<u>Number of brain metastases</u>	0.88	(0.51–1.49)	0.62
<u>BRAF status</u>	1.04	(0.68–1.61)	0.84
Intracranial progressors			
<u>Local treatment</u>	1.67	(0.65–4.28)	0.29
<u>LDH</u>	1.55	(0.82–2.92)	0.18
<u>Number of sites</u>	0.93	(0.83–1.05)	0.25
<u>Duration ICI</u>	1.18	(0.88–1.92)	0.19
<u>Treatment line</u>	1.05	(0.57–1.94)	0.88
<u>Number of brain metastases</u>	1.35	(0.67–2.72)	0.39
<u>BRAF status</u>	1.18	(0.63–2.18)	0.61

Pre-defined variables : - local treatment (yes/no) - LDH: normal /> ULN -CR: yes/no - Number of sites : >2/<=2 - Duration IT: >1 year/<=1 year - Line of treatment: 1st/>1 - Number of cerebral metastases: >3/<=3 - Braf: mutated/wild type. There are not enough events to analyze the following variables : leptomeningeal, symptomatic and diameter of the cerebral metastasis. The proportionality over time was studied for all the variables. Any variable <0.05 is considered significant

The only significant variables are for the global population : local treatment and first-line treatment

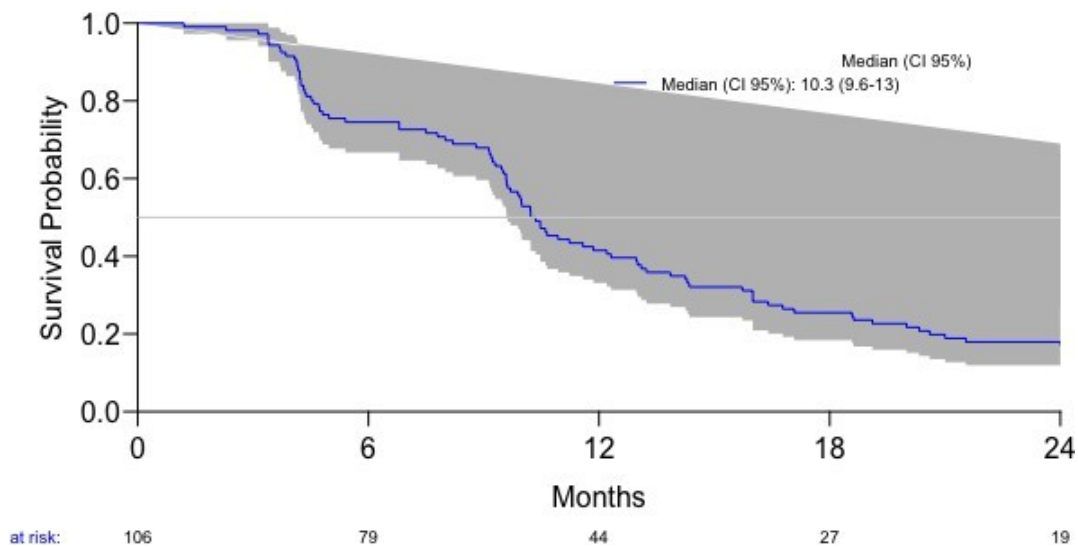


Figure 5 – TFS Ipilimumab+Nivolumab

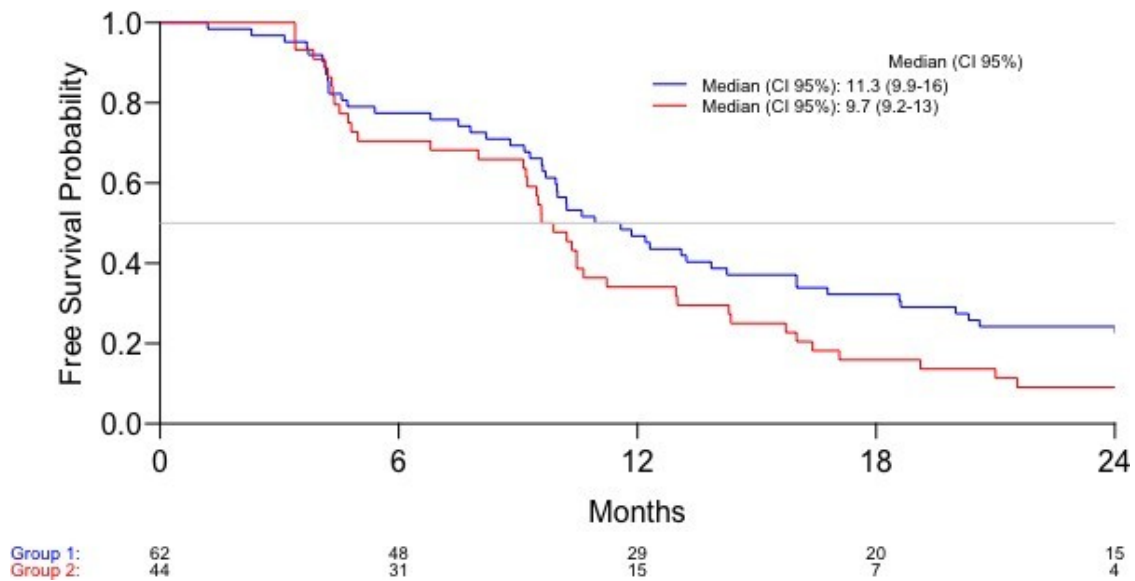


Figure 6 – TFS Ipilimumab+Nivolumab/Group

The difference in survival between the two groups is calculated using the log rank test. We obtain a p-value of 0.2 . We cannot therefore conclude that there is a significant difference in progression-free survival between the two groups.

Table 7 : Analysis of differences in predetermined baseline variables between group 1 et 2

Variables	P value
Gender (male/female)	0.99
ECOG (0-1 vs >2)	0.69
LDH (Normal vs > ULN)	0.29
BRAF status (mutated vs WT)	0.74
Numbers of metastatic site (≤ 2 vs > 2)	0.09
Local therapy (surgery or radiotherapy)	0.55
Number of MBM	0.52
MBM size	0.001
Leptomeningeal involvement	0.05
Treatment duration (≤ 1 year vs > 1 year)	0.56
Combi IT as first line of therapy	0.05
Number of Combi IT perfusions (≤ 2 vs > 2)	0.30
Response ≤ 6 months vs > 6 months	0.71
CR vs SD or PR	0.77

TABLE 8: Estimation TFS Ipilimumab+Nivolumab.

Months	All patients (%) (IC 95%)	Groupe 1(%) (IC 95%)	Groupe 2(%) (IC 95%)
6	74.5(66.7-83.3)	77.4(67.7-88.6)	70.5(58.2-85.3)
12	41.5(33.1-52.0)	46.8(35.9-61.0)	34.1(22.6-51.4)
24	17.9(11.9-26.9)	24.2(15.6-37.6)	9.1(3.6-23.1)

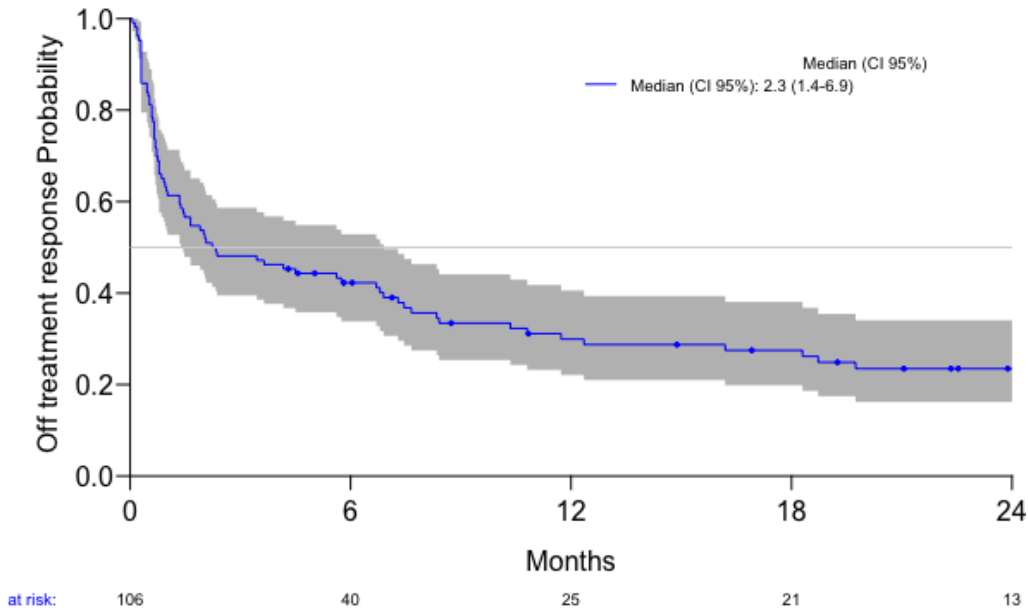


Figure 7 – OTRt Ipilimumab+Nivolumab

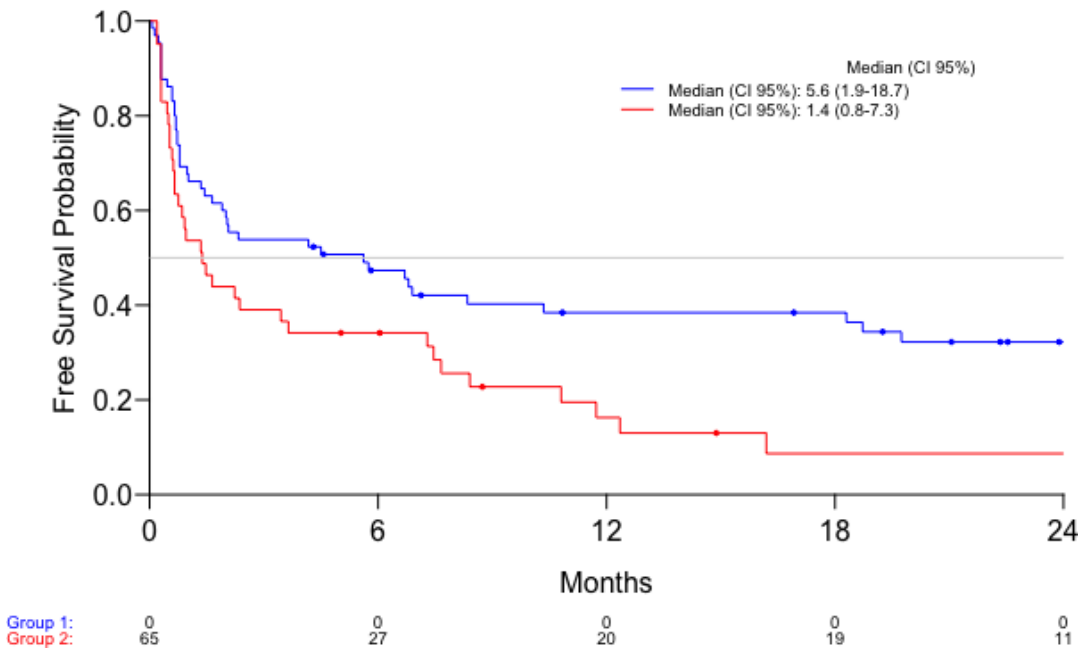


Figure 8 – OTRt Ipilimumab+Nivolumab/Group

The difference in survival between the two groups is calculated using the log rank test. We obtain a p-value of 0.01 . We can therefore conclude that there is a significant difference in progression-free survival between the two groups.

Table 9 : OTRt estimate Ipilimumab+Nivolumab.

<u>Months</u>	<u>All patients (%) (IC 95%)</u>	<u>Groupe 1(%) (IC 95%)</u>	<u>Groupe 2(%) (IC 95%)</u>
6	47.3(36.6-61.3)	58.1(45.1-74.9)	22.7(10.5-49.1)
12	38.4(28.0-52.7)	50.2(37.0-68.0)	18.2(7.5-44.1)
24	32.2(22.2-46.9)	41.3(28.4-60.1)	9.1 (2.4-34.1)

Table 10 - Cox models specific OS analyzes

<u>Variables</u>	<u>HR</u>	<u>IC 95(%)</u>	<u>p (effect)</u>
<u>All patients</u>			
<u>Local treatment</u>	2.46	(0.98-6.17)	0.06
<u>LDH</u>	1.46	(0.86-2.47)	0.16
<u>Number of sites</u>	1.14	(1.01-1.27)	0.03
<u>Duration ICI</u>	1.60	(0.88-2.16)	0.12
<u>Treatment line</u>	1.93	(1.14-3.24)	0.01
<u>Number of brain metastases</u>	0.70	(0.37-1.36)	0.30
<u>BRAF status</u>	0.96	(0.57-1.61)	0.9
<u>Intracranial progressors</u>			
<u>Local treatment</u>	2.63	(0.92-6.67)	0.10
<u>LDH</u>	1.59	(0.81-3.13)	0.18
<u>Number of sites</u>	1.03	(0.90-1.17)	0.69
<u>Duration ICI</u>	1.40	(0.85-2.32)	0.11
<u>Treatment line</u>	1.06	(0.54-2.08)	0.86
<u>Number of brain metastases</u>	0.65	(0.29-1.43)	0.28
<u>BRAF status</u>	0.84	(0.43-1.64)	0.61

Pre-defined variables: - local treatment (yes/no) - LDH: normal /> ULN -CR: yes/no - Number of sites : >2/<=2 - Duration IT : >1 year/<=1 year - Line of treatment: 1st/>1 - Number of cerebral metastases: >3/<=3 - Braf: mutated/wild type. There are not enough events to analyze the following variables: leptomeningeal, symptomatic and diameter of the cerebral metastasis. The proportionality over time was studied for all the variables. Any variable <0.05 is considered significant

The only significant variables are for the global population: the number of affected sites and the treatment by first line

Table 11 : Studies comparison

	PEREZ et al. n=46	DIMITRIOU et al. n =125	JANSEN et al. n=185	VALENTIN et al. n=65	Notre étude n=106
Target population	MM	MM	MM	MM	MBM
Reason for stopping IT	CR	CR or AE with a CR	Lack of progression or toxicity	3 groups : 1) CR, 2) EI, 3) SD/PR	Controlled disease (CD)
Overall relapse rate (%)	9%	8%	22%	18,5% 1) CR : 12% 2) EI : 25% 3) SD/PR : 16,5%	76%
Median time to relapse (months)	27 m	37 m	12 m	9 m 1) CR : 9,3m 2) EI : 7,1m 3) SD/PR : 11,9m	9,9 m
Time in treatment (months)	9,6 m	2-22 m	12 m	1) CR, 16,8m 2) EI, 7,2 m 3) SD/PR 21,2m	11,3 m
OS at 2 years	100%	NR	NC	NC	56 %
Relapse rate IC		8%			41%

MM: metastatic melanoma; MBM: melanoma with brain metastasis; CR: complete response; PR: partial response; SD : stable disease; AE: adverse events; DC: disease control; NR: not reached; NC: not communicated

SERMENT

- *En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Être suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.*

- *Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.*

- *Admise dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

- *Respectueuse et reconnaissante envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

- *Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couverte d'opprobre et méprisée de mes confrères si j'y manque.*

ABSTRACT

Background and purpose : Patients with melanoma brain metastases (MBM) represent a particular group in terms of treatment response and survival. Dual immunotherapy (IT) combining anti-CTLA4 and anti-PD1 is increasingly used in these patients as it can allow for long-term control which may lead to treatment discontinuation. However, little data is available regarding the duration of response after IT discontinuation, the subsequent evolution of brain metastases, factors associated with intracranial relapse, response to second-line treatments in case of relapse, and overall survival. Our objective was to collect corresponding data in a real-life setting using the French national database MELBASE.

Patients and Methods : This national retrospective real-life study included 106 MELBASE patients with MBM treated with dual IT who discontinued IT after disease control. The following data were analyzed: patient and disease characteristics at introduction of dual IT, intracranial relapse rate after discontinuation (primary endpoint), profile of non-relapsing vs relapsing patients, overall relapse rate, response to second-line treatment in case of intracranial relapse, factors associated with intracranial relapse, overall survival (OS), progression-free survival (PFS), and treatment-free survival.

Results : The median duration of treatment was 11.3 months (6.4-22.3 months) with a median follow-up of 20.6 months (6.7-30.6 months). The intracranial relapse rate was 41% vs an overall relapse rate of 76%. 48% of intracranial relapsers were controlled (CR, PR or SD) by subsequent treatment including resumption of IT. 2-years OS and PFS were estimated at 56.4% and 38.9% respectively for the entire cohort. The median PFS for group 1 (no brain relapse, n=62) was not reached, while it was 4.4 months (95% CI: 2.9-10.8) for group 2 (brain relapse, n=44). Only the size of brain metastases was statistically associated with the occurrence of intracranial relapse (Cox model).

Conclusion : Dual IT allows sustained control of melanoma brain metastases, even after IT discontinuation. In case of relapse, second-line treatment, including anti-PD-1, can be effective with an overall response rate of 22% and a control rate of 48%.

Keywords : melanoma, MBM, IT, immunotherapy, combined IT, anti PD1, Ipilimumab, relapse

RESUME

Contexte : Les patients avec métastases cérébrales de mélanome constituent un groupe particulier en termes de réponse au traitement et de survie. La double immunothérapie (IT) associant anti CTLA4 et anti PD1 est de plus en plus utilisée chez ces patients car elle peut permettre un contrôle à long terme ce qui peut amener à l'arrêt du traitement. Cependant, peu de données sont disponibles concernant la durée de la réponse après arrêt de l'IT, l'évolution ultérieure des métastases cérébrales, les facteurs associés à la rechute intra-crânienne, la réponse aux traitements de deuxième intention en cas de rechute et la survie globale. Notre objectif était de recueillir les données correspondantes dans un contexte de vie réelle à l'aide de la base de données nationale française MELBASE.

Patients et méthodes : Cette étude rétrospective nationale en vie réelle a porté sur 106 patients de MELBASE avec métastases cérébrales, traités par double IT et ayant arrêté l'IT après contrôle de la maladie. Les données suivantes ont été analysées : caractéristiques des patients et de la maladie à l'introduction de la double IT, taux de récurrence intracrânienne après arrêt (critère principal), profil des patients non rechuteurs vs rechuteurs, taux global de rechute, réponse au traitement de seconde ligne en cas de rechute intracrânienne, facteurs associés à la rechute intra-crânienne, survie globale (SG), survie sans progression (SSP) et survie sans traitement.

Résultats : La durée médiane du traitement était de 11,3 mois (6,4-22,3 mois) avec une médiane de suivi de 20,6 mois (6,7-30,6 mois). Le taux de rechute intracrânienne était de 41% vs un taux global de rechute de 76 %. 48% des rechuteurs intracrâniens ont été contrôlés (CR, PR ou SD) par un traitement ultérieur notamment la reprise d'une IT. SG et SSP à 2 ans ont été estimées à 56,4 % et 38,9 % respectivement pour l'ensemble de la cohorte. La SSP médiane pour le groupe 1 (pas de récurrence cérébrale n=62) n'a pas été atteinte alors qu'elle était de 4.4 mois (IC à 95 % : 2.9-10,8) pour le groupe 2 (rechute cérébrale, n = 44). Seule la taille des métastases cérébrales était statistiquement associée à la survenue d'une rechute intracrânienne (modèle de Cox).

Conclusion : La double IT permet d'obtenir un contrôle prolongé des métastases cérébrales de mélanome y-compris après arrêt de l'IT. En cas de rechute un traitement de seconde ligne notamment par anti-PD-1 peut être efficace avec un taux de réponse global de 22% et un taux de contrôle de 48%.

Mots clés : mélanome, MBM, IT, immunothérapie, double IT, anti PD1, Ipilimumab, rechute