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La régression histologique du mélanome au diagnostic constitue-t-elle un facteur de bonne réponse à l'immunothérapie en 1ère ligne métastatique ?

Jean-Baptiste Such

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UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Par

SUCH, Jean-Baptiste

Présentée et soutenue publiquement le 07/10/2022

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Dermatologie et Vénérologie

Chef de service de Dermatologie du CHU Estaing, Clermont-Ferrand

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Chef de Clinique des Universités-Assistant Hospitalier

Dermatologie et Vénérologie

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Professeur des Universités – Praticien Hospitalier
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Anatomie Pathologique
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Praticien Hospitalier
Dermatologie et Vénérologie
Service de Dermatologie du CHU Estaing, Clermont-Ferrand

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LISTE DES ABREVIATIONS

ALM : Acral Lentiginous Melanoma
APC : Antigen-Presenting Cell
AJCC : American Joint Committee on Cancer
BAP1 : Breast cancer Associated Protein 1
BI : Breslow Index
BRAF : B-Raf proto-oncogene
BWS : Blue White Scar
CDK4 : Cyclin-Dependent Kinase 4
CDKN2A : Cyclin-Dependent Kinase inhibitor 2A
CR : Complete Response
CTLA4 : Cytotoxic T-Lymphocytes Associated protein 4
DP : Disease Progression
ECOG : Eastern Cooperative Oncology Group
HLA : Human Leukocyte Antigen
HR : Histological Regression
ICI : Immune Checkpoint Inhibitor
IrAEs : Immune-related Adverse Events
LDH : Lactate Deshydrogenase
LMM : Lentigo Maligna Melanoma
LND : Lymph Node Dissection
MAP : Mitogen-activated Protein
MART : Melanoma Antigen Recognized by T-cells
MC1R : MelanoCortin 1 Receptor
MHC : Major Histocompatibility Complex
MITF : Melanocyte Inducing Transcription Factor
MLM : Mucosal Lentiginous Melanoma
NGS : Next Generation Sequencing
NK : Natural Killer
NM : Nodular Melanoma
NRM : Non Regressive Melanoma
OPM : Occult Primary Melanoma
OS : Overall Survival
PD1 : Programmed cell Death 1
PDL1 : Programmed cell Death Ligand 1
PFS : Progression-Free Survival
PR : Partial Response
RM : Regressive Melanoma
SD : Stable Disease
SLN : Sentinel Lymph Node
SSM : Superficial Spreading Melanoma
TIL : Tumor-Infiltrating Lymphocytes
UVR : Ultraviolet Radiation
VGP : Vertical Growth Phase

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I. Introduction

In 2020 in France, primary cutaneous melanoma accounts for more than 3 % of all cancers with 16449 new cases. (1) For the last decades, it has become one of the most rapidly growing cancers worldwide, with a consistent increase of incidence in Caucasian populations (2), probably related to recreational behaviour and sun exposure and specifically Ultraviolet Radiations (UVR).

Even though melanoma is much less frequent than cutaneous carcinoma (as it only represents < 5% of all cutaneous malignancies), it is one of the deadliest cutaneous tumors, responsible for 2125 deaths in France in 2020 (90% of deaths by skin cancer) (1). Meanwhile, the arrival of therapies targeting the MAP-kinases pathway or targeting two immune inhibitor checkpoints (CTLA 4 and PD1) has revolutionized therapeutic care in onco-dermatology.

Survival prognostic markers for primitive melanoma are mostly histological. Tumor thickness according to Breslow is the best indicator, combined with the presence or absence of ulceration (3). Histological regression (HR), which occurs in 10-35% of cases, is one of the other histological prognostic markers assessed on each melanoma. (4) It has been defined by Smoller et al. as “a partial host response to a malignant neoplasm, resulting in focal diminution of the process”. (5) Tumor regression probably results from an immune-mediated response of activated T lymphocytes directed against tumor antigens. (6) Even though HR suggests an antitumoral immune response, it could lead to underestimate Breslow index, hampering its prognostic interpretation. However, recent studies have highlighted that regressive melanomas are associated with a lower risk of metastatic sentinel lymph node (7), and that local regressive melanomas (stages I and II of AJCC) (8) and regressive melanomas with metastatic lymph nodes (stage III of AJCC) (9) would have a better prognosis.

Moreover, one of the other histologic criteria systematically studied on each melanoma is the « tumor-infiltrating lymphocytes (TIL) phenomenon »: it describes the lymphocyte infiltrate inside the tumor compartment and is categorized on the topography and the amount of the infiltrate. Primitive cutaneous melanomas concerned by TIL (and more particularly the “brisk” subtype) have shown a best survival rate (10) (11) (12) and TIL has even been described as a prognostic factor in metastatic melanomas. (13). Tumor infiltration by lymphocytes and

regression share a lot of similarities. Thus, we can consider TIL and regression as a spectrum of the same active immune system able to react against cancer cells. (14)

Furthermore, it has been reported that the risk for the development of vitiligo among melanoma patients can be considered 10-fold higher than in the general population (15), probably because of an immune response directed towards an antigenic target shared by both normal and tumoral melanocytes. The immune response responsible for vitiligo's clinical lesions also shares common points with the immune response associated with regression. (14) and vitiligo-like reaction are associated to a stronger immune response in melanoma patients under treatment for metastatic disease(16).

All these elements suggest that regression could play a role in the response to immunotherapy in metastatic melanomas.

In this thesis work, after a review of the literature on these different phenomena, we have tried to address the question of the relevance of regression as a prognostic factor in first-line immunotherapy in metastatic melanoma patients. To answer this question, we conducted a retrospective monocentric study at the Clermont-Ferrand University Hospital from January 2015 to June 2021 comparing 3 groups of patients: patients with a non-regressive melanoma (NRM), patients with a regressive melanoma (RM) and patients with an occult primary melanoma (OPM). Our primary outcome was progression-free survival, and our secondary endpoints were the response on imaging performed at 3 and 6 months. Finally, we compared our results to those already published in the literature.

II. State of the art

1. Melanoma

1.1 Definition

Melanoma is a malignant tumor that develops at the expense of melanocytes, the cells that produce melanin, which is responsible for the pigmentation of the skin.

The role of sun exposure in melanoma has been established on multiple arguments from descriptive epidemiological studies and numerous case-control studies (17): geographical (increased incidence with decreasing latitude), phenotypic (increased risk in Caucasian or fair-skinned subjects), clinical (higher risk in individuals with lesions considered to be indicators of actinic damage), and anatomical (higher risk in exposed areas) data.

Family predisposition and genetic factors are at least as important as UVR. Most of the identified phenotypic risk factors (fair pigmentation, poor tanning ability, multiple naevi, clinically atypical or dysplastic naevi and freckling) are genetically transmitted (18), (19)

1.2 Diagnosis

It is performed by the pathologist. The removal of the suspected lesion should ideally be complete to allow the best analysis.

In most cases, the pathologist will easily identify the melanocytic nature of the lesion, otherwise immunohistochemistry can rectify the diagnosis. Indeed, some cytoplasmic (HMB45, melan A/MART 1, S100) and nuclear (SOX 10, S100) markers will confirm the melanocytic nature of the lesion.

The subsequent affirmation of malignancy is based on architectural criteria (asymmetry of the lateral limits of the tumor, poor limitation of the lesion).

The analysis from the surface to the depth will allow to study the junctional activity (lentiginous proliferation, invasion of the superficial layers of the epidermis by isolated tumor cells (pagetoid ascension), thecal proliferation), the dermal component (absence of progressive

morphological gradient of the cells towards the depth in case of dermal component) and a possible stromal reaction (fibrosis, lichenoid inflammation).

By zooming in on the lesion, it will allow the study of cytological criteria of malignancy (anisocytosis, anisocariosis, high mitotic index). Immunohistochemistry and molecular analysis can sometimes refine the diagnosis.

At the end of the pathologist's analysis, and in correlation with the clinical description, the melanoma will then be classified according to one of the five main histological subtypes with, in order of frequency: superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), nodular melanoma (NM), acral lentiginous melanoma (ALM) and mucosal lentiginous melanoma (MLM).

Melanoma can also be labelled "unclassifiable": indeed, knowing that it is the lateral intraepidermal component that allows us to type a melanoma, when there is lateral regression then we can no longer type the melanoma.

1.3 Prognosis

In the primary tumor stage, prognostic markers are mainly histological. Among them, the **Breslow index (BI)**, which is the measurement with a micrometric ocular of the maximum thickness between the granular layer of the epidermis and the deepest tumor cell, is the most important. There is an almost linear correlation between thickness and mortality. The presence or absence of primary tumor **ulceration** (focal interruption of the epidermis with exposure of the deep epidermal cell layers or exposure of dermis) is the second most powerful predictor of survival. It has also been highlighted that the survival for patients with ulcerated melanomas diminished to a level equivalent to that for thicker melanomas that were not ulcerated. (3) As those two histological criteria (BI and ulceration) are the strongest prognostic factors, they are both included in the prognostic classification of the American Joint Committee on Cancer (AJCC). **The mitotic index** (number of mitoses per mm² of tumor surface), an also well-known prognostic factor, has been removed from the last update of the AJCC classification. Other criteria are routinely described on a pathology report but their prognostic role is not consensual and

therefore are not yet included in prognostic classifications: this concerns TIL and regression, which will be discussed in detail in sections I.4.1 and I.4.2.

At the stage of transit and/or regional lymph node metastases, the time to relapse is generally short (median <1 year). The number of affected nodes and the existence of a capsular rupture are the most pejorative markers.

At distant metastatic stage, several kinetics of disease are observed. If the median survival without treatment is estimated between 6 and 9 months, there are clearly different evolution course. (20) Some patterns (threatening brain metastases, serum LDH concentration $>3 \times$ upper limit of normal, a rapid decline in performance status or organ function, a rapid increase in the number and size of visceral metastases between two scans two months apart) will be those of explosive growth disease. On the other hand, a minority of patients are in a very slow evolutionary scenario, spontaneously achieving a chronic metastatic disease with a very prolonged spontaneous survival. Between these two extremes, most of patients are in an intermediate scenario with various localizations that undoubtedly progress but without true explosion between two imageries 3 months apart, often with normal or subnormal LDH levels.

1.4 Treatment

At the stage of primary tumor, the essential therapeutic gesture is the surgical removal which will be done in two steps. A first excision with minimal macroscopic margins to confirm the diagnosis and assess the main histopronostic criteria. Then, depending on the Breslow index of the tumor, an extended resection will be performed with consensual surgical margins.

At the stage of in-transit metastases or at the oligometastatic stage, several locoregional methods can be used to keep the disease under control before systemic medical treatments: surgery, stereotactic radiotherapy and local immunotherapies can be used. (viral vaccines such as talimogene laherparepvec).

At the stage of lymph node macrometastases, surgical lymph node dissection is the key treatment. At this stage, the *B-RAF* mutation status should be investigated to guide the choice of adjuvant systemic therapy.

At the distant metastasis stage, management has changed dramatically since the advent of therapies targeting the MAP-kinase pathway and immunotherapies targeting CTLA4 and PD1.

Targeted therapies are reserved for patients with tumors with a V600 mutation in the *B-RAF* gene. The *B-RAF* gene mutation is at the origin of the activation of an enzymatic cascade (MAP-kinase pathway), which ultimately leads to tumor cell proliferation. Currently, the therapeutic strategy is to target the enzymatic cascade at two different levels, by combining two molecules: a B-RAF inhibitor and a MEK-inhibitor.

Immunotherapy, on the other hand, can be prescribed as first-line therapy to any patient with metastatic melanoma, regardless of the mutation status of their tumor. A combination of factors (general condition of the patient, comorbidities, speed of progression of the disease, etc.) will determine the preferred choice between targeted therapy and immunotherapy for patients with B-RAF mutation.

As this thesis work concerns patients with metastatic melanoma who have received immunotherapy as a first line of treatment, we will discuss this therapeutic option in greater detail in the following paragraph.

2. Immunotherapy

Melanoma is one of the most immunogenic tumors due to its high mutational burden (21), explaining the preponderant role of the immunotherapy in the therapeutic strategy.

2.1 Immunosurveillance concept

During the tumor genesis, both cell proliferation and apoptosis are associated to the immune editing that includes inter-connected phases as, elimination of tumor cells based on immunosurveillance, equilibrium between tumor and immune cells, and escape or immune evasion. (22)

The first phase of “elimination” is largely mediated by cytotoxic lymphocytes in response to the immune response induced by the recognition of "non-self" antigens expressed on the surface of cancer cells.

The second phase of “equilibrium” is mostly characterized by a quiescence during which either proliferation or expansion of cancer cells are counterbalanced by the adaptive immune system.

The third phase of “escape” is characterized by the selection of resistant variants and the escape of the immune system which depends on the exhaustion of the immunosurveillance as well as on the activation of events that disable the immune-mediated recognition of malignant cells (= tolerance). The functional exhaustion of the immune system depends on the persistent antigen exposition by melanoma cells and induces **the hyper activation of inhibitory checkpoints on immune cells** as result of a negative feedback for the cytotoxic T-cells. Simultaneously, both enrichment of the melanoma environment with regulatory cells and the overproduction by melanoma cells of negative modulators of immune cells (adenosine, tumor necrosis factor- β , vascular endothelial growth factor) promote immune tolerance. (23)

The current strategy to treat melanoma with immunotherapy is to block some of these immune checkpoints with monoclonal antibodies called immune checkpoint inhibitors (ICI) and which target inhibitory receptors present on the surface of lymphocytes: Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4) and Programmed cell Death 1 receptor (PD-1).

2.2 Mechanism of action

2.2.1 Anti CTLA- 4: ipilimumab

After picking up one of the tumor antigens, the antigen-presenting cell (APC) migrates from the tumor microenvironment via the lymphatic network to a lymph node: this APC expresses a B7 receptor that binds to its CTLA-4 receptor on the T cell present in the lymph node and sends an immune tolerance message. (*Figure 1*)

By blocking the CTLA-4 receptor, ipilimumab restores antigenic stimulation and prevents immune tolerance by acting on the initial phase in lymphoid organs upstream of the immune response.

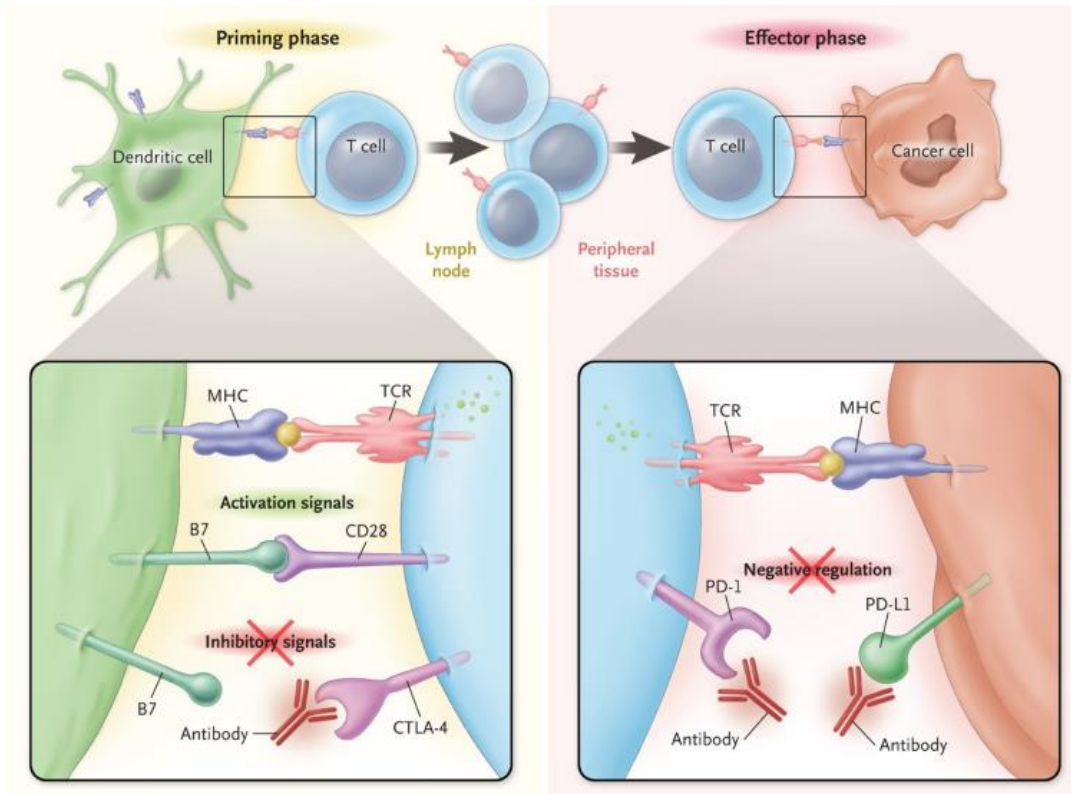


Figure 1 - Mechanisms of action of anti CTLA-4 and anti PD-1 according to Ribas A et al.

2.2.2 Anti PD-1: nivolumab and pembrolizumab

The effector T cell activated upstream in the lymph node expresses PD1. By binding to a tumor cell that expresses PDL1, the tumor cell inactivates the T cell and blocks its anti-tumor response. (Figure 1)

Thus, nivolumab and pembrolizumab act in the effector phase in peripheral tissues by blocking PD1, allowing T cells to regain their role in detecting and destroying cancer cells.

2.2.3 Efficiency

The Checkmate 066 study (24), (25) conducted on previously untreated patients with metastatic melanoma showed at 5 years that the overall rate of survival was 39% in the nivolumab group, as compared with 17% in the dacarbazine group and the progression-free survival rates were 28% with nivolumab and 3% with dacarbazine which was the classic chemotherapy used before the arrival of new generation therapies. The median progression-free survival was 5.1 months with nivolumab and 2.2 months with dacarbazine.

The Keynote 006 study (26), (27) conducted on previously untreated patients with metastatic melanoma, receiving either pembrolizumab or ipilimumab showed respectively a five-year overall survival of 38.7% and 31%. The median progression-free survival was 8.4 months and 3.4 months respectively.

As for the Checkmate 067 study (28),(29), the overall survival rate at 5 years was 52% in the nivolumab-plus-ipilimumab group and 44% in the nivolumab group, as compared with 26% in the ipilimumab group. The median progression-free survival was 11.5 months in the nivolumab-plus-ipilimumab group, 6.9 months in the nivolumab group, and 2.9 months in the ipilimumab group.

2.3 Immune-Related Adverse Events (irAEs) to immunotherapy

Although immunotherapy is targeting a specific action mechanism and therefore is better tolerated compared to common chemotherapy, it has been associated with the emergence of a new panel of dysimmune toxicities called irAEs. (30), (31)

By blocking the pathways that regulate the immune system, ICIs can increase the immune system's activity, causing organ inflammation and thus increasing the risk of irAEs that can potentially involve any organs or systems, including the skin (vitiligo, lichenoid eruption, maculopapulous rash, bullous dermatitis, induced lupus, ...).

2.4 Predictive factors of response to immunotherapy

When these ICI are effective, remission or even cure can be achieved. Reasons why some patients respond, and others do not, remain largely unclear.

Even more intriguing is the long tail of survivors on Kaplan-Meier curves: why do some patients, in addition to responding, achieve complete and sustained remissions, while others show only partial responses? To date, multiple molecular, biological, and clinical biomarkers have been proposed as correlates of immunotherapy success, but the mechanisms that explain why some melanomas respond to treatment and others do not remain incompletely understood.

The response to immunotherapy depends on many factors that fall into three main categories:

- those associated with melanoma cells;
- those linked to the tumor and its microenvironment;
- and those classified as individual features of the patient (biological and clinical).

The first category comprises expression of PD-L1, and HLA proteins on melanoma cells as well as genetic/genomic metrics such as mutational load. (32) Indeed, patients with tumor cells overexpressing PDL1 seem to respond better to immunotherapy and in a more durable way (33) for both anti PD1 and, less intuitively, for anti CTLA4. (34) Moreover, elimination of tumor cells by the immune system takes place upon recognition of their oncogenic peptides in the context of HLA proteins (MHC system). This process is strictly dependent on the presence of tumor-specific antigens, which appears on tumor cells due to the mutational process. A lack or a low number of these neoantigens can be caused by a low number of mutations in tumor cells, while a high number of mutations (>10/Mb) increases the chance of the appearance of new epitopes recognizable to the immune system. Tumor mutational burden may have predictive capacity in melanoma immunotherapy (35), (36), but obviously this is not the only factor affecting anti-tumor response. Equally important is the capacity for presentation of neoantigens by the MHC system. The number of mutations and neoantigens potentially recognized by immune cells may be irrelevant if the antigen-presenting system does not work properly. Down-regulating MHC I is one

tumor survival strategy that could feasibly detract from the efficacy of checkpoint blockade. Consequently, the decreased expression of HLA proteins and/or genes regulating antigens presentation correlates with a worse prognosis and a decreased response to immunotherapy. (37)

The second category is the inflammatory status of the tumor. The response to immunotherapy depends also on the immune cells existing in tumor microenvironments such as lymphocytes, macrophages, dendritic cells, and myeloid derived suppressor cells. Tumors can be divided into three types depending on their immune topographies: (i) "hot" ("inflamed"), with a high infiltration of immune cells, (ii) "cold" ("non-inflamed"), with a low amount of immune cells and (iii) "excluded", with a high density of immune cells outside of the tumor and a low density inside. (38) Melanoma has been historically considered as an immunogenic malignancy and the presence of tumor infiltrating lymphocytes (TILs), defined as a polymorphic group composed mainly by effector T lymphocytes, regulatory T lymphocytes, natural killer (NK) cells, dendritic cells, and macrophages is a well described favorable prognostic factor, as we will see later. However, the usefulness of the presence of immune cells in the tumor in predicting the clinical benefits of immunotherapy has not been fully elucidated so far. It seems that patients receiving anti-PD-1/PD-L1 immunotherapy and with a higher abundance of CD8⁺T cells at the invasive margin are better responders. (39) Nevertheless, further studies are needed to validate these observations.

The third category comprises biological and clinical features of the patient. Indeed, it seems essential in clinical practice to be able to identify biological and clinical markers (easily accessible compared to the molecular markers described above) that could help us anticipate the therapeutic response under immunotherapy. A study conducted on more than 600 patients with unresectable stage III or stage IV melanoma showed a better response to pembrolizumab (anti PD1 immunotherapy) in patients with lower serum LDH levels, higher relative lymphocytes counts and higher relative eosinophile counts. (40) Comparable results have also been described with ipilimumab (anti CTLA4 immunotherapy). (41) The study conducted on patients with pembrolizumab also shown that patients with unresectable stage III disease or metastases located to distant lymph nodes or lung had a significant longer overall survival as compared to

patients with other visceral metastases. (40) Ribas et al. also showed a better response to pembrolizumab in patients with a smaller baseline tumor size. (42) As for the role of vitiligo, it is further detailed in section I.4.3.3.

3. Regression, TIL and vitiligo

3.1 Regression

3.1.1 Definition

When we refer to regression within a melanocytic lesion, it implies a "regression of the melanoma", which is characterized by a spontaneous, total, or focal disappearance of the tumor melanocytes in the dermis and/or the epidermis. It is usually partial and may go unnoticed by the untrained pathologist. Thus, a primary melanoma may regress completely after metastasis, which may explain why in 3 to 7% of melanomas that metastasize at the outset, no primary lesion is found. (43), (44) Histological regression in primary cutaneous melanoma occurs in 10–35% of cases. (45) When Smoller et al. first referred to HR, they defined it as "a partial host response to a malignant neoplasm, resulting in focal diminution of the process". (5) Since then this histological phenomenon has been described in detail. Histopathologically, the changes occurring in regression are like those observed in a scar. More specifically, Kang et al. described three phases of regression. (46)

An early inflammatory phase (*Figure 2*) with a dense lymphocytic infiltrate encountering the nests of tumoral melanocytes this phase as itself is not sufficient to speak of regression. Indeed, it comes back to the definition of brisk TIL, which illustrates the difficulty to sometimes differentiate these two entities.

An intermediate phase (*Figure 3*) where the melanoma is still recognizable but there is tumour reduction or disappearance in the papillary dermis and, sometimes, in the overlying epidermis, as malignant tissue is replaced by lymphocytes and fibrosis. Some ectatic vessels and pigment-laden macrophages can be seen in this phase.

A late-phase regression (*Figure 4*) where part of the tumour (or the entire tumour) is replaced by dense fibrotic tissue with vessels and melanophages in varying numbers, with few or no lymphocytes under a thinned epidermis.

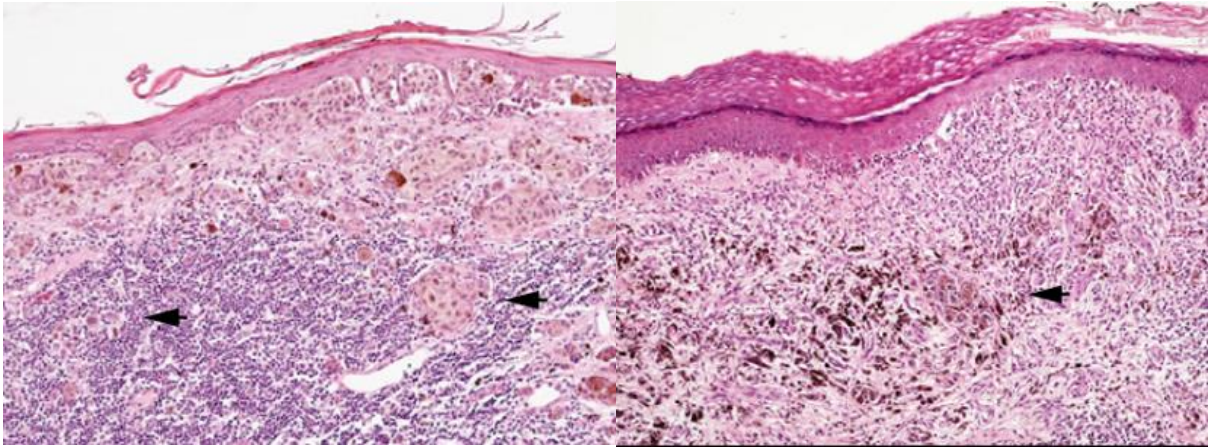


Figure 2 - Stage one of regression according to Ribero et al : some melanoma nests (arrows) are recognizable within a dense inflammatory infiltrate and many melanophages.

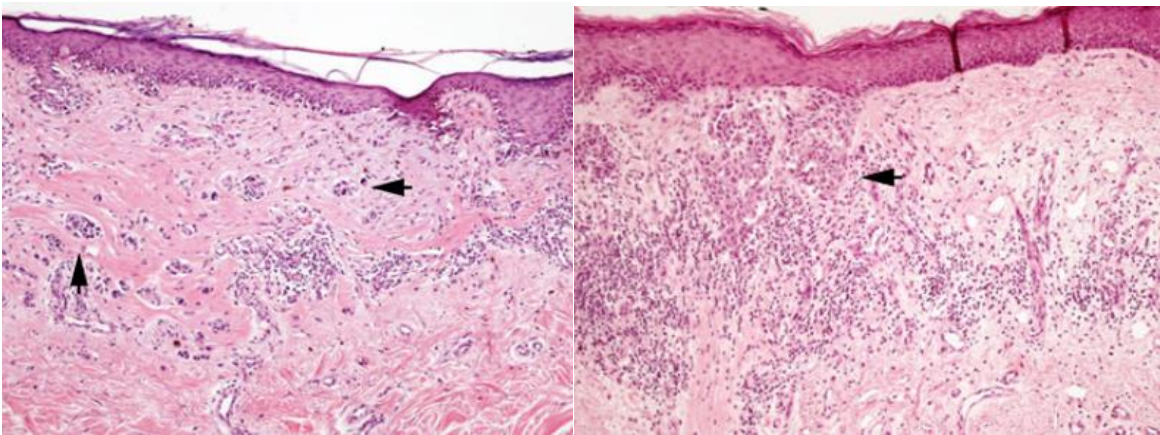


Figure 3 - Stage two of regression according to Ribero et al: the dermis is diffusely fibrotic and includes some neoplastic nests (arrows). Inflammation is less important than in stage one

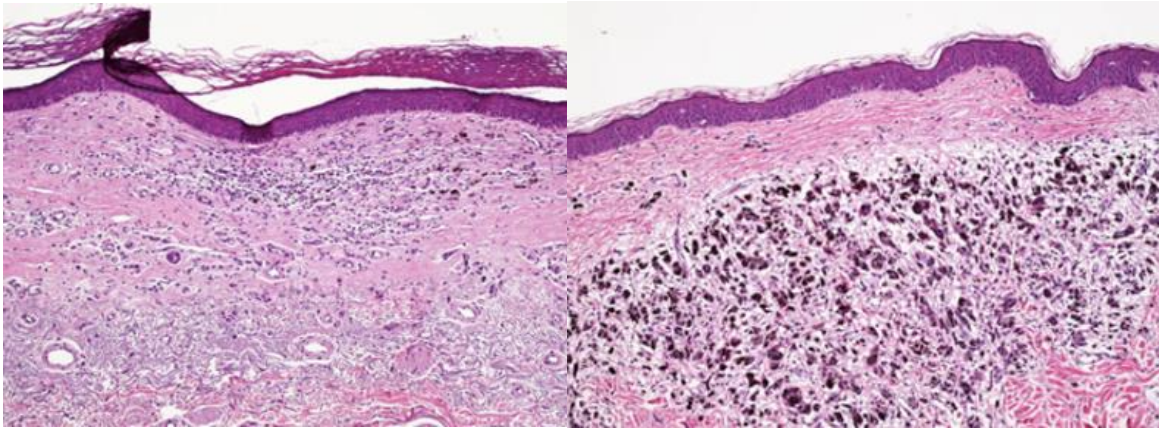


Figure 4 -Stage three of regression according to Ribero et al: neoplastic cells are absent. They have been replaced by fibrosis and inflammation (left panel) or by densely packed melanophages (right panel)

Upon dermoscopy, regression is also named Blue White Scarlike areas (BWS). BWS mostly appear as white scar-like depigmentation that is usually whiter in colour than the surrounding unaffected skin. BWS could be variably admixed with granularity or peppering (speckled multiple blue-grey granules within the hypopigmented areas). (4) Histopathologically, the presence of white and blue colour with variable arrangement corresponds to fibrosis and melanophages respectively. From a practical point of view, BWSs that show a combination of white scar-like areas and blue granularity over a flat, non-palpable area of the tumour, are a dermoscopic finding that should raise suspicion for melanoma undergoing regression. (Figure 5)



Figure 5 -Dermoscopic aspect of a regressive melanoma: combination of white scar-like depigmentation (orange arrow) and peppering (blue arrow). (47)

3.1.2 *Limitations*

While the concept and description of regression are relatively consensual, there is no internationally accepted standard definition. Many of the studies characterize regression as simply present vs absent, while others have examined it in more detail by including the stage of regression and/or the horizontal extent of involvement. Therefore, several limitations must be mentioned when evaluating it.

First, it should be noted that regression can be a purely focal phenomenon and if the histological specimen is insufficiently sampled, then it may be wrongly neglected. For this reason, additional cross-sections on histological specimens of melanoma where the clinician already suspected regression clinically or by dermoscopy could be recommended.

Once the phenomenon has been identified by the pathologist, it seems important to qualify and quantify it: is it rather horizontal and therefore without any real impact on the estimation of the tumor thickness or does it rather affect the vertical component thus underestimating the Breslow index?

Regression has been classified according to the area of loss of melanoma within the dermis and epidermis as a percentage of the whole horizontal extent of the melanoma. Based on this estimation, regression is classified into three groups: no or minimal, focal (<50 or <75% of the entire melanoma), and extensive (≥ 50 or $\geq 75\%$). (48), (49) While this semiquantitative assessment is typically applied to the entire lesion, in some studies only a representative section of the melanoma has been analysed for each case. (50) Currently, the AJCC classification recommends 75% as the cutoff for distinguishing focal from extensive regression since some studies have identified melanomas with $\geq 75\%$ regression being associated with metastasis. (48), (49)

As another attempt to quantify it, regression may be described as partial vs complete. Complete regression of melanoma has traditionally been defined as the absolute absence of any dermal or junctional melanocytes and replacement of the entire lesional area by varying amounts of fibrosis, inflammation, and sometimes abundant melanophages in the site of a previously documented pigmented lesion. (43) In such scenarios, since no melanocytes remain in the lesion, a definitive diagnosis of regressed melanoma cannot be rendered, but the optimal diagnosis would rather be 'pigment incontinence consistent with a completely regressed melanocytic

lesion'. As such, the malignant biologic potential of the regressed lesion is realized only if the patient develops regional or distant metastasis. However, some authors distinguish complete regression from generalized regression as the total absence of melanocytes in the epidermis and dermis, even if it is only one area in an otherwise intact melanoma. (51) These individual nuances in defining regression make it difficult to standardize practices.

Finally, there is the question of the numerous differential diagnoses. In case of superficial regression, the diagnosis of dermal blue nevus, melanoma metastasis or malignant blue nevus is also discussed. If the inflammatory reaction is very intense, then the question of a Sutton's halo nevus or a Brisk-type TIL on a melanoma in the vertical growth phase will arise. Melanophages arranged in a subepidermal band may correspond to a total regression but also to other inflammatory lesions such as a fixed erythema pigmentosa or certain lichens. It is then the clinical information provided by the dermatologist that will correct the diagnosis.

3.1.3 *Prognostic role*

To date, the biologic significance of melanoma regression has not been completely elucidated.

Several studies have failed to show a correlation between regression and patient outcome on either 5-year survival (52), risk of recurrence (53), or SLN status. (54) In contrast, other studies have indicated that the presence of regression in melanoma was associated with a poor prognosis with a greater metastatic risk (48) (55), a decreased disease-free interval (56) and a decreased 10-year survival rate. (57) On the other hand, additional studies have suggested that regression indicates a favorable outcome. Histological regression has been associated with lower involvement of lymph node metastases (7) (58) (59) and a better prognosis in two different meta-analyses of over 10,000 patients. (60) (61) Furthermore, it has recently been associated with a more favorable prognosis in primary (8) and Stage III metastatic melanoma. (9) No clear data on Stage IV has been reported so far. Thus, we can speculate that the immune system more activated against the primary melanoma can do the same towards metastases as well.

3.2 TIL

3.2.1 Definition

For decades, pathologists have described within the tumor microenvironment a procession of lymphocytic inflammatory cells that seems to be a witness of the host response against the tumor. It is only in 1969, that Wallace Clark applied the term, 'tumour-infiltrating lymphocytes' (TIL) to refer to these immune cells. In order to be regarded as TILs, lymphocytes must be in direct contact with tumour and/or infiltrate tumour nests. (13) Even more subtly, the term TIL is applicable only to the lymphocytic infiltrate concerning the infiltrative component of the melanoma. Indeed, when we are confronted to a lymphocytic infiltrate within an intra-epidermal melanoma, we speak of lichenoid reaction stroma.

The first classification dates back to 1989 and establishes a graded system that categorises the nature and extent of TIL involvement within a tumour. They classified TILs as 'absent' when no lymphocytes were present or when the lymphocytes did not appose the melanoma cells (immunotype A). 'Non-brisk' (immunotype B), described a focal TIL infiltrate while 'brisk' (immunotype C) described either an infiltrate at the base of the vertical growth phase (VGP) of the tumour or a diffuse infiltration of the entire VGP of the melanoma lesion. (*Figure 6*) The most frequent presentation is immunotype A (>60%) while immunotype C is described in less than 10% of melanomas. TILs are a heterogenous group comprised of not only effector T cells (CD8+), but also of T regulatory (Treg) cells (CD4+, CD25+, FoxP3+), natural killer (NK) cells (CD56+, CD16+), macrophages (CD68+, CD 163+), dendritic cells (DC-LAMP +), B cells (CD20+) and other immune cell types. Erdag et al. (10) tried to define the phenotypes of tumor-infiltrating immune cells: not surprisingly, among the 183 patients with metastatic melanoma they analysed, the greatest numbers of immune cells were in immunotype C (Brisk) tumors, with intermediate numbers in immunotype B, and rare cells in immunotype A. (*Figure 7*) We can also note that the cellular distribution varies between the different immunotypes: the denser the infiltrate, the richer it is in CD20+ B lymphocytes and less in CD163+ macrophages.

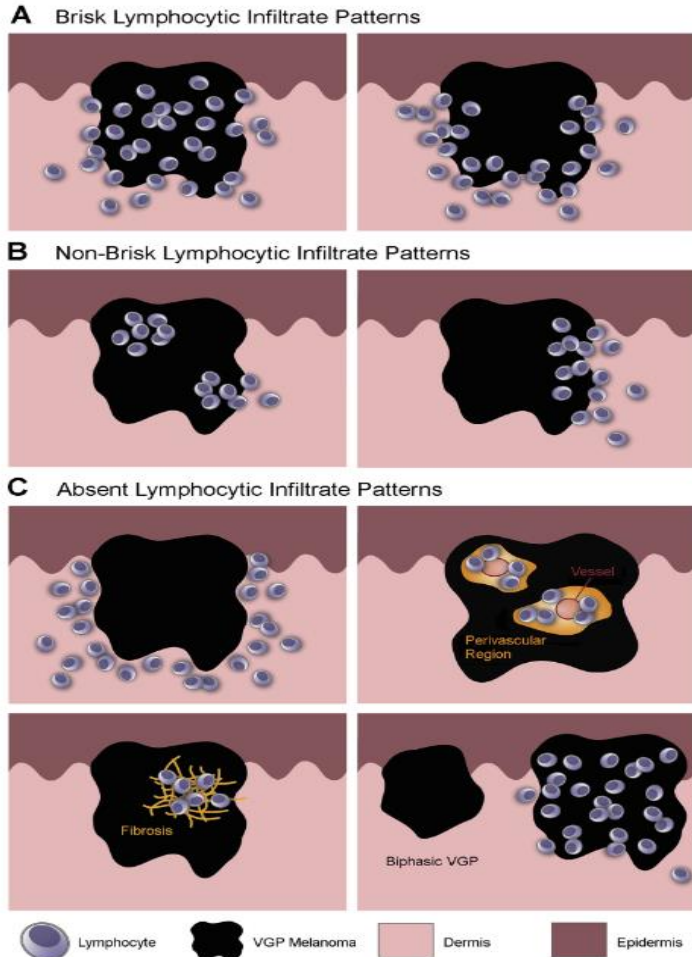


Figure 6 -Schematic figure illustrating the classification of lymphocytic infiltrate patterns in vertical growth phase (VGP) melanomas, as defined by Clark and colleagues. (according to Lee et al.)

A) A lymphocytic infiltrate pattern is classified as 'brisk' when TILs diffusely infiltrate the entire invasive component of the tumour ('diffuse', left panel) or when they infiltrate the entire base of the tumour ('peripheral', right panel).

(B) Isolated, multifocal, and segmental TIL infiltrate patterns are classified as 'non-brisk'.

(C) A VGP melanoma is classified as 'absent' when no TILs are infiltrating tumour tissue (top left panel) or when lymphocytes are confined to perivascular areas (top right panel) or to areas of fibrosis (bottom left panel). In cases where there are multiple tumour nodules, the overall TIL grade should be determined by the grade of the nodule with the lowest number of TILs (bottom right panel).

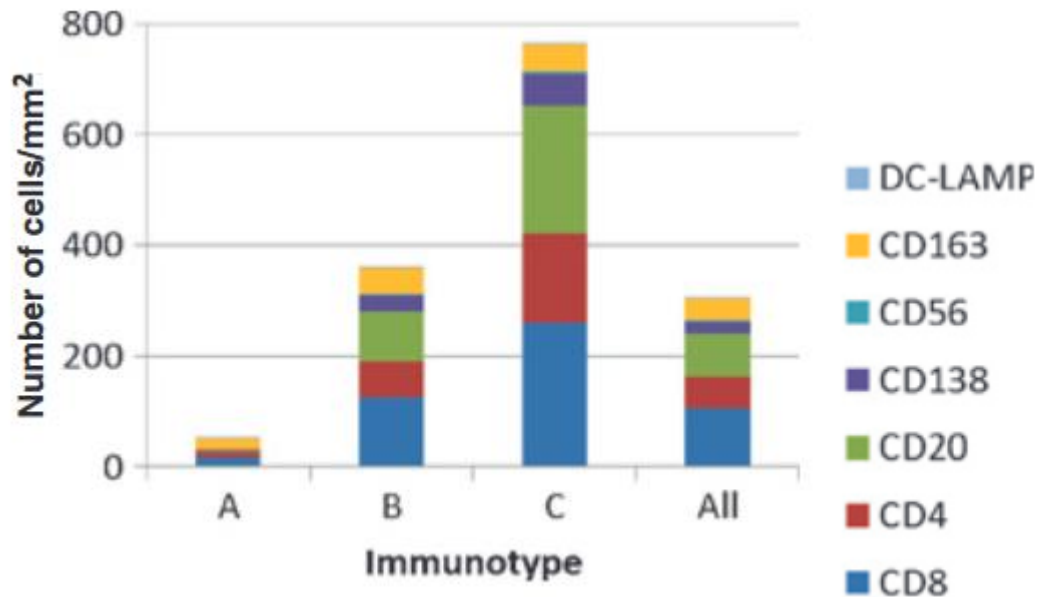


Figure 7 -Mean numbers of each immune cells by immunotype (according to Erdag et al.)

3.2.2 *Prognostic Role*

TILs have been identified as a favourable prognostic marker across multiple cancers including breast (62) and seems to serve as a surrogate indicator of the strength of the host anti-tumour immune response. It was recently shown by Melanoma Institute Australia investigators that TIL grade inversely correlates with incidence of SLN metastases. (63) This study, on 1865 patients, also revealed that TIL grade, independently of SLN positivity, predicted melanoma specific survival as well as recurrence-free survival in patients with cutaneous melanoma greater than or equal to 0.75 mm in thickness. Clemente et al. (64) also showed a better 5-year and 10-year survival in melanomas with a vertical growth phase and a brisk infiltrate compared to tumors with non-brisk infiltrate or without TIL. However, some authors have reported no independent prognostic value of TILs, and others have demonstrated no correlation between TILs and prognosis (65), (66). Because TILs seem to be more prognostically important in thicker tumors (64) it has been suggested that a possible reason for the apparently discordant results in the latter studies may be related to the inclusion of a predominance of thin and radial growth phase melanomas. (65), (66).

3.2.3 *Similarities with regression*

The lymphocyte infiltrate within the TIL (in particular Brisk) seems to share several common points with those present within the regression with notably a high number of CD8+ cytotoxic lymphocytes and a low population of CD4+ CD25+ FOXP3+ regulatory lymphocytes which participate in the anergy of the immune response. (14)

The TIL response is directed against the deeper invasive part of the lesion and begins to infiltrate it. It is questionable whether the TIL Brisk is not an early stage of regression and whether the lymphocyte population of the TIL Brisk will eventually cause lysis of the tumor melanocytes.

3.3 Vitiligo and melanoma

3.3.1 *Incidence and physiopathology*

Vitiligo or vitiligo-like patches associated with malignant melanoma have been observed by several investigators over the past: it has been reported that the risk for the development of vitiligo among melanoma patients can be considered 10-fold higher than in the general population. (15)

The relationship between vitiligo and melanoma could follow an immune-mediated destruction through recognition of melanoma-associated antigens (MART-1, gp100, tyrosinase 1–2) that are shared by normal melanocytes and melanoma cells. (67), (68)

The immune response that takes place in vitiligo patches appear to be mediated, almost exclusively by T lymphocytes, and more specifically by CD8+. (69)

If even without a treatment, vitiligo is more frequent in patients with a melanoma than in general population, it is a much more common adverse event in melanoma immunotherapy compared to other solid tumor immunotherapy (68) suggesting that the presence of a growing melanoma can sensitize patients to melanocyte-differentiation antigens and that the immune response against these antigens could be boosted by immunotherapy.

3.3.2 *Prognostic role and predictive factor of response to immunotherapy*

Many studies have already suggested that the appearance of vitiligo in patients with metastatic melanoma portends a longer survival than expected. (70), (71)

A 2009 retrospective analysis performed on a large cohort included 2954 patients with melanoma and reported that vitiligo could be associated with an improved prognosis. In that study, vitiligo was present in 2.8% of patients with melanoma and was found to be an independent positive prognostic factor associated with overall survival in patients with stages III and IV melanoma and with distant metastasis-free survival in patients with stage III melanoma. (72)

Although their sample size was small and the trials were often underpowered to detect significant differences, several clinical trials (73),(74) evaluating immunotherapies in advanced

metastatic melanoma also found a correlation between vitiligo and an improved clinical response, suggesting an immunomodulating effect against metastatic disease.

The results of a 2016 prospective cohort study also suggest that the onset of vitiligo in patients treated with pembrolizumab for metastatic melanoma could be a clinically visible IrAE associated with clinical benefit. (75)

3.3.3 *Similarities with regression*

As we have seen, the effector cells of both phenomena are the CD8 + lymphocytes. (69), (76)

Moreover, in segmental vitiligo area reduced levels of CD4+CD25+FOXP3+ regulatory T cells were detected when compared to healthy individuals skin (77) The same lower level of infiltrate immune CD4+CD25+FOXP3+ cells in the regressed area have been found when compared to the non-regressed area in melanoma (76) as we also saw in TIL brisk. (14)

Thus, the cellular immune response in regressed area seems to share a lot of similarities with the immune infiltrate of vitiligo induce in melanoma patients and even more in vitiligo-like reaction induced by immune therapy.

III. Material and methods

1. Objective

To determine if the presence of histological regression at diagnosis is a predictive factor for response to immunotherapy in stage IV metastatic cutaneous melanoma. We split our population into 3 groups: NRM patients, RM patients and OPM patients. Our primary outcome was progression-free survival, and our secondary endpoints were the response on imaging performed at 3 and 6 months. We compared the data from the RM and OPM groups to the NRM group (our reference group), separately, and then, combined. We also considered overall survival and collected various data related to histology, disease progression and treatment received to profile our patients and allow a review of practices in our Dermatology Department.

2. Patients and data (Figure 8)

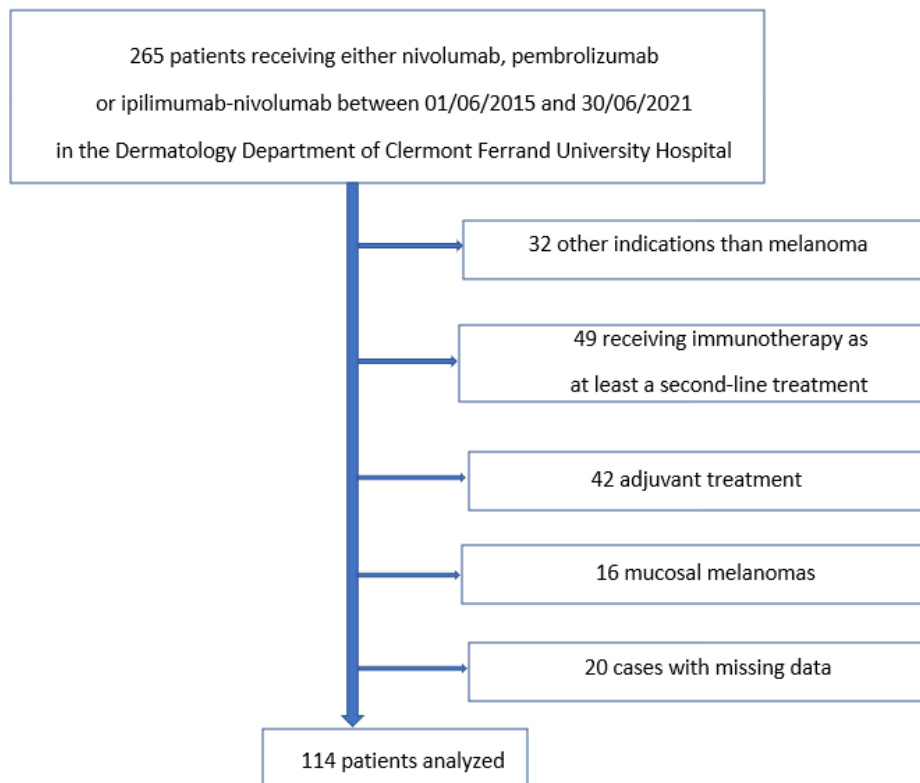


Figure 8 –Flow Chart

We retrospectively reviewed the antineoplastic prescription software database Chimio® (78) to select all patients who had received between January 1, 2015 and June 30, 2021 at least one cure of immunotherapy (nivolumab, pembrolizumab or ipilimumab/nivolumab) for the indication "metastatic melanoma" in the Dermatology Department at the Clermont-Ferrand University Hospital (in daily hospital or in full hospitalization). We reported all the files data until December 31, 2021 in order to have at least 6 months of follow-up since the initiation of immunotherapy.

Among all patients meeting these criteria, we first excluded patients who had received one of these three immunotherapies for an indication other than melanoma.

Then, we excluded patients who had received another line of treatment before the initiation of one of the immunotherapies and kept only patients with AJCC stage IV melanoma at the time of initiation of treatment. Finally, we excluded the few patients with stage IV melanoma who had undergone surgery and had received adjuvant immunotherapy.

Our sample was therefore composed only of patients with metastatic melanoma who had received first-line immunotherapy. Within this population we excluded mucosal melanomas, considering these tumors as a separate entity.

At the end of this selection, we eliminated the cases for which the data were missing (incomplete pathology report, histological analysis done in a foreign country, impossibility of repatriating the pathology slides to the Clermont-Ferrand University Hospital).

We therefore included 114 patients in our study.

3. Histological analysis

The pathology reports were all performed by 4 dermatopathologists from Clermont-Ferrand, prior to this retrospective study. For patients coming from another hospital center, a second reading by our pathologists was performed.

In addition to determining the main histopronostic criteria (Breslow index, ulceration, ...) on each histological slides stained with haematoxylin and eosin from primary cutaneous melanoma tumours, they established the presence or absence of regression.

To define this regression, dermatopathologists have referred to the consensus of the College of American Pathologists. (79)

4. Data collection

For the 114 patients, we listed the main characteristics specific to the patients (age, sex, ECOG score at diagnosis, LDH level, lymphocyte level, albumin level), specific to their histology (histological subtype, Breslow index, Clark index, presence of an ulceration, presence of regression, mitotic index, primary or secondary lesion) and their molecular biology (results of New Generation Sequencing NGS), specific to their disease and its evolution (date of diagnosis, realization of the sentinel lymph node technique, date of discovery of metastases, location of metastases, presence of brain metastases at diagnosis, imaging therapeutic response at 3 months, 4 months and 6 months, occurrence of metastatic progression, occurrence of death), specific to the treatment received (name of immunotherapy, date of initiation of immunotherapy, adverse events occurring during treatment, performance of radiotherapy during treatment, date of introduction of a second line of treatment, duration of treatment, reason for discontinuation of treatment).

We focussed particularly on the therapeutic response at 3 months (M3) and 6 months (M6) by comparing the M3 and M6 imaging with that performed at baseline. We referred to the imaging reports written before this retrospective study by the radiology team of the Clermont-Ferrand University Hospital who defined the therapeutic response according to the international iRECIST guidelines, which can be classified into four categories: complete response CR (= disappearance of all measurable and non-measurable lesions, no new lesions), partial response PR (decrease of at least 50% of the tumor mass compared to baseline, new lesions possible), stable disease SD (= increase of less than 25% or decrease of less than 50% of the tumor mass), disease progression DP (= increase of at least 25% of the tumor mass compared to nadir).

For the statistical analysis, we first made an analysis in 3 groups: regressive melanoma (RM), non-regressive melanoma (NMR) and occult primary melanoma (OPM).

For each group we determined the overall survival (OS) and the progression-free survival (PFS).

We subsequently repeated all these analyses, this time comparing two groups: NRM on the one hand, and the association of RM and OPM on the other, based on the conjecture that a melanoma of unknown primary origin can be assimilated to a fully regressive cutaneous melanoma.

5. Statistical analysis

Statistical analysis was performed using Stata software (version 15; StataCorp, College Station, Texas, USA). All tests were two-sided, with an alpha level set at 5%. Categorical variables were expressed as number of patients and associated percentages, and continuous variables as mean \pm standard deviation or median [25th; 75th percentiles], according to statistical distribution.

The three groups of patients (NRM vs RM vs OPM) were compared by the chi-squared test or the Fisher's exact test for categorical variables (followed by the Marascuilo procedure if omnibus p-value less than 0.05), and with ANOVA or Kruskal-Wallis test for continuous variables (followed respectively by Tukey-Kramer test and Dunn's test if appropriate).

The two groups of patients (NRM vs RM+OPM) were compared by the chi-squared test or the Fisher's exact test for categorical variables and with the Student's t-test or the Mann-Whitney test for continuous variables.

Censored data (progression-free survival and overall survival) were estimated using the Kaplan-Meier method, and comparisons between groups were made with the log-rank test.

IV. Results

1. Comparison between the 3 groups: NRM, RM and OPM

1.1 Clinicopathological characteristics of the included patients (Table I)

Table 1 - Clinicopathological characteristics of the included patients

	Total (n=114)	NRM (n=62)	RM (n=32)	OPM (n=20)	<i>p</i>
Age (years)	65.4 ± 13.7	65.9 ± 12.9	63.8 ± 15.1	66.4 ± 14.3	0.74
Male gender	74 (64.9)	36 (58.0)	25 (78.1)	13 (65.0)	0.16
Histological subtype					
SSM	50 (53.0)	31 (50)	19 (59.3)		
ALM	15 (15.9)	15 (24.1)	0 (0)		
LM	5 (5.3)	3 (4.8)	2 (6.2)		
Nodular	16 (17.0)	9 (14.5)	7 (21.8)		
Desmoplastic	4 (4.26)	3 (3.1)	1 (3.1)		
Unclassifiable	4 (4.26)	1 (1.6)	3 (9.3)		
Clark level					
I	2 (2.1)	2 (3.3)	0 (0)		
II	3 (3.2)	3 (4.9)	0 (0)		
III	21 (22.6)	12 (19.7)	9 (28.1)		
IV	47 (50.5)	28 (45.9)	19 (59.4)		
V	20 (21.5)	16 (26.2)	4 (12.5)		
Ulceration	56 (59.6)	36 (58)	20 (62.5)		
Mitotic index					
I (0 or 1 mitosis/mm ²)	20 (21.5)	13 (21.3)	7 (21.9)		
II (2 to 4 mitosis/mm ²)	52 (55.9)	35 (57.4)	17 (53.1)		
III (>4 mitosis/mm ²)	21 (22.6)	13 (21.3)	8 (25)		
Mutation					
BRAF	26 (22.8)	11 (17.7)	7 (21.9)	8 (40)	0.05
CKIT	5 (4.4)	5 (8.1)	0 (0)	0 (0)	
NRAS	15 (13.1)	5 (8.1)	8 (25)	2 (10)	
Unmutated	68 (59.7)	41 (66.1)	17 (53.1)	10 (50)	
Breslow index (millimeters)	4.0 [2.1; 6.0]	4.0 [2.1; 7.0]	4.0 [2.3; 5.7]		0.79

ECOG score					
0	59 (51.8)	36 (58)	17 (53.1)	6 (30)	0.07
1	23 (20.2)	11 (17.7)	7 (21.9)	5 (25)	
2	23 (20.2)	13 (21)	3 (9.4)	7 (35)	
3	7 (6.1)	1 (1.6)	4 (12.5)	2 (10)	
4	2 (1.7)	1 (1.6)	1 (3.1)	0 (0)	
LDH rate					
N	80 (70.2)	39 (62.9)	28 (87.5)	13 (65)	0.05
N to 2N	19 (16.7)	14 (22.6)	3(9.4)	2 (10)	
>2N	15 (13.1)	9 (14.5)	1 (3.1)	5 (25)	
Albumine rate (g/L)					
<20	1 (0.9)	0 (0)	0 (0)	1 (5)	0.38
20-30	14 (12.3)	8 (12.9)	3 (9.4)	3 (15)	
30-35	18 (15.8)	9 (14.5)	4 (12.5)	5 (25)	
>35	81 (71)	45 (72.6)	25 (78.1)	11 (55)	
Lymphocytes rate (G/L)					
<1.5	60 (52.6)	33 (53.2)	16 (50)	11 (55)	0.92
1.5-4.0	52 (45.6)	27 (43.6)	16 (50)	9 (45)	
>4.0	2 (1.8)	2 (3.2)	0 (0)	0 (0)	
<p><i>NRM= Non Regressive Melanoma; RM = Regressive Melanoma; OPM = Occult Primary Melanoma; SSM = Superficial Spreading Melanoma; ALM = Acro Lentiginous Melanoma; LM= Lentigo Melanoma; ECOG = Eastern Cooperative Oncology Group; LDH = Lactate Deshydrogenase</i></p>					

Of the 114 patients included in this analysis, 32 (28%) had histological regression and for 20 patients (17%) no primary melanoma was identified. The median age at diagnosis was 65 years. 74 (65%) patients were male, with a slightly higher representation of males in patients with regressive melanoma (78%).

Histologically, melanomas were most often SSM (53%), followed by nodular (17%) and ALM (16%), with a surprising distribution of ALM exclusively in the non-regressive group (24% vs. 0% in regressive melanomas). The median Breslow index was 4mm with a Clark level greater than or equal to 3 in 94% of cases, and the presence of an ulceration in 59% of cases. 73 patients (79%) had a moderate (II) or high (III) mitotic index.

In 68 (59%) of the melanomas no mutation was found. Among the 3 mutations identified, the BRAF mutation was more frequent in melanomas of unknown origin (40%), the CKIT mutation was exclusively identified in melanomas without regression, and the NRAS mutation was

overrepresented in patients with regressive melanoma (25% versus 10% in occult primary melanoma (OPM) and 8% in NRM). ($p=0,05$)

It should also be noted that 22.8% of our patients who received first-line immunotherapy were BRAF-mutated, probably because their disease was slowly progressing and because their general condition was sufficiently preserved to support immunotherapy.

Among the 114 patients, immunotherapies targeting the PD1 pathway were the most prescribed with 55 people (48.2%) who received nivolumab and 33 people (28.9%) who received pembrolizumab.

At the time of initiation of immunotherapy, more than half of the patients with regressive (53%) and non-regressive (58%) melanoma were in excellent general condition with an ECOG score of 0; they were only 6 (30%) in the case of an unknown primary. We also note that the patients with a very poor general condition (ECOG 3 or 4) were 5 (15%) in the regressive group against 2 (3%) in the non-regressive group.

Biologically, at the initiation of immunotherapy, the LDH level was most often (70%) within laboratory standards. However, we note that in patients with regressive melanoma, only 4 (12%) had LDH above normal compared to 23 (37%) in non-regressive and 7 (35%) in OPM ($p=0.05$). Nutritional status was excellent (albumin >35 g/L) in 81 (71%) patients with however more malnourished patients (albumin <30g/L) in 20% of OPM versus 13% of non-regressives and 9% of regressives. More than half of the patients were lymphopenic (52%) at the initiation of treatment and only 2 (1.75%) had hyperlymphocytosis.

1.2 Disease characteristics and evolution (Table II)

Table 2 - Disease characteristics and its evolution among the 3 groups

	Total (n=114)	NRM (n=62)	RM (n=32)	OPM (n=20)	<i>p</i>
SLN procedure					
Yes and positive LND	11 (13.3)	8 (14.8)	3 (10.7)	0 (0)	0.86
Yes and negative LND	17 (20.5)	10 (18.5)	7 (25)	0 (0)	
No	55 (66.2)	36 (66.7)	18 (64.3)	1 (100)	
Delay between diagnosis and metastasis (in months)		17.5 [5.9 ;37.0]	13.8 [3.0 ; 24.0]		0.70

Metastatic location					
Brain	30 (26.3)	15 (24.2)	7 (21.9)	8 (40)	0.31
Liver	19 (16.7)	9 (14.5)	5 (15.6)	5 (25)	0.55
Thyroid	1 (0.9)	0 (0)	1 (3.1)	0 (0)	0.46
Lung	59 (51.7)	33 (53.2)	17 (53.1)	9 (45)	0.80
Spleen	6 (5.3)	4 (6.5)	1 (3.1)	1 (5)	0.86
Oropharynx	1 (0.9)	1 (1.6)	0 (0)	0 (0)	1.00
Muscle	3 (2.6)	3 (4.8)	0 (0)	0 (0)	0.58
Adrenal gland	5 (4.4)	5 (8.1)	0 (0)	0 (0)	0.19
Gastrointestinal tract	8 (7)	0 (0)	5 (15.6)	3 (15)	0.002
Lymph node	31 (27.2)	18 (29)	8 (25)	5 (25)	0.89
Subcutaneous	34 (29.8)	17 (27.4)	11 (34.4)	6 (30)	0.78
Bone	22 (19.3)	14 (22.6)	4 (12.5)	4 (20)	0.53
Kidney	2 (1.7)	2 (3.2)	0 (0)	0 (0)	0.69
Pancreas	4 (3.5)	2 (3.2)	1 (3.1)	1 (5)	1.00
Peritoneal carcinosis	5 (4.4)	1 (1.6)	1 (3.1)	3 (15)	0.06
Eye	1 (0.9)	1 (1.6)	0 (0)	0 (0)	1.00
Nasal cavity	1 (0.9)	1 (1.6)	0 (0)	0 (0)	1.00
Imaging response M3					
Disease progress PD	37 (36.6)	26 (48.1)	5 (16.6)	6 (35.2)	0.029
Stable disease SD	29 (28.7)	9 (16.6)	14 (46.6)	6 (35.2)	
Partial response PR	30 (29.7)	15 (27.7)	10 (33.3)	5 (29.4)	
Complete response CR	5 (4.9)	4 (7.41)	1 (3.33)	0 (0.0)	
Imaging response M3					
DP	37 (36.6)	26 (48.1)	5 (16.7)	6 (35.3)	0.016
SD+PR+CR	64 (63.4)	28 (51.9)	25 (83.3)	11 (64.7)	
Imaging response M4					
Disease progress PD	25 (67.5)	19 (86.3)	5 (50.0)	1 (20.0)	0.007
Stable disease SD	10 (27.0)	3 (13.6)	4 (40.0)	3 (60.0)	
Partial response PR	2 (5.4)	0 (0.0)	1 (10.0)	1 (20.0)	
Imaging response M4					
PD	25 (67.5)	19 (86.4)	5 (50)	1 (20)	0.006
SD+PR	12 (32.4)	3 (13.6)	5 (50)	4 (80)	
Imaging response M6					
Disease progress PD	27 (32.1)	18 (40.9)	7 (25.9)	2 (15.3)	0.45
Stable disease SD	21 (25.0)	9 (20.4)	9 (33.3)	3 (23.0)	
Partial response PR	23 (27.3)	11 (25.0)	6 (22.2)	6 (46.1)	
Complete response CR	13 (15.4)	6 (13.6)	5 (18.5)	2 (15.3)	
Imaging response M6					
PD	27 (32.1)	18 (40.9)	7 (25.9)	2 (15.4)	0.19
SD+PR+CR	57 (67.9)	26 (59.1)	20 (74.1)	11 (84.6)	
Deaths	58 (50.8)	35 (56.4)	14 (43.7)	9 (45.0)	0.43
<p><i>NRM= Non Regressive Melanoma; RM = Regressive Melanoma; OPM = Occult Primary Melanoma; SLN = Sentinel Lymph Node; LND = Lymph Node Dissection</i></p>					

The median time between diagnosis of melanoma and the appearance of metastases was 13.8 months in patients with regressive melanoma, which was slightly faster than in non-regressive patients (17.5 months).

The distribution of the different metastatic sites at the introduction of immunotherapy is shown in *Figure 9*.

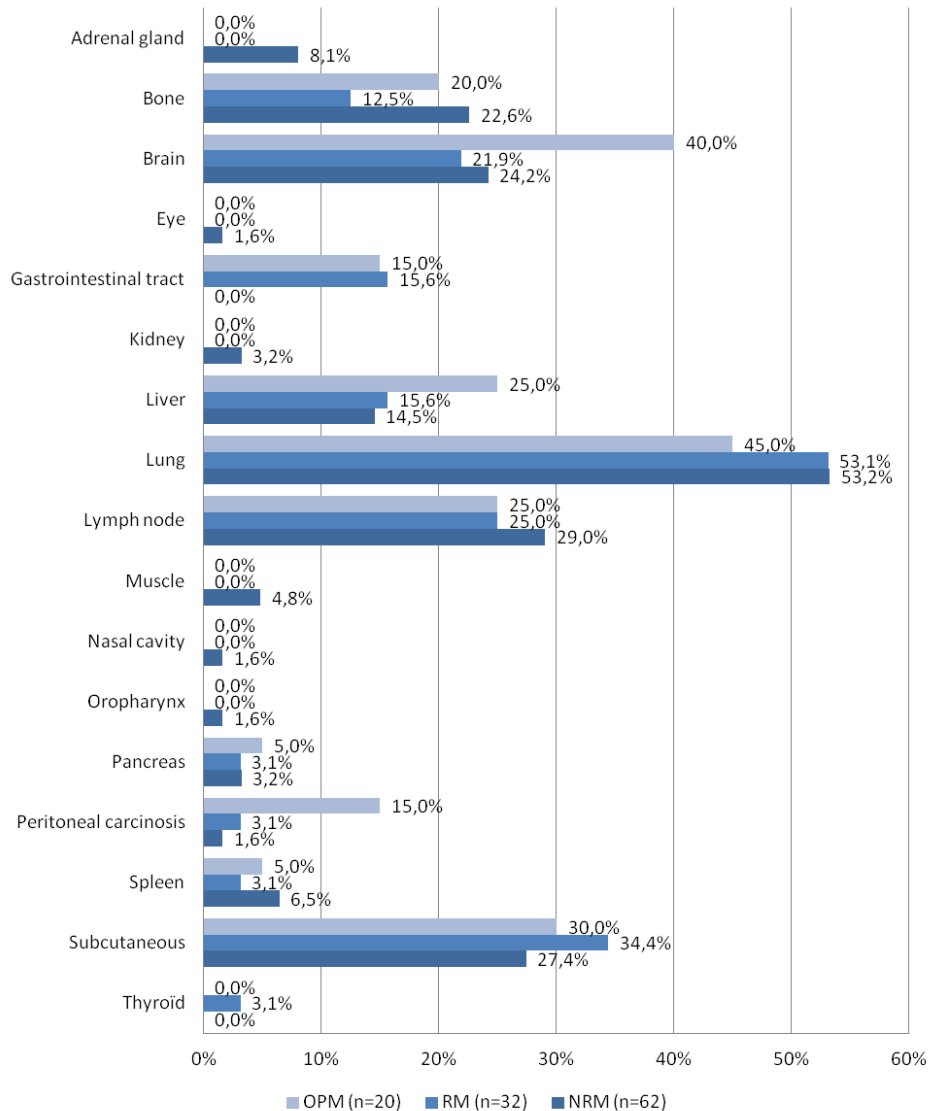


Figure 9 - Metastatic location distribution among the 3 groups

Metastases were most frequently pulmonary (51.8%), subcutaneous (29.8%), in the lymph nodes (27.2%) and cerebral (26.3%). Surprisingly, all adrenal metastases were in NRM ($p=0.19$). Conversely, no metastasis of the digestive tract was found in patients with NRM, whereas this represents 15% of MR and OPM ($p=0.002$). There were also more brain metastases in the OPM group (40% vs. 21.8% in MR and 24% in NRM) and more peritoneal carcinosis (15% vs. 3.1% in MR and 1.6% in NRM), which are classically metastatic sites that are difficult to treat.

1.3 Response to immunotherapy

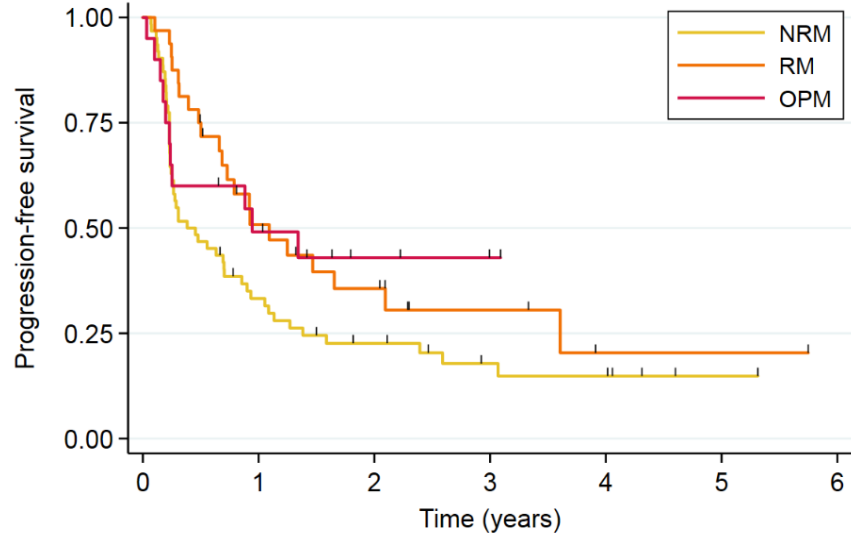
On the CT scan performed 3 months after initiation of immunotherapy, 37 patients (36.6%) among the 101 still alive, had a disease progression (DP): among them 26 patients had NRM (48% of NRM) and only 5 had MR (16.6% of MR). Similarly, of the 37 patients with imaging at 4 months, 22 were patients with NRM and among them 19 (86.3%) were in DP.

At 6 months, among the 84 patients still alive (7 deaths (35%) in OPM, 18 deaths (29%) in NRM and 5 deaths (15%) in RM), there was still a predominance of patients in DP (32%), in particular in NRM (40.9% vs 25.9% in RM) but an increase in patients in CR (15.4%).

The curves of progression-free survival (delay in months between the initiation of immunotherapy and the occurrence of either metastatic progression or death) and overall survival (delay in months between the initiation of immunotherapy and the occurrence of death) in the 3 groups are shown in *Figure 10* and *Figure 11* respectively.

The median progression-free survival was 8.4 months in our population with 4.6 months in the NRM group versus 11.3 months in the OPM group (*hazard ratio for median progression-free survival in OPM group vs NRM group, 0.60 [p=0.13]*) and 13.1 months in the RM group (*hazard ratio for median progression-free survival in RM group vs NRM group, 0.61 [p=0.05]*).

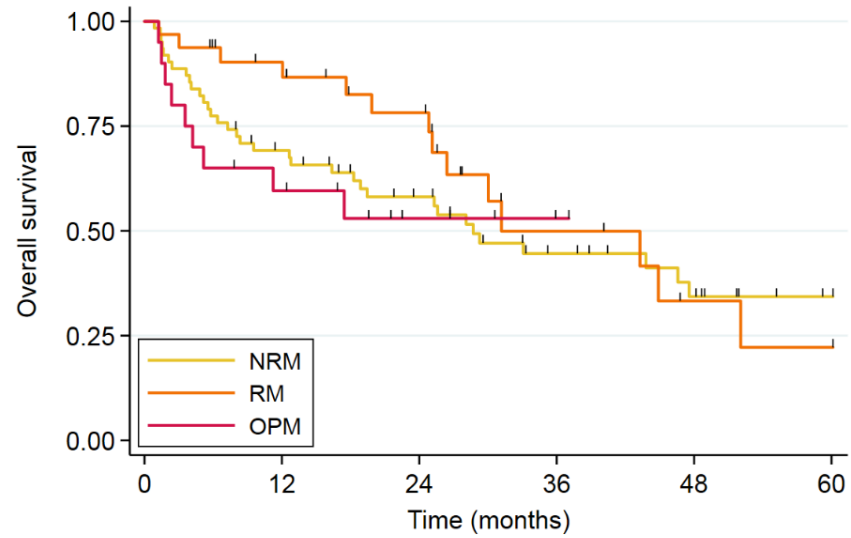
The global five-year overall survival rate was 31.6% with 5% in the OPM group, 34.3% in the RM group and 38.7% in the NRM group (*hazard ratio for death in OPM groups vs NRM group, 2.32 [p=0.03]*; *hazard ratio for death in RM group vs RPM group, 0.89 [p=0.73]*)



Number at risk

NRM	62	19	11	6	5	1	0
RM	32	14	9	4	1	1	0
OPM	20	9	4	2	0	0	0

Figure 10 - Progression-free survival within the 3 groups



Number at risk

NRM	62	40	28	16	10	3
RM	32	25	18	7	3	2
OPM	20	11	5	2	0	0

Figure 11- Overall survival within the 3 groups

1.4 Immunotherapy characteristics (Table III)

Table 3 - Characteristics of the treatment received in each of the 3 groups

	Total (n=114)	NRM (n=62)	RM (n=32)	OPM (n=20)	<i>p</i>
Immunotherapy					
Nivolumab	55 (48.2)	28 (45.1)	17 (53.1)	10 (50)	0.78
Pembrolizumab	33 (29)	19 (30.7)	7 (21.9)	7 (35)	
Ipilimumab/Nivolumab	26 (22.8)	15 (24.2)	8 (25)	3 (15)	
Adverse effect					
Any	50 (43.8)	28 (45.1)	16 (50.0)	6 (30.0)	0.35
Colitis	13 (11.4)	8 (12.9)	3 (9.3)	2 (10.0)	0.92
Hepatitis	7 (6.1)	4 (6.4)	3 (9.3)	0 (0.0)	0.43
Thyroid disorder	10 (8.7)	4 (6.4)	5 (15.6)	1 (5.0)	0.36
Vitiligo	8 (7.0)	5 (8.0)	1 (3.1)	2 (10.0)	0.69
Alopecia	1 (0.8)	1 (1.6)	0 (0.0)	0 (0.0)	1.00
Lupus induced	1 (0.8)	1 (1.6)	0 (0.0)	0 (0.0)	1.00
Myocarditis	1 (0.88)	0 (0.0)	1 (3.1)	0 (0.0)	0.46
Adrenal insufficiency	4 (3.51)	2 (3.2)	2 (6.2)	0 (0.0)	0.64
Myositis	3 (2.6)	2 (3.2)	0 (0.0)	1 (5.0)	0.58
Nephritis	4 (3.51)	4 (6.4)	0 (0.0)	0 (0.0)	0.29
Pneumonitis	2 (1.7)	2 (3.2)	0 (0.0)	0 (0.0)	0.69
Diabetes	1 (0.8)	0 (0.0)	1 (3.1)	0 (0.0)	0.46
Hypophysitis	2 (1.7)	1 (1.6)	0 (0.0)	1 (5.0)	0.40
Myasthenia	1 (0.8)	0 (0.0)	0 (0.0)	1 (5.0)	0.18
Nevritis	2 (1.7)	0 (0.0)	2 (6.2)	0 (0.0)	0.11
Synovitis	1 (0.8)	0 (0.0)	1 (3.1)	0 (0.0)	0.46
Bullous eruption	1 (0.8)	1 (1.6)	0 (0.0)	0 (0.0)	1.0
Lichenoid eruption	1 (0.8)	1 (1.6)	0 (0.0)	0 (0.0)	1.0
Exanthema	1 (0.8)	0 (0.0)	1 (3.1)	0 (0.0)	1.0
Radiotherapy					
Any	51 (44.7)	37 (59.6)	9 (28.1)	5 (25.0)	0.002
Brain radiotherapy	20 (17.5)	12 (19.3)	5 (15.6)	4 (15.0)	0.95
Bone radiotherapy	13 (11.4)	8 (12.9)	3 (9.3)	2 (10.0)	0.92
Tumoral site radiotherapy	5 (4.3)	4 (6.4)	1 (3.1)	0 (0.0)	0.58
Subcutaneous metastasis radiotherapy	3 (2.6)	3 (4.8)	0 (0.0)	0 (0.0)	0.58
Lymph node radiotherapy	8 (7.0)	8 (12.9)	0 (0.0)	0 (0.0)	0.034
Lung radiotherapy	4 (3.5)	3 (4.8)	0 (0.0)	1 (5.0)	0.50
Number of treatment lines					
1	65 (57.0)	30 (48.3)	19 (59.3)	16 (80.0)	0.04
≥2	49 (42.9)	32 (51.6)	13 (40.6)	4 (20.0)	

Treatment duration (in months)	7 [2 ;16]	5 [2 ;13]	9 [5 ;18]	9 [2 ;20]	0.12
Reason for discontinuation of immunotherapy					
Alteration of the general state	7 (6.1)	3 (4.8)	3 (9.3)	1 (5.0)	
BRAF mutation	2 (1.75)	0 (0.0)	1 (3.1)	1 (5.0)	
Severe adverse effect	10 (8.7)	7 (11.2)	1 (3.1)	2 (10.0)	
Progression	42 (36.8)	27 (43.5)	13 (40.6)	2 (10.0)	
Complete response	14 (12.2)	8 (12.9)	3 (9.3)	3 (15.0)	
Death	23 (20.1)	13 (20.9)	3 (9.3)	7 (35.0)	
No discontinuation	16 (14.0)	4 (6.4)	8 (25.0)	4 (20.0)	

NRM= Non Regressive Melanoma; RM = Regressive Melanoma; OPM = Occult Primary Melanoma

The median duration of treatment was 5 months in NRM versus 9 months in RM and OPM ($p=0.12$). If treatment was discontinued (86% of patients) it was mainly due to metastatic progression (36.8%), death (20.2%), complete response (12.3%) or severe adverse events (8.8%).

Fifty patients (43.8%) were affected by at least one adverse event attributed to immunotherapy. (Figure 12)

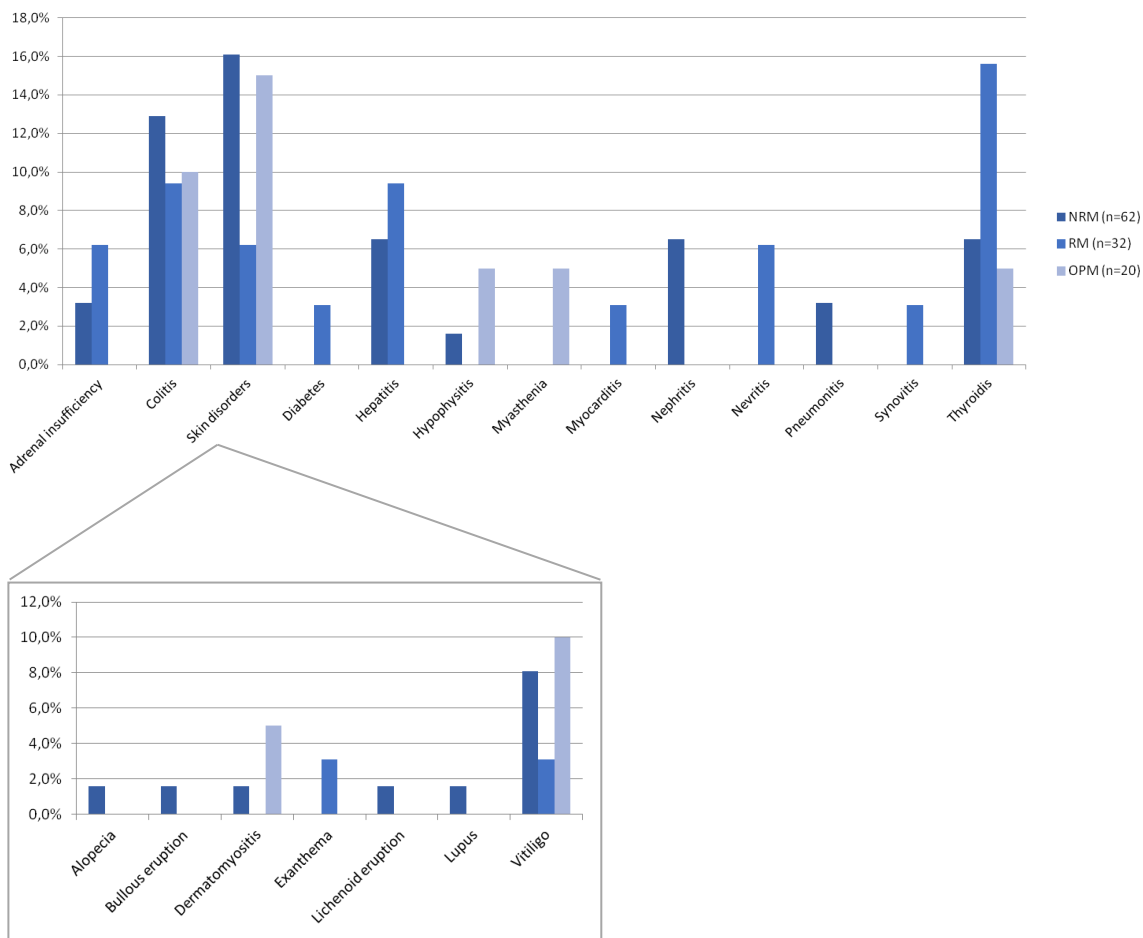


Figure 12 - Adverse effects attributed to immunotherapy within the 3 groups

The most frequent adverse events were colitis (11.4%), thyroiditis (8.7%), vitiligo (7%) and hepatitis (6.1%) with a homogenous distribution between the 3 groups.

If we group together the various cutaneous adverse events (occurrence of lupus, vitiligo, dermatomyositis, maculopapular rash, lichenoid rash, bullous eruption, or alopecia) they become the most frequent, concerning 14% of patients.

During the period of immunotherapy, 51 patients (44.7%) also had radiotherapy with a large predominance in the NRM group (59.6% vs 28% in MR and 25% in OPM) ($p=0.002$). The most frequent sites of irradiation were the brain (17.4%), bones (11.4%) and the lymph node drainage area (7%). It should be noted that all lymph node radiotherapy was performed in the NRM group ($p=0.03$).

2. Two groups comparison : NRM versus RM+OPM

We then grouped RM and OPM patients by conjecturing that OPM are completely regressive melanomas and thus with RM-like behaviour in vivo. We compared this set of patients against those with NRM. The different characteristics of the two groups are detailed in *Appendix 1*.

This additional analysis supports the trends already expressed in the 3-group analysis.

When the NGS was performed, we noted an overrepresentation of BRAF (28.9% vs 17.7%) and NRAS (19.2% vs 8.1%) mutations in the RM/OPM group compared to the NRM group, whereas the latter group included all patients with a CKIT mutation (8.1% vs 0%) ($p=0.02$).

Regarding metastatic sites, no patient in the RM/OPM group developed an adrenal metastasis (0% vs. 8.1%) ($p=0.06$), whereas they accounted for all cases of digestive tract metastasis (15.4% vs. 0%) ($p=0.001$). The difference of patients with peritoneal carcinosis is less marked than in the 3-group analysis (7.7% in RM/OPM vs. 1.6% in NRM) ($p=0.18$).

For the LDH rate above normal, RM were under-represented when analysed separately, whereas in the 3-group analysis, the difference is erased.

It should be noted that among the adverse events described under immunotherapy, there was a homogeneous distribution of vitiligo in the two groups with a slight predominance in the NRM group (8.1% vs. 5.8%) ($p=0.73$).

In the NRM group, 59.7% of patients had radiotherapy during the immunotherapy treatment, i.e. more than twice as many as in the RM/OPM group (26.9%) ($p<0.001$).

If the distribution of radiotherapy sites is globally homogeneous in the 2 groups, we note that the exclusivity of lymph node irradiations concerned patients with NRM (12.9% vs 0%) ($p=0.008$).

The curves of progression-free survival and overall survival in the 2 groups are shown in *Figure 13* and *Figure 14* respectively.

When we grouped the OPM and RM patients, the median progression-free survival was 13.1 months (*hazard ratio for median progression-free survival in OPM+RM group vs NRM group, 0.61 [p=0.03]*) and the five-year overall survival rate was 23.1% (*hazard ratio for death in OPM + RM group vs NRM group, 0.90 [p=0.70]*).

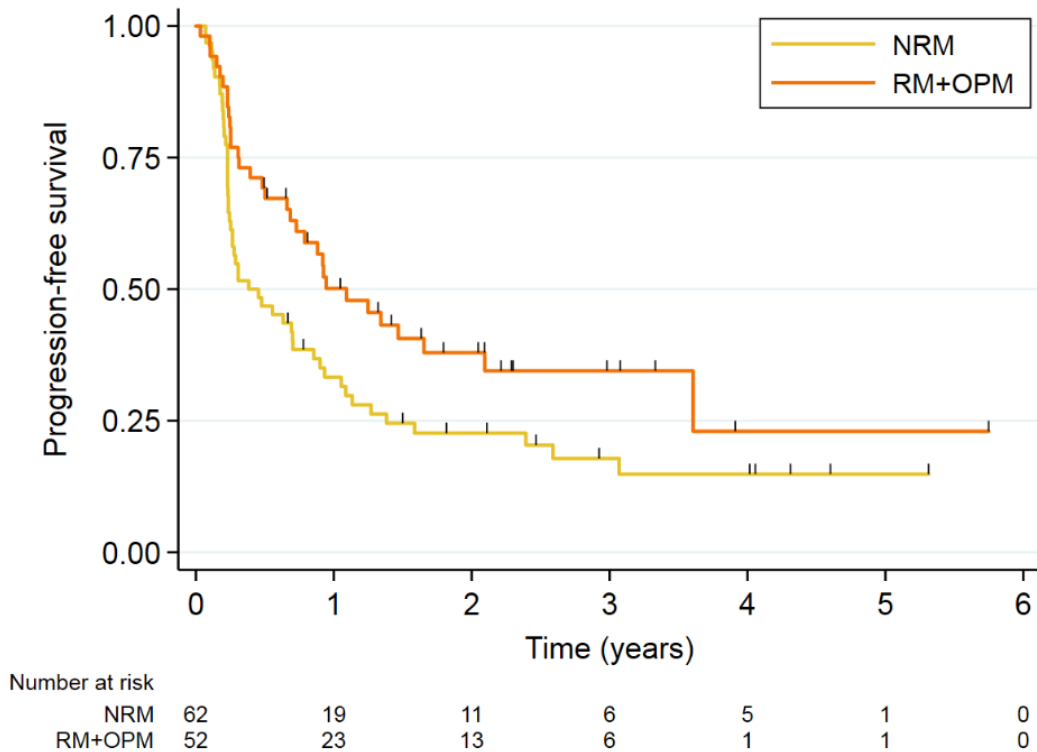
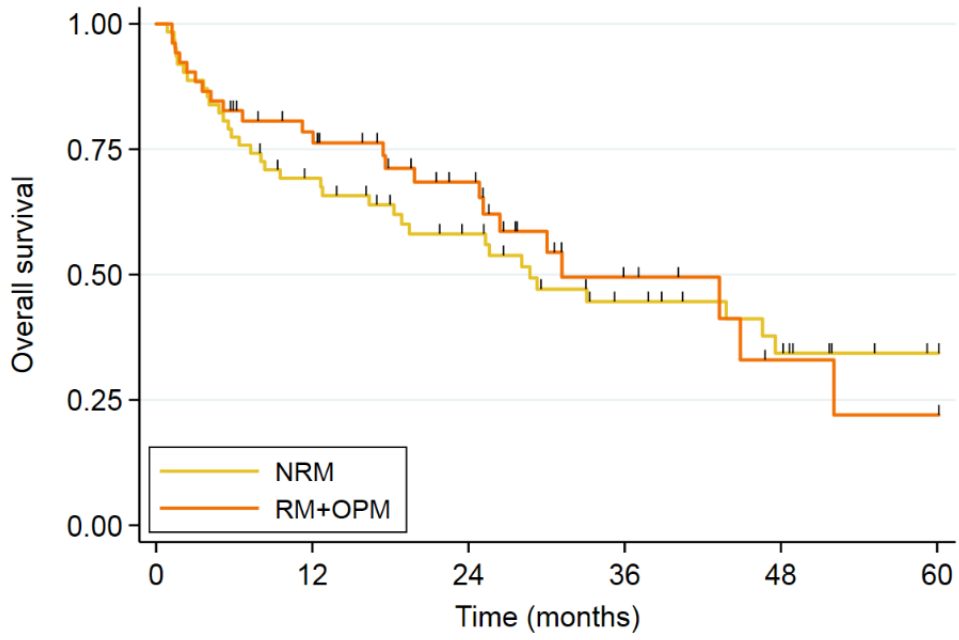


Figure 13 - Progression-free survival within the 2 groups



Number at risk		0	12	24	36	48	60
NRM	62		40	28	16	10	3
RM+OPM	52		36	23	9	3	2

Figure 14 - Overall survival within the 2 groups

V. Discussion

This retrospective work allowed us to establish the profile of the patients with a metastatic melanoma, naïve of treatment, and eligible for immunotherapy in first line of treatment in the Dermatology Department of Clermont-Ferrand.

In agreement with national and international data, there is an over-representation of males and a median age at diagnosis in the seventh decade. Gender has been confirmed as an independent predictive factor in stage IV melanoma after adjusting for other known factors, such as lifestyle, age, and Breslow thickness. This has suggested that biological differences between men and women may play a role (80) but also sociological differences as thick melanomas are more frequent in male patients who are more likely to neglect their health, especially if they are single. (81)

The main histological features are comparable to those observed in the literature: a quarter of the metastatic patients had regression at diagnosis. By likening OPM to melanomas with complete regression, the population of interest of this study becomes non-negligible, as it concerns 45% of our sample, underlining the importance of a better understanding of this phenomenon and the identification of criteria to anticipate the response to treatment. However, it should be noted that OPMs are over-represented in our sample of patients: in fact, they are three to four times more common than those reported in the literature. (82) It would be interesting to verify that for our patients qualified as OPM, an exhaustive dermatological examination was correctly performed, that a meticulous interrogation was carried out in order not to ignore a previous melanoma omitted by the patient or his medical file and finally that the endoscopic exploration in search of a mucosal melanoma was as exhaustive as possible. This observation may also be an incidental finding in our small sample of patients.

In accordance with other studies, we observed that the most common site of distant metastases is the lungs (83), (84). It could be explained by the fact that blood and lymphatic fluid returning from the periphery are first pumped through the pulmonary vasculature, making the lungs a hub of the human body. (83)

Our patients are affected by the same irAEs as those described in the literature and the most frequently affected organs are the same (in decreasing order of frequency skin, colon, liver, and thyroid). However, we observe that the cutaneous adverse effects are much less frequent than what has been described in the former studies. (85) This can be explained by the fact that in most tolerance studies every symptom was reported, even the most trivial ones (dry mouth, pruritis, xerosis), whereas in our data collection we focused on more serious but less frequent irAEs (bullous rash, vitiligo, induced lupus, alopecia, lichenoid rash).

The most frequent sites of irradiation in our patients are, in decreasing order, the brain, the bones and the lymph node drainage area. As our sample is exclusively composed of patients who are already metastatic, the indication for radiotherapy is either still for disease control in oligometastatic patients or for palliative purposes as a symptomatic treatment. It is therefore not surprising the most irradiated sites are brain metastases causing headaches, sensory and/or motor deficits or behavioural disorders, and bone metastases known to be responsible for intense pain.

The objective of this study was to compare two population of patients: those with melanoma without histological regression and those with regressive melanoma, with progression-free survival as the primary outcome. The median progression-free survival was almost 40% shorter in the NRM group than in the RM group ($p=0.05$), the OPM group ($p=0.13$) and the combined pool of RM+OPM ($p=0.03$) with values comparable to those of the main phase III trials. (25), (27), (29)

Our secondary endpoints were the response on imaging performed at 3 and 6 months.

After 3 months of immunotherapy, the NRM group showed the highest proportion of patients with disease progression: 48.1% in the NRM group versus 16.7% in the RM group and 35.3% in the OPM group ($p=0.016$).

The difference was even more pronounced when comparing the NRM to the pool constituted by RM and OPM patients: 48.1% of DP versus 23.4% respectively ($p=0.01$). If the same trend is observed at 6 months of treatment, the difference is no longer significant between the two groups ($p=0.07$).

These results thus seem to support the hypothesis that histological regression is a histological witness of an immune response of the host against its tumor and that this response seems to be enhanced by immunotherapy. It would be interesting to re-evaluate this therapeutic response on a much longer term to observe if this better response to immunotherapy in regressive patients is not only temporary and does not fade with time.

However, if a more intense response to immunotherapy seems to be apparent in patients with regressive melanoma, the impact on overall survival remains to be shown. Although the differences were not significant between the NRM and MR groups, it is noteworthy that patients with an occult primary melanoma have a doubled risk of death in the first five years compared to patients with a NRM ($p=0.03$). Otherwise, the global five-year overall survival is consistent with the literature.

Apart from the therapeutic response and survival, we compared many characteristics of the NRM and RM groups related to their disease and its evolution. If the 2 groups are quite homogeneous on most of the studied criteria, several statistically significant differences are to be noted.

First, it is surprising to note that among our patients, none of the ALMs showed regression, whereas, in the literature, regression seems to occur in the same proportion in ALMs than in the other subtypes in this histological subtype.(86) (87) This finding seems fortuitous and probably related to the absence of a sufficiently large sample of patients.

Secondly, concerning the molecular biology data, it is remarkable to note that all melanomas with a CKIT mutation were concerned by regression. No publication has yet been published on the link between mutation status and regression. The CKIT mutation is one of the least frequent, affecting only 3 to 4% of melanomas. (88) In view of the small number of patients concerned by this mutation in our study, it is therefore advisable to remain cautious about the interpretation of such a difference between our two groups, which may be incidental. It would be interesting to observe on a larger cohort the impact of this mutation on the occurrence of regression and why not of a "better responder" immune profile to immunotherapy.

Thirdly, we note significantly ($p=0.002$) a more frequent usage of radiotherapy in the NRM group (59.6%) than in the RM (28.1%) and OPM (25%) groups. This may confirm our hypothesis

that the presence of regression in a patient undergoing immunotherapy would constitute a factor of better response with less need for radiotherapy.

Regression therefore remains a complex parameter to include in our therapeutic approach. A prospective collection of new melanoma cases would be necessary with a double-blind reading of the slides by two pathologists with a standard histological report with common criteria for identification, description, and quantification of the regression.

The constitution of such a sample of patients would then allow us to prospectively evaluate the therapeutic response and the survival data of these patients presenting a regression and thus we could include the latter in the arsenal of data to be considered at the time of the initiation of our treatments and to be kept in mind during the follow-up of our patients.

While it is more intuitive to assess the relationship between regression and immunotherapy, targeted therapies also seem to modulate the immune response and why not the one present within the areas of regression.

Targeted therapies have indeed been shown to induce modifications in the expression of some surface molecules thus affecting the melanoma-specific immune response at a level of antigen-specific T-lymphocyte response. (89) In fact, anti-*BRAF* targeted therapies seems to play a role in the immune reaction towards cancer cells with an increase of T-Lymphocytes infiltrating the tumor and a higher cytotoxicity. (90) (91)

It would therefore also be relevant in the future studies, to look at the predictive role of regression in patients receiving this alternative line of therapy.

VI. Conclusion

The incidence of cutaneous melanoma has been steadily increasing over the last few years. Although the risk factors are now well known, its evolution remains unpredictable. At the same time, the last decade has been marked by numerous therapeutic advances with the advent of immunotherapy and targeted therapies.

Being one of the most immunogenic cancers, it is not surprising that melanoma in its metastatic form was one of the first validated indications for immunotherapy with anti PD1 and anti CTLA4 targeting immune locks and thus restoring the immune response. As the response to these treatments is not consistent, it would be interesting to establish predictive criteria for a good response in our patients.

It has already been established that melanoma patients with a lymphocytic tumor infiltrate called "TIL" have better progression-free and overall survival. Similarly, patients who have developed vitiligo subsequent to their melanoma diagnosis have been identified as better responders to immunotherapy.

Regression, a histological criterion systematically described on a pathological report, is defined as an immune response of the host to the tumor cells resulting in a focal or complete reduction of the tumor. This last case would be a potential explanation for the so-called "unknown primary" melanomas discovered only on a metastatic location. Its prognostic role remains controversial, largely due to the lack of consensus criteria in its recognition, description, and quantification.

These three phenomena (TIL, vitiligo, and regression) involve an immune response mediated by the same panel of lymphocytes. The similarities between these different manifestations suggest that they belong to the same spectrum of anti-tumor response. Naturally, the question arises as to the prognostic role of regression and its inclusion in the factors of response to immunotherapy. Although the various studies aimed at evaluating the prognostic

role of regression have led to discordant results, no study has been conducted on patients with stage IV melanoma.

These observations led to this retrospective study to draw up a profile of our metastatic patients and to compare the therapeutic response and survival of regressive and non-regressive melanomas.

The results of this work seem to show, in patients with regressive melanoma or of unknown origin, a better early therapeutic response on imaging performed at 3 and 6 months after initiation of immunotherapy. We also observed a favourable trend of regression on progression-free survival without impacting overall survival.

Nevertheless, these results must be interpreted with caution due to the small sample size and the lack of consensus on the evaluation of regression.

If with this thesis work, we have initiated the reflection on regression as a predictive factor of response to immunotherapy for metastatic melanoma, we will inevitably be led to ask ourselves the same question on the role of regression with targeted therapies because of the immune effects recently described with this therapeutic range.

Le Doyen de l'UFR de Médecine,

Pierre CLAVELOU



Le Président du Jury,

Michel D'INCAN

A handwritten signature in black ink, consisting of a large loop followed by a horizontal line.

VII. References

1. Cancer today [Internet]. [cité 3 août 2022]. Disponible sur: <http://gco.iarc.fr/today/home>
2. Nikolaou V, Stratigos AJ. Emerging trends in the epidemiology of melanoma. *Br J Dermatol.* janv 2014;170(1):11-9.
3. Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, et al. Prognostic Factors Analysis of 17,600 Melanoma Patients: Validation of the American Joint Committee on Cancer Melanoma Staging System. *J Clin Oncol.* 15 août 2001;19(16):3622-34.
4. Ribero S, Moscarella E, Ferrara G, Piana S, Argenziano G, Longo C. Regression in cutaneous melanoma: a comprehensive review from diagnosis to prognosis. *J Eur Acad Dermatol Venereol.* déc 2016;30(12):2030-7.
5. Smoller BR. Histologic criteria for diagnosing primary cutaneous malignant melanoma. *Mod Pathol.* févr 2006;19(52):S34-40.
6. Saleh FH, Crotty KA, Hersey P, Menzies SW. Primary melanoma tumour regression associated with an immune response to the tumour-associated antigen melan-A/MART-1. *Int J Cancer.* 15 nov 2001;94(4):551-7.
7. Ribero S, Gualano MR, Osella-Abate S, Scaioli G, Bert F, Sanlorenzo M, et al. Association of Histologic Regression in Primary Melanoma With Sentinel Lymph Node Status: A Systematic Review and Meta-analysis. *JAMA Dermatol.* 1 déc 2015;151(12):1301.
8. Ribero S, Osella-Abate S, Sanlorenzo M, Savoia P, Atrua C, Cavaliere G, et al. Favourable prognostic role of regression of primary melanoma in AJCC stage I-II patients. *Br J Dermatol.* déc 2013;169(6):1240-5.
9. Zugna D, Senetta R, Osella-Abate S, Fierro MT, Pisacane A, Zaccagna A, et al. Favourable prognostic role of histological regression in stage III positive sentinel lymph node melanoma patients. *Br J Cancer.* 6 févr 2018;118(3):398-404.
10. Erdag G, Schaefer JT, Smolkin ME, Deacon DH, Shea SM, Dengel LT, et al. Immunotype and Immunohistologic Characteristics of Tumor-Infiltrating Immune Cells Are Associated with Clinical Outcome in Metastatic Melanoma. *Cancer Res.* 1 mars 2012;72(5):1070-80.
11. Piras F, Colombari R, Minerba L, Murtas D, Floris C, Maxia C, et al. The predictive value of CD8, CD4, CD68, and human leukocyte antigen-D-related cells in the prognosis of cutaneous malignant melanoma with vertical growth phase. *Cancer.* 15 sept 2005;104(6):1246-54.
12. Clemente CG, Mihm MC, Bufalino R, Zurrida S, Collini P, Cascinelli N. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. *Cancer.* 1 avr 1996;77(7):1303-10.
13. Lee N, Zakka LR, Mihm MC, Schatton T. Tumour-infiltrating lymphocytes in melanoma prognosis and cancer immunotherapy. *Pathology (Phila).* févr 2016;48(2):177-87.

14. Osella-Abate S, Conti L, Annaratone L, Senetta R, Bertero L, Licciardello M, et al. Phenotypic characterisation of immune cells associated with histological regression in cutaneous melanoma. *Pathology (Phila)*. août 2019;51(5):487-93.
15. Schallreuter KU, Levenig C, Berger J. Vitiligo and Cutaneous Melanoma. *Dermatology*. 1991;183(4):239-45.
16. Ramondetta A, Ribero S, Conti L, Fava P, Marra E, Broganelli P, et al. Clinical and Pathological Relevance of Drug-induced Vitiligo in Patients Treated for Metastatic Melanoma with Anti-PD1 or BRAF/MEK Inhibitors. *Acta Derm Venereol*. 2020;100(1):1-5.
17. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer*. janv 2005;41(1):45-60.
18. Olsen CM, Carroll HJ, Whiteman DC. Familial Melanoma: A Meta-analysis and Estimates of Attributable Fraction. *Cancer Epidemiol Biomarkers Prev*. janv 2010;19(1):65-73.
19. Udayakumar D, Mahato B, Gabree M, Tsao H. Genetic Determinants of Cutaneous Melanoma Predisposition. *Semin Cutan Med Surg*. sept 2010;29(3):190-5.
20. Grob JJ, Long GV, Schadendorf D, Flaherty K. Disease kinetics for decision-making in advanced melanoma: a call for scenario-driven strategy trials. *Lancet Oncol*. oct 2015;16(13):e522-6.
21. Marzagalli M, Ebelt ND, Manuel ER. Unraveling the crosstalk between melanoma and immune cells in the tumor microenvironment. *Semin Cancer Biol*. 1 déc 2019;59:236-50.
22. Passarelli A, Mannavola F, Stucci LS, Tucci M, Silvestris F. Immune system and melanoma biology: a balance between immunosurveillance and immune escape. *Oncotarget*. 1 déc 2017;8(62):106132-42.
23. Polak ME, Borthwick NJ, Gabriel FG, Johnson P, Higgins B, Hurren J, et al. Mechanisms of local immunosuppression in cutaneous melanoma. *Br J Cancer*. 18 juin 2007;96(12):1879-87.
24. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in Previously Untreated Melanoma without BRAF Mutation. *N Engl J Med*. 22 janv 2015;372(4):320-30.
25. Robert C, Long GV, Brady B, Dutriaux C, Di Giacomo AM, Mortier L, et al. Five-Year Outcomes With Nivolumab in Patients With Wild-Type *BRAF* Advanced Melanoma. *J Clin Oncol*. 20 nov 2020;38(33):3937-46.
26. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med*. 25 juin 2015;372(26):2521-32.
27. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol*. sept 2019;20(9):1239-51.
28. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med*. 5 oct 2017;377(14):1345-56.

29. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med*. 17 oct 2019;381(16):1535-46.
30. Ralli M, Botticelli A, Visconti IC, Angeletti D, Fiore M, Marchetti P, et al. Immunotherapy in the Treatment of Metastatic Melanoma: Current Knowledge and Future Directions. *J Immunol Res*. 28 juin 2020;2020:1-12.
31. Chang CY, Park H, Malone DC, Wang CY, Wilson DL, Yeh YM, et al. Immune Checkpoint Inhibitors and Immune-Related Adverse Events in Patients With Advanced Melanoma: A Systematic Review and Network Meta-analysis. *JAMA Netw Open*. 25 mars 2020;3(3):e201611.
32. Byrne EH, Fisher DE. Immune and molecular correlates in melanoma treated with immune checkpoint blockade: Immunotherapy Resistance in Melanoma. *Cancer*. 1 juin 2017;123(S11):2143-53.
33. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 28 juin 2012;366(26):2443-54.
34. Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature*. 16 avr 2015;520(7547):373-7.
35. Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. *Science*. 9 oct 2015;350(6257):207-11.
36. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med*. 25 juin 2015;372(26):2509-20.
37. Zaretsky JM, Garcia-Diaz A, Shin DS, Escuin-Ordinas H, Hugo W, Hu-Lieskovan S, et al. Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma. *N Engl J Med*. 1 sept 2016;375(9):819-29.
38. Kather JN, Suarez-Carmona M, Charoentong P, Weis CA, Hirsch D, Bankhead P, et al. Topography of cancer-associated immune cells in human solid tumors. *eLife*. 7:e36967.
39. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJM, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 27 nov 2014;515(7528):568-71.
40. Weide B, Martens A, Hassel JC, Berking C, Postow MA, Bisschop K, et al. Baseline Biomarkers for Outcome of Melanoma Patients Treated with Pembrolizumab. *Clin Cancer Res Off J Am Assoc Cancer Res*. 15 nov 2016;22(22):5487-96.
41. Delyon J, Mateus C, Lefevre D, Lanoy E, Zitvogel L, Chaput N, et al. Experience in daily practice with ipilimumab for the treatment of patients with metastatic melanoma: an early increase in lymphocyte and eosinophil counts is associated with improved survival. *Ann Oncol Off J Eur Soc Med Oncol*. juin 2013;24(6):1697-703.

42. Ribas A, Hamid O, Daud A, Hodi FS, Wolchok JD, Kefford R, et al. Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma. *JAMA*. 19 avr 2016;315(15):1600-9.
43. Emanuel PO, Mannion M, Phelps RG. Complete regression of primary malignant melanoma. *Am J Dermatopathol*. avr 2008;30(2):178-81.
44. Shai A, Avinoach I, Sagi A. Metastatic malignant melanoma with spontaneous and complete regression of the primary lesion. Case report and review of the literature. *J Dermatol Surg Oncol*. mai 1994;20(5):342-5.
45. Blessing K, McLaren KM, McLean A, Davidson P. Thin malignant melanomas (less than 1.5 mm) with metastasis: a histological study and survival analysis. *Histopathology*. nov 1990;17(5):389-95.
46. Kang S, Barnhill RL, Mihm MC, Sober AJ. Histologic regression in malignant melanoma: an interobserver concordance study. *J Cutan Pathol*. avr 1993;20(2):126-9.
47. Melanoma with regression and multiple network patterns [Internet]. *Dermoscopy*. 2011 [cité 4 sept 2022]. Disponible sur: <https://dermoscopy.wordpress.com/2011/03/25/melanoma-with-regression-and-multiple-network-patterns/>
48. Ronan SG, Eng AM, Briele HA, Shioura NN, Das Gupta TK. Thin malignant melanomas with regression and metastases. *Arch Dermatol*. oct 1987;123(10):1326-30.
49. Byers HR, Bhawan J. Pathologic parameters in the diagnosis and prognosis of primary cutaneous melanoma. *Hematol Oncol Clin North Am*. août 1998;12(4):717-35.
50. Guitart J, Lowe L, Piepkorn M, Prieto VG, Rabkin MS, Ronan SG, et al. Histological characteristics of metastasizing thin melanomas: a case-control study of 43 cases. *Arch Dermatol*. mai 2002;138(5):603-8.
51. Crowson AN, Magro CM, Mihm MC. Prognosticators of melanoma, the melanoma report, and the sentinel lymph node. *Mod Pathol Off J U S Can Acad Pathol Inc*. févr 2006;19 Suppl 2:S71-87.
52. Kelly JW, Sagebiel RW, Blois MS. Regression in malignant melanoma. A histologic feature without independent prognostic significance. *Cancer*. 1 nov 1985;56(9):2287-91.
53. Shaw HM, McCarthy SW, McCarthy WH, Thompson JF, Milton GW. Thin regressing malignant melanoma: significance of concurrent regional lymph node metastases. *Histopathology*. sept 1989;15(3):257-65.
54. Burton AL, Gilbert J, Farmer RW, Stromberg AJ, Hagendoorn L, Ross MI, et al. Regression does not predict nodal metastasis or survival in patients with cutaneous melanoma. *Am Surg*. août 2011;77(8):1009-13.
55. Blessing K, McLaren KM. Histological regression in primary cutaneous melanoma: recognition, prevalence and significance. *Histopathology*. avr 1992;20(4):315-22.
56. Slingluff CL, Vollmer RT, Reintgen DS, Seigler HF. Lethal « thin » malignant melanoma. Identifying patients at risk. *Ann Surg*. août 1988;208(2):150-61.

57. Søndergaard K, Hou-Jensen K. Partial regression in thin primary cutaneous malignant melanomas clinical stage I. A study of 486 cases. *Virchows Arch A Pathol Anat Histopathol.* 1985;408(2-3):241-7.
58. Testori A, De Salvo GL, Montesco MC, Trifirò G, Mocellin S, Landi G, et al. Clinical considerations on sentinel node biopsy in melanoma from an Italian multicentric study on 1,313 patients (SOLISM-IMI). *Ann Surg Oncol.* juill 2009;16(7):2018-27.
59. Morris KT, Busam KJ, Bero S, Patel A, Brady MS. Primary cutaneous melanoma with regression does not require a lower threshold for sentinel lymph node biopsy. *Ann Surg Oncol.* janv 2008;15(1):316-22.
60. Ribero S, Gualano MR, Osella-Abate S, Scaioli G, Bert F, Sanlorenzo M, et al. Association of Histologic Regression in Primary Melanoma With Sentinel Lymph Node Status: A Systematic Review and Meta-analysis. *JAMA Dermatol.* 1 déc 2015;151(12):1301-7.
61. Gualano MR, Osella-Abate S, Scaioli G, Marra E, Bert F, Faure E, et al. Prognostic role of histological regression in primary cutaneous melanoma: a systematic review and meta-analysis. *Br J Dermatol.* févr 2018;178(2):357-62.
62. Gao G, Wang Z, Qu X, Zhang Z. Prognostic value of tumor-infiltrating lymphocytes in patients with triple-negative breast cancer: a systematic review and meta-analysis. *BMC Cancer.* 4 mars 2020;20(1):179.
63. Azimi F, Scolyer RA, Rumcheva P, Moncrieff M, Murali R, McCarthy SW, et al. Tumor-Infiltrating Lymphocyte Grade Is an Independent Predictor of Sentinel Lymph Node Status and Survival in Patients With Cutaneous Melanoma. *J Clin Oncol.* 20 juill 2012;30(21):2678-83.
64. Clemente CG, Mihm MC, Bufalino R, Zurrida S, Collini P, Cascinelli N. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. *Cancer.* 1 avr 1996;77(7):1303-10.
65. Barnhill RL, Fine JA, Roush GC, Berwick M. Predicting five-year outcome for patients with cutaneous melanoma in a population-based study. *Cancer.* 1 août 1996;78(3):427-32.
66. Taylor RC, Patel A, Panageas KS, Busam KJ, Brady MS. Tumor-infiltrating lymphocytes predict sentinel lymph node positivity in patients with cutaneous melanoma. *J Clin Oncol Off J Am Soc Clin Oncol.* 1 mars 2007;25(7):869-75.
67. Naveh HP, Rao UNM, Butterfield LH. Melanoma-associated leukoderma - immunology in black and white? *Pigment Cell Melanoma Res.* nov 2013;26(6):796-804.
68. Rosenberg SA, White DE. Vitiligo in patients with melanoma: normal tissue antigens can be targets for cancer immunotherapy. *J Immunother Emphas Tumor Immunol Off J Soc Biol Ther.* janv 1996;19(1):81-4.
69. Le Gal FA, Avril MF, Bosq J, Lefebvre P, Deschemin JC, Andrieu M, et al. Direct evidence to support the role of antigen-specific CD8(+) T cells in melanoma-associated vitiligo. *J Invest Dermatol.* déc 2001;117(6):1464-70.

70. Nordlund JJ, Kirkwood JM, Forget BM, Milton G, Albert DM, Lerner AB. Vitiligo in patients with metastatic melanoma: a good prognostic sign. *J Am Acad Dermatol.* nov 1983;9(5):689-96.
71. Bystryn JC, Rigel D, Friedman RJ, Kopf A. Prognostic significance of hypopigmentation in malignant melanoma. *Arch Dermatol.* août 1987;123(8):1053-5.
72. Quaglino P, Marengo F, Osella-Abate S, Cappello N, Ortoncelli M, Salomone B, et al. Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study. *Ann Oncol Off J Eur Soc Med Oncol.* févr 2010;21(2):409-14.
73. Phan GQ, Yang JC, Sherry RM, Hwu P, Topalian SL, Schwartzentruber DJ, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. *Proc Natl Acad Sci U S A.* 8 juill 2003;100(14):8372-7.
74. Boasberg PD, Hoon DSB, Piro LD, Martin MA, Fujimoto A, Kristedja TS, et al. Enhanced survival associated with vitiligo expression during maintenance biotherapy for metastatic melanoma. *J Invest Dermatol.* déc 2006;126(12):2658-63.
75. Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, et al. Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab. *JAMA Dermatol.* janv 2016;152(1):45-51.
76. Osella-Abate S, Conti L, Annaratone L, Senetta R, Bertero L, Licciardello M, et al. Phenotypic characterisation of immune cells associated with histological regression in cutaneous melanoma. *Pathology (Phila).* août 2019;51(5):487-93.
77. van Geel NAC, Mollet IG, De Schepper S, Tjin EPM, Vermaelen K, Clark RA, et al. First histopathological and immunophenotypic analysis of early dynamic events in a patient with segmental vitiligo associated with halo nevi. *Pigment Cell Melanoma Res.* juin 2010;23(3):375-84.
78. Chimio [Internet]. Computer Engineering. [cité 11 août 2022]. Disponible sur: <https://www.computer-engineering.fr/applications/chimio/>
79. Régression déf CAP [Internet]. [cité 9 août 2022]. Disponible sur: <https://documents.cap.org/protocols/cp-melanoma-skin-2017-v4000.pdf>
80. Joosse A, Collette S, Suci S, Nijsten T, Patel PM, Keilholz U, et al. Sex is an independent prognostic indicator for survival and relapse/progression-free survival in metastasized stage III to IV melanoma: a pooled analysis of five European organisation for research and treatment of cancer randomized controlled trials. *J Clin Oncol Off J Am Soc Clin Oncol.* 20 juin 2013;31(18):2337-46.
81. Grange F, Barbe C, Aubin F, Lipsker D, Granel-Brocard F, Velten M, et al. Clinical and Sociodemographic Characteristics Associated With Thick Melanomas: A Population-Based, Case-Case Study in France. *Arch Dermatol.* 1 déc 2012;148(12):1370.
82. Scott JF, Gerstenblith MR. Melanoma of Unknown Primary. In: Scott JF, Gerstenblith MR, éditeurs. *Noncutaneous Melanoma* [Internet]. Brisbane (AU): Codon Publications; 2018 [cité 15 sept 2022]. Disponible sur: <http://www.ncbi.nlm.nih.gov/books/NBK506989/>

83. Damsky WE, Rosenbaum LE, Bosenberg M. Decoding Melanoma Metastasis. *Cancers*. 30 déc 2010;3(1):126-63.
84. Zhou C, Louwman M, Wakkee M, van der Veldt A, Grünhagen D, Verhoef C, et al. Primary Melanoma Characteristics of Metastatic Disease: A Nationwide Cancer Registry Study. *Cancers*. 2 sept 2021;13(17):4431.
85. Darnell EP, Mooradian MJ, Baruch EN, Yilmaz M, Reynolds KL. Immune-Related Adverse Events (irAEs): Diagnosis, Management, and Clinical Pearls. *Curr Oncol Rep*. avr 2020;22(4):39.
86. Paladugu RR, Winberg CD, Yonemoto RH. Acral lentiginous melanoma A clinicopathologic study of 36 patients. *Cancer*. 28 juin 2006;52(1):161-8.
87. Lee TL, Lin MH, Liao YH, Liao JY, Sheen YS. Clinicopathological characteristics and prognosis in significantly thick acral lentiginous melanoma in Taiwan. *J Formos Med Assoc* [Internet]. 25 déc 2021 [cité 17 sept 2022]; Disponible sur: <https://www.sciencedirect.com/science/article/pii/S0929664621005349>
88. Yaman B, Akalin T, Kandiloğlu G. Clinicopathological Characteristics and Mutation Profiling in Primary Cutaneous Melanoma. *Am J Dermatopathol*. mai 2015;37(5):389-97.
89. Long GV, Wilmott JS, Haydu LE, Tembe V, Sharma R, Rizos H, et al. Effects of BRAF inhibitors on human melanoma tissue before treatment, early during treatment, and on progression. *Pigment Cell Melanoma Res*. juill 2013;26(4):499-508.
90. Hu-Lieskovan S, Mok S, Homet Moreno B, Tsoi J, Robert L, Goedert L, et al. Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in *BRAF*^{V600E} melanoma. *Sci Transl Med* [Internet]. 18 mars 2015 [cité 17 sept 2022];7(279). Disponible sur: <https://www.science.org/doi/10.1126/scitranslmed.aaa4691>
91. Wilmott JS, Long GV, Howle JR, Haydu LE, Sharma RN, Thompson JF, et al. Selective BRAF Inhibitors Induce Marked T-cell Infiltration into Human Metastatic Melanoma. *Clin Cancer Res*. 1 mars 2012;18(5):1386-94.

VIII. Appendix

Appendix 1 - Patient characteristics in the 2 groups analysis

	Total (n=114)	NRM (n=62)	RM + OPM (n=52)	<i>p</i>
Age (years)	65.4 ± 13.7	65.9 ± 12.9	64.8 ± 14.7	0.67
Male gender	74 (64.9)	36 (58.0)	38 (73.1)	0.094
Histological subtype				
SSM	50 (53.0)	31 (50)	19 (59.4)	
ALM	15 (15.9)	15 (24.1)	0 (0)	
LM	5 (5.3)	3 (4.8)	2 (6.2)	
Nodular	16 (17.0)	9 (14.5)	7 (21.9)	
Desmoplastic	4 (4.26)	3 (3.1)	1 (3.1)	
Unclassifiable	4 (4.26)	1 (1.6)	3 (9.4)	
Clark level				
I	2 (2.1)	2 (3.3)	0 (0)	
II	3 (3.2)	3 (4.9)	0 (0)	
III	21 (22.6)	12 (19.7)	9 (28.1)	
IV	47 (50.5)	28 (45.9)	19 (59.4)	
V	20 (21.5)	16 (26.2)	4 (12.5)	
Ulceration	56 (59.6)	36 (58)	20 (62.5)	
Mitotic index				
I	20 (21.5)	13 (21.3)	7 (21.9)	
II	52 (55.9)	35 (57.4)	17 (53.1)	
III	21 (22.6)	13 (21.3)	8 (25)	
Mutation				
BRAF	26 (22.8)	11 (17.7)	15 (28.9)	
CKIT	5 (4.4)	5 (8.1)	0 (0)	
NRAS	15 (13.1)	5 (8.1)	10 (19.2)	
Unmutated	68 (59.7)	41 (66.1)	27 (51.9))	
Breslow index (milimeters)	4.0 [2.1 ;6.0]	4.0 [2.1 ; 7.0]	4.0 [2.3 ; 5.7]	
ECOG score				
0	59 (51.8)	36 (58)	23 (44.2)	0.16
1	23 (20.2)	11 (17.7)	12 (23.1)	
2	23 (20.2)	13 (21)	10 (19.2)	
3	7 (6.1)	1 (1.6)	6 (11.5)	
4	2 (1.7)	1 (1.6)	1 (1.9)	
LDH rate				
N	80 (70.2)	39 (62.9)	41 (78.9)	0.13
N to 2N	19 (16.7)	14 (22.6)	5 (9.6)	
>2N	15 (13.1)	9 (14.5)	6 (11.5)	

Albumine rate (g/L)				
<20	1 (0.9)	0 (0)	1 (1.9)	0.83
20-30	14 (12.3)	8 (12.9)	6 (11.5)	
30-35	18 (15.8)	9 (14.5)	9 (17.3)	
>35	81 (71)	45 (72.6)	36 (69.2)	
Lymphocytes rate (G/L)				
<1.5	60 (52.6)	33 (53.2)	27 (51.9)	0.58
1.5-4.0	52 (45.6)	27 (43.6)	25 (48.1)	
>4.0	2 (1.8)	2 (3.2)	0 (0)	
SLN procedure				
Yes and positive LND	11 (13.3)	8 (14.8)	3 (10.3)	0.79
Yes and negative LND	17 (20.5)	10 (18.5)	7 (24.1)	
No	55 (66.2)	36 (66.7)	19 (65.5)	
Metastatic location				
Brain	30 (26.3)	15 (24.2)	15 (28.5)	0.57
Liver	19 (16.7)	9 (14.5)	10 (19.2)	0.50
Thyroid	1 (0.9)	0 (0)	1 (1.9)	0.46
Lung	59 (51.7)	33 (53.2)	26 (50)	0.73
Spleen	6 (5.3)	4 (6.5)	2 (3.9)	0.69
Oropharynx	1 (0.9)	1 (1.6)	0 (0)	1.00
Muscle	3 (2.6)	3 (4.8)	0(0)	0.25
Adrenal gland	5 (4.4)	5 (8.1)	0(0)	0.06
Gastrointestinal tract	8 (7)	0 (0)	8(15.4)	0.001
Lymph node	31 (27.2)	18 (29)	13 (25)	0.63
Subcutaneous	34 (29.8)	17 (27.4)	17 (32.7)	0.54
Bone	22 (19.3)	14 (22.6)	8 (15.4)	0.33
Kidney	2 (1.7)	2 (3.2)	0 (0)	0.50
Pancreas	4 (3.5)	2 (3.2)	2 (3.9)	1.00
Peritoneal carcinosis	5 (4.4)	1 (1.6)	4 (7.7)	0.18
Eye	1 (0.9)	1 (1.6)	0 (0)	1.00
Nasal cavity	1 (0.9)	1 (1.6)	0 (0)	1.00
Imaging response M3				
Disease progress DP	37 (36.6)	26 (48.1)	11 (23.4)	0.007
Stable disease SD	29 (28.7)	9 (16.6)	20 (42.6)	
Partial response PR	30 (29.7)	15 (27.7)	15 (31.9)	
Complete response CR	5 (4.9)	4 (7.41)	1 (2.1)	
Imaging response M3				
DP	37 (36.6)	26 (48.1)	11 (23.4)	0.01
SD+PR+CR	64 (63.4)	28 (51.9)	36 (76.6)	
Imaging response M4				
Disease progress DP	25 (67.5)	19 (86.3)	6 (40.0)	0.006
Stable disease SD	10 (27.0)	3 (13.6)	2 (13.3)	
Partial response PR	2 (5.4)	0 (0.0)	7 (46.7)	

Imaging response M4				
DP	25 (67.6)	19 (86.4)	6 (40)	0.003
SD+PR	12 (32.4)	3 (13.6)	9 (60)	
Imaging response M6				
Disease progress	27 (32.1)	18 (40.9)	9 (22.5)	0.34
Stable disease	21 (25.0)	9 (20.4)	12 (30.0)	
Partial response	23 (27.3)	11 (25.0)	12 (30.0)	
Complete response	13 (15.4)	6 (13.6)	7 (17.5)	
Imaging response M6				
DP	27 (32.1)	18 (40.9)	9 (22.5)	0.07
SD+PR+CR	57 (67.9)	26 (59.1)	31 (77.5)	
Deaths	58 (50.8)	35 (56.4)	23 (44.2)	0.19
Immunotherapy				
Nivolumab	55 (48.2)	28 (45.1)	27 (51.9)	0.77
Pembrolizumab	33 (29)	19 (30.7)	14 (28.9)	
Ipilimumab/Nivolumab	26 (22.8)	15 (24.2)	11 (21.2)	
Adverse effect				
Any	50 (43.8)	28 (45.1)	22 (42.3)	0.76
Colitis	13 (11.4)	8 (12.9)	5 (9.6)	0.58
Hepatitis	7 (6.1)	4 (6.4)	3 (5.8)	1.00
Thyroid disorder	10 (8.7)	4 (6.4)	6 (11.5)	0.51
Vitiligo	8 (7.0)	5 (8.0)	3 (5.8)	0.73
Alopecia	1 (0.8)	1 (1.6)	0 (0)	1.00
Lupus induced	1 (0.8)	1 (1.6)	0 (0)	1.00
Myocarditis	1 (0.88)	0 (0.0)	1 (1.9)	0.46
Adrenal insufficiency	4 (3.51)	2 (3.2)	2 (3.8)	1.00
Myositis	3 (2.6)	2 (3.2)	1 (1.9)	1.00
Nephritis	4 (3.51)	4 (6.4)	0 (0)	0.12
Pneumonitis	2 (1.7)	2 (3.2)	0 (0)	0.50
Diabetes	1 (0.8)	0 (0.0)	1 (1.9)	0.46
Hypophysitis	2 (1.7)	1 (1.6)	1 (1.9)	1.00
Myasthenia	1 (0.8)	0 (0.0)	1 (1.9)	0.46
Nevritis	2 (1.7)	0 (0.0)	2 (3.8)	0.21
Synovitis	1 (0.8)	0 (0.0)	1 (1.9)	0.46
Bullous eruption	1 (0.8)	1 (1.6)	0 (0)	1.00
Lichenoid eruption	1 (0.8)	1 (1.6)	0 (0)	1.00
Exanthema	1 (0.8)	0 (0.0)	1 (1.9)	1.00

Radiotherapy				
Any	51 (44.7)	37 (59.6)	14 (26.9)	<0.001
Brain radiotherapy	20 (17.5)	12 (19.3)	8 (15.4)	0.58
Bone radiotherapy	13 (11.4)	8 (12.9)	5 (9.6)	0.58
Tumoral site radiotherapy	5 (4.3)	4 (6.4)	1 (1.9)	0.37
Subcutaneous metastasis radiotherapy	3 (2.6)	3 (4.8)	0 (0)	0.25
Lymph node radiotherapy	8 (7.0)	8 (12.9)	0 (0)	0.008
Lung radiotherapy	4 (3.5)	3 (4.8)	1 (1.9)	0.62
Number of treatment lines				
1	65 (57.0)	30 (48.3)	35 (67.3)	0.04
≥2	49 (42.9)	32 (51.6)	17 (32.7)	
Treatment duration (in months)	7 [2 ;16]	5 [2 ;13]	9 [3 ;19]	0.07
Reason for discontinuation of immunotherapy				
Alteration of the general state	7 (6.1)	3 (4.8)	4 (7.7)	
BRAF mutation	2 (1.75)	0 (0.0)	2 (3.9)	
Severe adverse effect	10 (8.7)	7 (11.2)	3 (5.4)	
Progression	42 (36.8)	27 (43.5)	15 (28.9)	
Complete response	14 (12.2)	8 (12.9)	6 (11.5)	
Death	23 (20.1)	13 (20.9)	10 (19.2)	
No discontinuation	16 (14.0)	4 (6.4)	12 (23.1)	
<p><i>NRM= Non Regressive Melanoma; RM = Regressive Melanoma; OPM = Occult Primary Melanoma; SSM = Superficial Spreading Melanoma; ALM = Acro Lentiginous Melanoma; LM= Lentigo Melanoma; ECOG = Eastern Cooperative Oncology Group; LDH = Lactate Deshydrogenase; SLN = Sentinel Lymph Node; LND = Lymph Node Dissection</i></p>				

(Conseil national de l'ordre des médecins)

SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés.

Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque.

SUCH, Jean-Baptiste

Signature

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure 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 je n'exigerai jamais un salaire au-dessus de mon travail. Admis 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.

Respectueux et reconnaissant 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 couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

SUCH Jean-Baptiste

Signature

La régression histologique du mélanome au diagnostic constitue-t-elle un facteur de bonne réponse à l'immunothérapie en 1^{ère} ligne métastatique ?

Introduction : La prise en charge du mélanome cutané métastatique a été révolutionnée ces dix dernières années avec l'arrivée de l'immunothérapie. Les critères permettant de distinguer les patients répondeurs des non répondeurs à cette thérapeutique restent peu connus. 10 à 35% des mélanomes présentent au diagnostic une régression histologique, définie contre une réponse immune face aux cellules tumorales. Ce phénomène est à rapprocher des lymphocytes infiltrant la tumeur (=TIL) et du phénomène de vitiligo induit sous mélanome, respectivement facteurs de bon pronostic et prédictif de réponse à l'immunothérapie. Le rôle de la régression comme facteur prédictif de réponse à l'immunothérapie dans les mélanomes métastatiques n'a pas encore été étudiée.

Matériel et méthodes : Nous avons recueilli sur le CHU de Clermont-Ferrand les données de 114 patients atteints d'un mélanome métastatique ayant reçu une immunothérapie en 1^{ère} ligne sur la période du 1^{er} janvier 2015 au 30 juin 2021. Nous avons comparé chez les mélanomes régressifs et les non régressifs la réponse thérapeutique basée sur l'imagerie et la survie globale ainsi que sans progression.

Résultats : Les patients avec un mélanome régressif survivent plus longtemps sans progression métastatique ($HR=0.60$; $p=0.03$) et présentent une meilleure réponse thérapeutique d'après les imageries réalisées à M3 et M6 avec respectivement seulement 23,4% et 22,5% de progression métastatique dans le groupe régressif contre 48.1% et 40.9% dans le groupe non régressif ($p=0.01$ et $p=0.07$). Si précocement la survie globale semble meilleure dans le groupe régressif, cette tendance ne se vérifie pas sur le plus long terme.

Conclusion : La régression semble prédictive d'une meilleure réponse à l'immunothérapie sans pour autant impacter la survie globale.

Mots-clés :

- Mélanome métastatique
- Lymphocytes infiltrant la tumeur (TIL)
- Immunothérapie
- Vitiligo
- Régression histologique