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Perrine Rousset

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**CLINICAL OUTCOMES OF SYSTEMIC THERAPIES IN METASTATIC MELANOMA
OF UNKNOWN PRIMARY VERSUS KNOWN CUTANEOUS:
A MULTI-CENTER RETROSPECTIVE STUDY FROM MELBASE,
A NATIONWIDE PROSPECTIVE COHORT**

Thèse d'exercice de Médecine

Présentée et soutenue publiquement devant la Faculté de Médecine de Nice

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Pour obtenir le diplôme d'Etat de Docteur en Médecine

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ABRÉVIATIONS

AJCC: American Joint Committee on Cancer

CNS: Central Nervous System

CT: Chemotherapy

CTLA4: Cytotoxic T-lymphocyte-associated antigen 4

ECOG: Eastern Cooperative Oncology Group

irAEs: Immune-related Adverse Events

ICIs: Immune Checkpoint Inhibitors

LDH: Lactate Dehydrogenase

MUP: Melanoma of unknown primary

MKP: Melanoma of known primary

cMKP: Melanoma of known cutaneous primary

OS: Overall Survival

PFS: Progression-Free Survival

PD- (L)1: Programmed cell death (Ligand) 1

TRAEs: Treatment-Related Adverse Events

TT: Targeted Therapy

I- ABSTRACT

1. Abstract

IMPORTANCE

Melanoma of unknown primary (MUP) account for 3% of all melanomas. Clinical outcomes of advanced MUP in the era of novel therapies including immunotherapies (ICI) and targeted therapies (TT) have been only scarcely studied, whereas a possibly different biologic background might introduce changes in its management. Recent retrospective studies suggested that patients with advanced MUP could benefit at least as much from novel therapies as patients with known primary cutaneous melanoma (cMKP).

OBJECTIVE

To investigate the efficacy and safety of systemic treatments (ICI, TT and chemotherapy (CT)) in patients with advanced MUP compared to patients with stage-matched cMKP.

MATERIAL AND METHODS

Based on the nationwide MelBase prospective database (NCT02828202) this retrospective study included patients with advanced melanoma treated with first-line ICI, TT or CT. MUP was defined as the upfront occurrence of (sub)cutaneous, nodal and/or visceral metastasis without any known prior or concomitant primary tumor. Patients with primary mucosal or ocular melanoma were excluded. Both progression-free survival (PFS) and overall survival (OS) were analyzed as co-primary variables in MUP vs cMKP, stratified by treatment subset (ICI vs TT vs CT vs whole cohort). Secondary outcome was treatment-related toxicities. Multivariate and propensity score analyses were performed.

RESULTS

A total of 1882 patients were analyzed, including 265 (14.1%) MUP. Most patients were treated with first-line ICI, followed by first-line TT. The median follow-up duration was 16 months. MUP patients more often displayed unfavorable initial prognostic factors. PFS and OS did not differ significantly between the two groups ($P= 0.73$ and $P= 0.93$; respectively). Stratification

by treatment type and application of propensity score did not lead to data modification. The treatment-related toxicity rate and severity did not differ between MUP and cMKP patients, regardless of treatment type, especially for immune-related adverse events in ICI cohort.

CONCLUSIONS AND RELEVANCE

Our results suggest that advanced MUP should be managed with similar strategies as advanced cMKP. In our cohort, MUP patients benefited from novel therapies as much as cMKP patients despite less favorable baseline prognostic factors. Exploratory studies investigating mutational burden and host immunity are needed to identify the underlying mechanisms.

2. Résumé

INTRODUCTION

Le mélanome de primitif inconnu (MPI) représente environ 3 % des mélanomes et est défini par une atteinte d'emblée métastatique sans lésion primitive antérieure ou synchrone identifiée. Plusieurs hypothèses physiopathologiques ont été émises parmi lesquelles la transformation maligne de mélanocytes ectopiques localisés dans les tissus extra-cutanés ou encore la régression du mélanome primitif sous l'effet d'une réaction immunitaire impliquant des mécanismes humoraux et cellulaires.

A l'ère des nouveaux traitements systémiques par immunothérapie (ICI) et thérapie ciblée (TC) qui ont révolutionné la prise en charge des mélanomes avancés, les essais cliniques n'ont pas spécifiquement évalué les résultats cliniques de ces thérapies dans la population des MPI alors que ces considérations immunologiques pourraient impliquer une prise en charge thérapeutique plus spécifique. Plusieurs études rétrospectives ont suggéré que les patients atteints de MPI avancé répondraient aussi bien à ces nouveaux traitements, voire mieux à l'ICI, que les mélanomes avec primitif cutané connu (cMPC).

OBJECTIF

Aussi, avons-nous évalué l'efficacité et la tolérance des différents traitements systémiques (ICI, TC et chimiothérapie (CT)) chez les MPI comparativement aux cMPC.

MATÉRIEL ET MÉTHODES

Cette étude rétrospective a été menée à partir de la cohorte française prospective MelBase. Les patients atteints de mélanome avancé (stade III non résecable ou IV selon AJCC) traités en 1^{ère} ligne par ICI, TC et CT entre mars 2013 et juin 2021 étaient inclus.

Les MPI étaient définis par une atteinte d'emblée métastatique (sous-)cutanée, ganglionnaire ou viscérale documentée histologiquement, sans identification d'un primitif synchrone ou antérieur. Les patients qui présentaient un mélanome muqueux ou choroïdien étaient exclus.

Les co-critères de jugement principaux étaient l'association entre survie sans progression (SSP) et survie globale (SG) selon le statut MPI ou cMPC, stratifiés selon l'âge, le sexe et le traitement

(tout type de traitement vs ICI vs TC vs CT). La tolérance était analysée comme critère de jugement secondaire. Des analyses multivariées et un score de propension ont été pratiqués.

RÉSULTATS

Un total de 1882 patients a été inclus, parmi lesquels 265 (14.1%) MPI. La majorité était traitée par une 1^{ère} ligne d'ICI, suivie par une 1^{ère} ligne de TC. Le suivi médian était de 16 mois. Les MPI présentaient plus fréquemment des caractéristiques initiales péjoratives. La SSP et la SG n'étaient significativement pas différentes entre MPI et cMPC ($P= 0.73$ et $P= 0.93$ respectivement). L'analyse multivariée, stratifiée selon l'âge, le sexe et le type de traitement ainsi que l'application d'un score de propension ne modifiaient pas ces résultats. Le taux de réponse objective ne différait pas non plus entre MPI et cMPC, dans la cohorte totale ainsi que dans chaque sous-groupe de traitement.

La fréquence et la sévérité des effets secondaires ne différaient pas entre MPI et cMPC, dans la cohorte globale (tout grade : 71% (cMPC) vs 66% (MPI); $P = 0.18$ et grade 3-4: 24% (cMPC) vs 22% (MPI) ; $P = 0.73$) et dans chaque sous-groupe de traitement.

CONCLUSION

Nos résultats suggèrent que la stratégie thérapeutique des MPI doit être similaire à celle des cMPC avancés, compte tenu d'une efficacité et d'un profil de tolérance similaires malgré des caractéristiques initiales plus péjoratives chez ces patients. Malgré l'hypothèse préalablement suggérée d'un terrain immunologique plus favorable chez les patients MPI, nous n'avons pas identifié de différence d'efficacité ni de tolérance dans le sous-groupe traité par ICI.

Des études exploratoires, évaluant la charge mutationnelle et l'immunité de l'hôte sont nécessaires pour comprendre les mécanismes sous-jacents.

II- INTRODUCTION

Melanoma of unknown primary (MUP) accounts for 3% of all melanomas. MUP is defined as the upfront occurrence of (sub)cutaneous, nodal and/or visceral metastasis without any known prior or concomitant primary tumor.^{1,2} This condition appears to be twice as frequent in males than in females with a peak age in the fourth and fifth decades of life.^{3,4}

The first diagnosis of MUP dates back to 1917⁵, but its first formal description was established by Das Gupta et al. in 1963, who defined exclusion criteria including prior orbital exenteration or enucleation, previous skin intervention on a mole, freckle, birthmark, paronychia or skin blemish without pathological examination, nodal metastasis with a scar in the skin drainage area, and lack of a complete physical examination including ophthalmological and anogenital evaluations.⁶

Several hypotheses have been proposed to explain the occurrence of a MUP, which could result from the malignant transformation of ectopic melanocytes in extracutaneous tissues or the complete regression of a primary melanoma after metastasis has occurred.⁷⁻¹² This immune-mediated regression involves both cellular and humoral mechanisms, including an increased number of tumor-infiltrating lymphocytes.¹³⁻¹⁶

Molecularly, MUP shares a mutational pattern similar to cutaneous ones, with comparable rates of *BRAF* and *NRAS* mutations, as well as a high mutational burden consistent with the ultraviolet signature, which suggests a cutaneous origin. Mutations in the TERT-promoter have also been hypothesized to function as driver mutations in MUP pathogenesis. Finally, *KIT* mutations are uncommon in MUP and may differentiate them from mucosal melanomas.¹⁷⁻¹⁹

This biological background might confer better survival for patients with MUP compared to those with stage-matched melanoma of known primary (MKP), as suggested by a meta-analysis and several retrospective studies conducted before the era of novel therapies.^{4,20-22} However, contradictory findings have also been reported, suggesting an equal or worse prognosis for patients with MUP.²³⁻²⁵

Over the past decade, the advent of targeted therapy (TT) and immune checkpoint inhibitors (ICIs) has considerably improved the survival of patients with advanced melanoma. The response rates of ICIs and TT significantly exceed those of conventional chemotherapy (CT),

ranging from 40% to 60% -70% in case of combination therapies, with prolonged responses over time.²⁶⁻³⁰

Thus, the question arises whether these treatments are more effective in MUP since both ICIs and TT have the potential to enhance the robust anti-tumoral immune response of the host at baseline.³¹ Indeed, clinical outcomes of advanced MUP in the era of novel therapies have been scarcely studied, whereas a possibly different biological background might introduce changes in its management.

The adverse side of this increased request of immunity, both related to immunomodulatory therapies and MUP biology, could be a substantial increase in the frequency and/or severity of immune-related adverse events (irAEs).

In this current study, we aimed to investigate the clinical outcomes of systemic therapies used for patients with advanced MUP compared to those with stage-matched cutaneous MKP (cMKP) in a large multicenter retrospective cohort of metastatic melanoma treated with ICIs, TT and CT.

III- MATERIAL AND METHODS

1. Study design and population

This retrospective study enrolled patients from the French multicenter prospective cohort MelBase, dedicated to the prospective follow-up of adults with advanced melanoma (unresectable stage III or IV melanoma) at the time of metastasis declaration across 26 participating centers. It was conducted from March 2013 to June 2021.

Inclusion criteria required an age over 18 years-old, a diagnosis of unresectable stage III or stage IV MUP or cMKP, treated with ICI (anti-programmed cell death-1 [PD-1] and/or anti-cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4], or anti-programmed cell death-ligand-1 [PD-L1]), TT (BRAF and/or MEK inhibitors), CT (dacarbazine, fotemustine, temozolomid, carboplatin or other platinum-based CT) with at least a 3-months follow-up period. Clinical trial participants were also included (open trials as well as others after unblinding).

Patients with primary mucosal or ocular melanoma were excluded.

Four treatment cohorts were defined, including whole treatment, ICI, TT and CT cohorts.

2. Definition of melanoma of unknown primary

MUP was defined as the upfront occurrence of (sub)cutaneous, nodal and/or visceral metastasis, without any known prior or concomitant primary tumor according to Das Gupta's⁶ criteria, which is based on the patient's medical history and clinical skin, ophthalmological, otorhinolaryngological and anogenital examinations, along with the histopathology of a metastatic sample confirming the presence of malignant melanocytes. The diagnosis of MUP was left to the discretion of the physicians from each participating center.

3. Outcomes

Both progression-free survival (PFS) and overall survival (OS) were analyzed as co-primary outcomes in MUP compared with cMKP, stratified by treatment type (ICI vs TT vs CT vs whole treatment cohorts), sex and age.

Secondary outcomes were overall responses, prognostic variables affecting survival, treatment-related adverse events (TRAEs) and immune-related adverse events (irAEs) in MUP compared with cMKP, stratified by treatment type (ICI vs TT vs CT vs whole treatment cohorts), sex and age (integrated in the propensity score).

PFS was defined as the time from the start of the first systemic therapy to the date of disease progression or death, whichever occurred first. Patients who were alive without disease progression were censored on the date of their last disease assessment. OS was defined as the time from the start of the first systemic therapy to death. Patients who were still alive were censored at the date of the last contact.

Disease progression and response were evaluated using the Response Evaluation Criteria in Solid Tumors (version 1.1) by radiologists from each participating institution.³²

Data on the incidence of TRAEs and irAEs were collected and graded according to the US National Cancer Institute Common Toxicity Criteria for Adverse Events (version 4.0). The subtypes of TRAEs and irAEs were categorized as follow: cardiovascular, endocrinologic, rheumatologic, cutaneous, gastro-intestinal, hepatic, pulmonary, hematological, ophthalmological, musculoskeletal, and general symptoms.

Data on relevant confounding factors were evaluated, taking account on patients' age (<65 vs ≥ 65 years old), sex (male vs female), disease stage (III vs IV according to the AJCC 7th edition), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs ≥ 1), serum lactate dehydrogenase level (LDH, \leq the upper limit of normal vs >normal), brain metastasis (absent or present), liver metastasis (absent or present), BRAF V600 status (wild type vs mutated), first-line treatment (ICI vs TT/CT), medical history of auto-immune disease (absent vs present), neutrophil-to-lymphocyte ratio at baseline (normal vs >normal) and number of metastatic sites (<3 vs ≥ 3).

4. Statistical analysis

Statistical analyses were performed for the whole MUP and cMKP cohorts and subsequently stratification by treatment subtype (ICI, TT and CT).

Baseline demographic and disease characteristics are presented as numbers and percentages for categorical variables, and as mean with standard deviation (SD) and median with interquartile range (IQR), and range for continuous variables, as appropriate.

Comparison of variable distribution between MUP and cMKP populations was performed using either Chi-squared test and Fisher's exact test for categorical variables and Student's t-test for continuous variables.

Missing baseline data were processed using multiple imputations for survival data, and all predictors considered in the model development were used in the imputation model. We imputed 25 independent data sets, generated and analyzed them separately and pooled all imputations according to the standard rules by Rubin to provide point estimates for each parameter.

A multivariate Cox proportional hazard model was used to determine the prognostic variables in the treated MUP and cMKP populations. The propensity score, defined as the probability of treatment assignment conditional on observed baseline characteristics, was applied, using inverse probability of treatment weighting (IPTW). To assess whether the propensity score model was successful in balancing the groups, imbalance in patient characteristics between groups before and after weighting, was measured by standardized differences. We considered standardized differences above 10% as meaningful imbalance.

Survival analysis was performed using the Kaplan–Meier method and Cox regression model in weighted sas. The PFS and OS values across subgroups were compared using the log-rank test.

All statistical tests were two-sided, with $p < 0.05$ indicating statistical significance.

All analysis were performed using R statistical software version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

5. Patient's consent and ethical approval

The MelBase protocol, registered in the National Institute Health Clinical Trials Database (NCT02828202), was approved by the French Ethics Committee (Comité de Protection des Personnes Ile-de-France XI, n°12027, 2012), the local ethics committee, and the ethics committees of all participating institutions. Written informed consent was obtained from all the patients.

IV- RESULTS

1. Population characteristics

A total of 1882 patients with advanced melanoma treated with ICI, TT or CT, between March 2013 and June 2021, were included. Among them, 265 patients (14.1%) had advanced MUP; the remaining 1617 patients (85.9%) had advanced cMKP.

The median patient age was 66 years (interquartile range [IQR]: 18-97), and men accounted for a major proportion of these patients (60%). Most patients received first-line ICI (65%), followed by first-line TT (31%), with no difference between the MUP and cMKP cohorts ($P = 0.44$). The median follow-up duration for the MUP cohort was 11 months (IQR: 4.5-21.1 months) and for the cMKP cohort was 16.3 months (IQR: 6.2-33.3 months).

Patients in the MUP cohort more often displayed unfavorable initial prognostic factors, such as more stage IV disease cases (97% vs 85 %, $P < 0.001$), higher number of metastatic sites (48 % had ≥ 3 metastatic sites vs 39 % in the cMKP group, $P = 0.01$), higher proportion of central nervous system (CNS) metastasis (38% vs 18 %, $P < 0.001$) and LDH levels $> 2xULN$ (12% vs 8%, $P = 0.01$). Other characteristics, including baseline ECOG performance status and *BRAF*-mutated status were comparable in both groups (**Table 1**).

Table 1. Patient characteristics in whole population, cMKP and MUP cohorts regardless treatment subset

Baseline Characteristics	Whole population	cMKP	MUP	p-value
Number of patients	1882	1617	265	-
Age, years				
- Mean, years	64	64	64	1.0
- Median (range), years	66 (18-97)	66 (21-97)	64 (18-92)	
- ≥ 65 years, N (%)	1007 (53)	876 (54)	131 (49)	0.16
Sex, N (%)				
Men	1129 (60)	965 (60)	164 (62)	0.54
Women	753 (40)	652 (40)	101 (38)	
AJCC 7th edition, N (%)				
III	255 (14)	247 (15)	8 (3)	<0.001
IV	1627 (86)	1370 (85)	257 (97)	
- M1a	199 (11)	167 (10)	32 (12)	
- M1b	310 (16)	290 (18)	20 (8)	
- M1c	1118 (59)	913 (56)	205 (77)	

Brain metastasis, N (%)				
Yes	389 (21)	289 (18)	100 (38)	<0.001
Symptomatic	114 (6)	82 (5)	32 (12)	
Liver metastasis, N (%)				
Yes	476 (25)	402 (25)	74 (28)	0.32
Number of disease sites N (%)				
<3	1117 (59)	979 (61)	138 (52)	0.01
≥3	765 (41)	638 (39)	127 (48)	
ECOG PS, N (%)				
0	1367 (73)	1189 (74)	178 (67)	0.27
1	370 (19)	309 (19)	61 (23)	
≥2	145 (8)	119 (7)	26 (10)	
Mutations Status, N (%)				
<i>BRAF V600</i>	750 (40)	653 (40)	97 (37)	0.24
LDH, N (%) > ULN ; IC (95%)				
N > ULN	552 (29)	467 (29)	85 (32)	0.32
N > 2 x ULN	158 (8)	125 (8)	33 (12)	0.01
First line treatment, N (%)				
Immune checkpoint inhibitors	1224 (65)	1059 (66)	165 (63)	0.44
- Anti PD1	785 (42)	683 (42)	102 (38)	
- Ipilimumab	183 (10)	162 (10)	21 (8)	
- Ipilimumab + Nivolumab	256 (13)	214 (13)	42 (16)	
Targeted therapy	574 (31)	488 (30)	86 (32)	
- BRAFi + MEKi*	379 (20)	326 (20)	53 (20)	
- BRAFi**	186 (10)	153 (9)	53 (12)	
- MEKi***	9 (1)	9 (1)	0 (0)	
Chemotherapy	84 (4)	70 (4)	14 (5)	
- monoCT•	79 (4)	66 (4)	13 (5)	
- polyCT†	5 (0)	4 (0)	1 (0)	
Delay between diagnosis and first-line systemic treatment				
- Mean, months	12.7	13	11.6	0.30
- Median [IQR], months	2.2 [1-21.4]	2.2 [1-22.1]	2.2 [1.2-15]	
Follow-up				
- Mean, months	22.6	23.3	18.2	<0.001
- Median [IQR], months	16 [6-32.5]	16.3 [6.2-33.3]	11 [4.5-21.1]	

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase

*Vemurafenib + Cobimetinib (N= 51), Dabrafenib + Trametinib (N = 321), Encorafenib + Binimetinib (N= 7); ** Vemurafenib (N= 120), Dabrafenib (N= 66); *** Cobimetinib (N= 9); • Dacarbazine (N= 47), Temozolomid (N= 19), Fotemustine (N= 13); † Carboplatin-Paclitaxel (N= 4), Dacarbazine-Temozolomid (N=1)

Of the 1224 patients who received first-line ICI, 165 had MUP (13.5%). Among them, 62% were treated with anti-PD1, 13% with anti-CTLA4 monotherapy and 25% with combination therapy, which was similar to that observed in patients with cMKP ($P = 0.56$, $P = 0.46$ and $P =$

0.15 respectively). MUP patients displayed significantly more unfavorable initial prognostic factors. Particularly, they presented with more stage IV disease cases (96% vs 84%, $P < 0.001$), with a higher number of metastatic sites (42% had ≥ 3 metastatic sites vs 34%, $P = 0.01$), more CNS metastasis (34% vs 16%, $P < 0.001$) and LDH levels $> 2 \times \text{ULN}$ (12% vs 7%, $P = 0.01$). The median follow-up duration was significantly shorter in the MUP cohort (8.8 months, IQR: 3.2-26.0 vs 15.4 months, IQR: 5.6-32.3 for the cMKP cohort, $P < 0.001$, **Supplementary Table 1**).

Of the 574 patients who received first-line TT, 86 had MUP (15%). Among them, 62% were treated with BRAFi + MEKi, 38% with BRAFi monotherapy and none received MEKi alone, which did not differ from that observed in the cMKP cohort ($P = 0.42$, $P = 0.25$ and $P = 0.37$, respectively). Once again, MUP patients more often displayed unfavorable initial prognostic factors, presenting significantly more stage IV disease cases (99% vs 90% in cMKP cohort, $P = 0.007$) and CNS metastasis (39% vs 23% $P < 0.001$). The median follow-up duration did not differ significantly between the two cohorts (**Supplementary Table 2**).

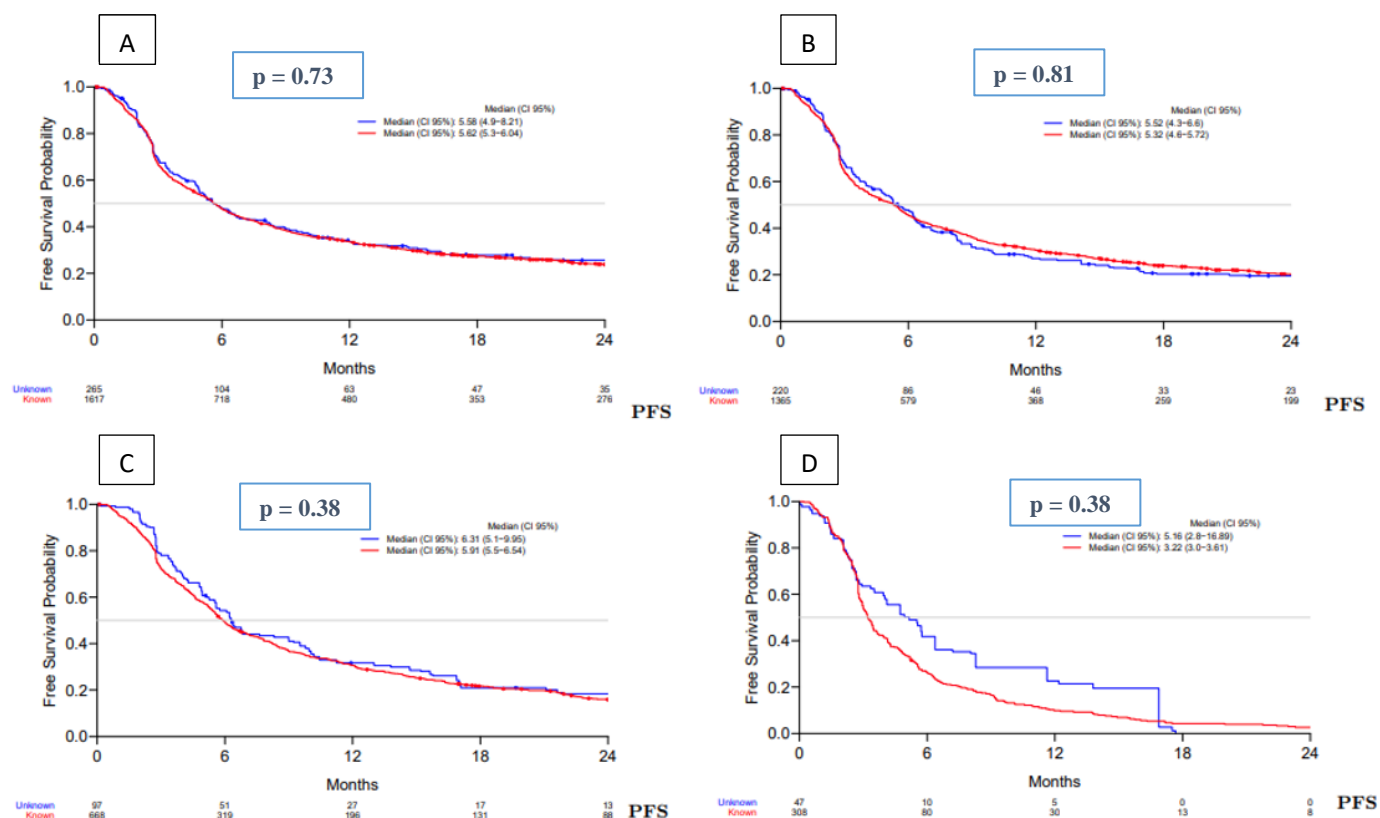
Of the 84 patients who received first-line CT, 14 had MUP (16.7%). Among them, 93% were treated with mono-CT and 7% with polyCT, with no difference compared with that observed in patients with cMKP ($P = 1.00$). MUP patients more often displayed unfavorable baseline prognostic factors (**Supplementary Table 3**). The median follow-up duration was significantly shorter in the MUP cohort (3.5 months, IQR: 1.3-7.7 for MUP vs 5.7 months IQR: 2.5-12.5, $P < 0.001$).

2. Survival analysis

After applying the propensity score, the PFS duration of patients with MUP did not differ from that of patients with cMKP in the whole treatment cohort (**Figure 1A**: 5.6 months for MUP vs 5.6 months for cMKP, $P = 0.73$). Stratification by treatment type did not lead to data modification and showed the following results: 5.5 months for MUP treated with ICI versus 5.3 months, $P = 0.81$ (**Figure 1B**), 6.3 months for MUP treated with TT versus 5.9 months, $P = 0.38$ (**Figure 1C**), and 5.2 months for MUP treated with CT vs 3.2 months, $P = 0.38$ (**Figure 1D**).

Figure 1. Progression-free survival according to known or unknown advanced primary melanoma, after applying the propensity score

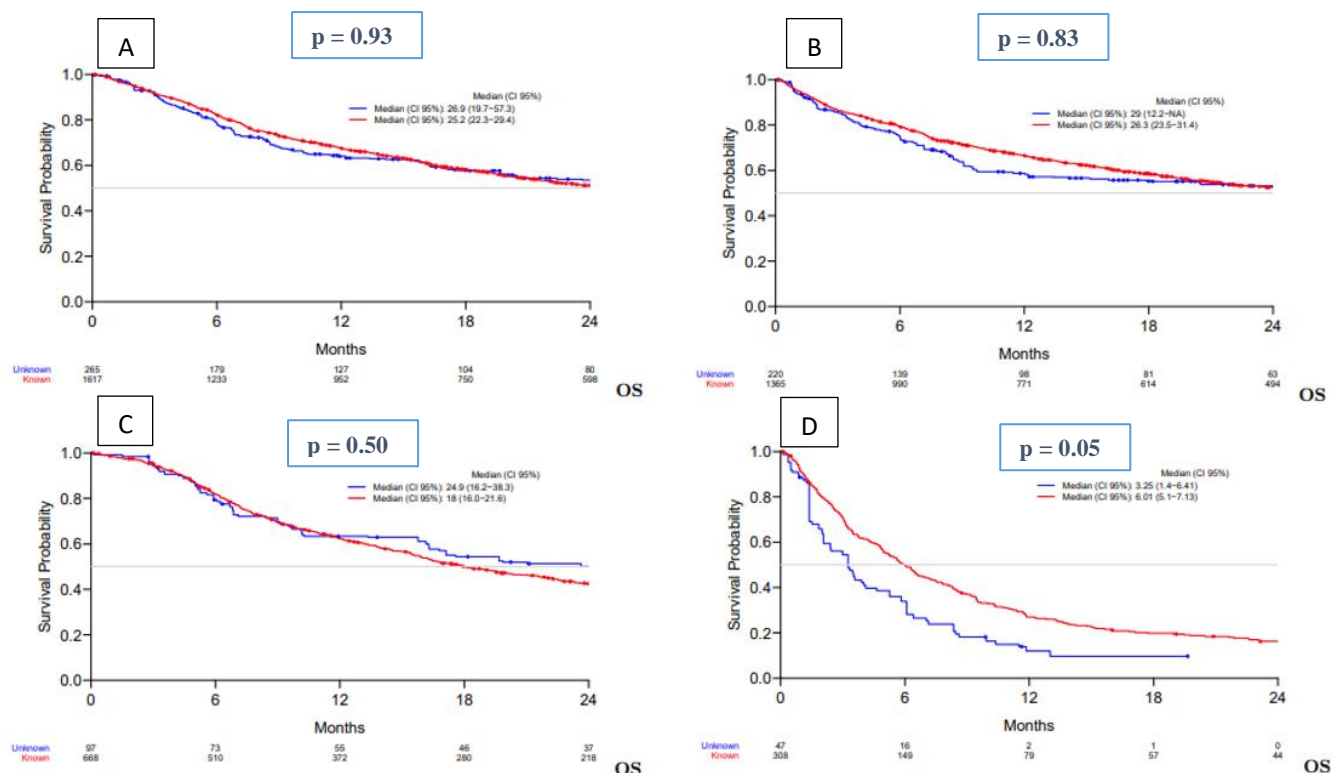
Known (red arrow) or unknown (blue curve) advanced primary melanoma. Progression-free survival among patients in the (A) whole, (B) immune checkpoint inhibitor, (C) targeted therapy, and (D) chemotherapy cohorts.



After applying the propensity score, the OS duration of patients with MUP did not statistically significantly differ from that of patients with cMKP in the whole treatment cohort (**Figure 2A**: 26.9 months for MUP vs 25.2 months, $P = 0.93$). However, the OS was significantly shorter in the MUP cohort treated with CT (3.3 months vs 6.0 months, $P = 0.05$, **Figure 2D**), whereas there was no difference between patients with MUP and with cMKP treated with ICI and TT (respectively 29.0 months for MUP vs 26.3 months, $P = 0.83$ and 24.9 months for MUP vs 18 months, $P = 0.50$, **Figures 2B-2C**).

Figure 2. Overall survival according to known or unknown advanced primary melanoma, after applying the propensity score

Known (red arrow) or unknown (blue curve) advanced primary melanoma. Overall survival among patients in the (A) whole, (B) immune checkpoint inhibitor, (C) targeted therapy, and (D) chemotherapy cohorts.



OS and PFS data at 6 months, 1 year and 2 years, before and after applying the propensity score, are shown in **Supplementary Tables 4 and 5** respectively.

3. Prognostic factors for survival

The prognostic factors affecting PFS in the total MUP cohort were BRAF-mutated status (HR = 0.56, $P < 0.001$), CNS metastasis (HR = 1.49, $P < 0.01$) and LDH level (HR = 2.00, $P < 0.001$).

Multivariate analysis indicated only the AJCC stage (HR = 2.91, $P < 0.001$) and LDH level (HR = 2.25, $P < 0.001$) affected the OS in the whole MUP cohort, whereas AJCC stage (HR = 1.22, $P = 0.04$), ECOG performance status (HR = 1.28, $P < 0.001$), LDH level (HR = 1.51, $P < 0.01$), hepatic and CNS metastasis (HR = 1.31, $P < 0.01$ and HR = 1.48 $P < 0.001$,

respectively), number of metastatic sites (HR = 1.31, $P < 0.01$) and treatment subtype (HR = 1.43, $P < 0.001$) remained the most prognostic factors in the whole cMKP cohort.

In particular, treatment subtype did not impact nor OS neither PFS in patients with MUP, and only affected the OS in patients with cMKP (HR = 1.43, $P < 0.001$, **Supplementary Table 6**).

For the sub-group treated with ICI, multivariate analysis indicated that LDH level (HR = 1.78, $P < 0.001$) and number of metastatic sites (HR = 1.38, $P = 0.04$) were the most prognostic factors for PFS, and AJCC stage (HR = 2.68, $P < 0.001$) and LDH level (HR = 1.97, $P < 0.001$) the most prognostic factors for OS in the MUP cohort (**Supplementary Table 7**).

For the TT-treated cohort, multivariate analysis indicated that ECOG performance status (HR = 1.64, $P = 0.04$) was the most prognostic factor for PFS, and the number of metastatic sites (HR = 2.63, $P < 0.001$) remained the most prognostic factor for OS in the MUP cohort (**Supplementary Table 8**).

For the CT-treated cohort, age (HR = 0.34, $P < 0.01$) and BRAF-mutated status (HR = 0.41, $P = 0.02$) were the most prognostic factors for PFS, whereas there was no prognostic factor affecting OS in the MUP cohort (**Supplementary Table 9**).

4. Response rates

The response to systemic therapies were not significantly different between the MUP and cMKP cohorts, regardless of treatment type (**Table 2**). An objective response was observed in 42% of the patients with MUP versus 46% of the patients with cMKP, with no difference between the two groups in the whole treatment cohort ($P = 0.36$).

In the ICI cohort, 47% of the patients with MUP and 52% of the patients with cMKP experienced an objective response, with no difference between the groups ($P = 0.19$).

Particularly, for ICI treatment, 20% of patients with MUP experienced complete response, 25% experienced partial response, and 27% presented with stable disease (vs 27%, $P = 0.10$, 25%, $P = 0.9$ and 22%, $P = 1.0$, respectively in patients with cMKP).

Similarly, an objective response was observed in 62% of patients with MUP and 60% of patients with cMKP treated with TT, with no difference between the two groups ($P = 0.69$). Similar results were observed in CT cohort (**Table 2**).

Table 2. Response rates of patients according to treatment types

	TOTAL POPULATION				
		Whole cohort (n=1882)	MKP (n=1617)	MUP (n=265)	p-value
ALL TREATMENTS (ICI + TT + CT)	Best overall response – no. (%)				
	Complete response	385 (20)	340 (21)	45 (17)	0.15
	Partial response	463 (25)	396 (24)	67 (25)	0.84
	Stable disease	498 (27)	420 (26)	78 (29)	0.27
	Progressive disease	536 (28)	461 (29)	75 (28)	1.0
	Objective response				
	No. of patients	848 (45)	736 (46)	112 (42)	0.36
	Disease control				
No. of patients	1346 (72)	1156 (71)	190 (72)	1.0	
IMMUNOTHERAPY		Whole cohort (n=1585)	MKP (n=1365)	MUP (n=220)	p-value
	Best overall response – no. (%)				
	Complete response	384 (24)	339 (25)	45 (20)	0.10
	Partial response	434 (28)	375 (27)	59 (25)	0.90
	Stable disease	403 (25)	347 (25)	56 (27)	1.0
	Progressive disease	364 (23)	304 (22)	60 (25)	0.12
	Objective response				
	No. of patients	818 (52)	714 (52)	104 (47)	0.19
Disease control					
No. of patients	1221 (77)	1061 (78)	160 (73)	0.12	
TARGETED THERAPY		Whole cohort (n=765)	MKP (n=668)	MUP (n=97)	p-value
	Best overall response – no. (%)				
	Complete response	167 (22)	148 (22)	19 (20)	0.66
	Partial response	294 (38)	253 (38)	41 (42)	0.47
	Stable disease	152 (20)	130 (19)	22 (23)	0.54
	Progressive disease	152 (20)	137 (21)	15 (15)	0.30
	Objective response				
No. of patients	461 (60)	401 (60)	60 (62)	0.69	

	Disease control				
	No. of patients	613 (80)	531 (79)	82 (85)	0.30
CHEMOTHERAPY		Whole cohort (n=355)	MKP (n=308)	MUP (n=47)	p-value
	Best overall response – no. (%)				
	Complete response	26 (8)	23 (7)	3 (6)	1.0
	Partial response	100 (28)	89 (29)	11 (23)	0.55
	Stable disease	111 (31)	97 (31)	14 (30)	0.95
	Progressive disease	118 (33)	99 (32)	19 (42)	0.34
	Objective response				
	No. of patients	126 (36)	112 (36)	14 (30)	0.48
	Disease control				
	No. of patients	237 (67)	209 (67)	28 (60)	0.34

5. Tolerance data

A total of 1320 (70%) patients experienced AEs of any grade and 438 (23%) experienced grade 3-4 AEs. The incidence rate and severity of AEs did not significantly differ between the cMKP and MUP groups in the whole treatment cohort (all grades: 71% [cMKP] vs 66% [MUP]; $P = 0.18$, and grade 3-4: 24% [cMKP] vs 22% [MUP]; $P = 0.73$, **Table 3**).

The occurrence of AEs of any grade in the cMKP and MUP groups, categorized according to the different organs/systems involved, is presented in **Supplementary Table 10**.

In the ICI-treated cohort, 1104 (70%) patients experienced irAEs of any grade and 369 (23%) experienced grade 3-4 AEs. The incidence rate and severity of irAEs did not significantly differ between the cMKP and MUP groups (all grades: 70% [cMKP] vs 65% [MUP]; $P = 0.09$, and grade 3-4: 23% [cMKP] vs 23% [MUP]; $P = 0.92$).

In the TT-treated cohort, 610 (80%) patients experienced AEs of any grade and 261 (34%) experienced grade 3-4 AEs. The incidence rate and severity of AEs did not significantly differ between the cMKP and MUP groups (all grades: 80% [cMKP] vs 77% [MUP]; $P = 0.62$, and grade 3-4: 34% [cMKP] vs 33% [MUP]; $P = 0.89$).

In the CT-treated cohort, 184 (52%) patients experienced AEs of any grade and 84 (24%) experienced grade 3-4 AEs. The incidence rate and severity of AEs did not significantly differ

between the cMKP and MUP groups (all grades: 54% [cMKP] vs 40% [MUP]; $P = 0.54$, and grade 3-4: 22% [cMKP] vs 32% [MUP]; $P = 0.21$).

Table 3. Rate and severity of adverse events according to treatment type in the two patient groups

Population	Patient No.	Adverse events		
		All grades (No. patients, %)	Grade I-II (%)	Grade III-IV (%)
ALL COHORTS (ICIs + TT +CT)				
Total	1882	1320 (70%)	882 (47%)	438 (23%)
cMKP	1617	1144 (71%)	764 (47%)	380 (24%)
MUP	265	176 (66%)	118 (44%)	58 (22%)
p-value	-	P= 0.18	-	P= 0.73
IMMUNOTHERAPY				
Total	1585	1104 (70%)	735 (47%)	369 (23%)
cMKP	1365	962 (70%)	643 (47%)	319 (23%)
MUP	220	142 (65%)	92 (42%)	50 (23%)
p-value	-	P= 0.09	-	P= 0.92
TARGETED THERAPY				
Total	765	610 (80%)	349 (46%)	261 (34%)
cMKP	668	535 (80%)	306 (46%)	229 (34%)
MUP	97	75 (77%)	43 (44%)	32 (33%)
p-value	-	P= 0.62	-	P= 0.89
CHEMOTHERAPY				
Total	355	184 (52%)	100 (28%)	84 (24%)
cMKP	308	165 (54%)	96 (31%)	69 (22%)
MUP	47	19 (40%)	4 (9%)	15 (32%)
p-value	-	P= 0.54	-	P= 0.21

V- DISCUSSION

To our knowledge, the present study is the first to compare the efficacy and tolerance of novel therapies, especially ICI and TT, used in patients with advanced MUP and stage-matched cMKP.

Our cohort, which is one of the largest about advanced MUP and cMKP, included 14% of patients with MUP, a rate that is consistent with that in previous reports.^{20,33,34} Majority of the patients in both groups received first-line ICI, followed by first-line TT, with no imbalance in the distribution of treatments (monotherapy or combined treatments), which shows that patients were treated according to similar strategies. We observed that OS, PFS and response rates were similar between patients with advanced MUP and cMKP, as well as in the whole treatment cohort and the ICI and TT-treated cohorts. Nevertheless, it is interesting to note that patients with MUP exhibited significantly more unfavorable prognostic factors at baseline (higher frequency of stage IV disease, higher number of metastatic sites, higher prevalence of CNS metastasis and LDH levels > 2xULN) compared with that observed in patients with cMKP, as reported in previous studies.^{20,33} Moreover, these studies, conducted before and at the era of novel treatments, demonstrated improved OS for MUP patients in the adjusted analysis, suggesting that MUP patients might display favorable but still unknown factors, independent of the type of treatment. In addition, the multivariate analysis we performed highlighted that OS and PFS for MUP patients were not affected by any treatment subtype contrary to OS for cMKP patients. OS for MUP appeared to be affected by LDH level and AJCC stage, whereas PFS was affected by *BRAF*-mutated status, CNS metastasis and LDH level, in the whole treatment cohort. Moreover, it is interesting to note that the neutrophil-to-lymphocyte count did not affect nor OS neither PFS in any of the cohorts.

In accordance with our results, Ellebaek et al.³⁵ concluded on a similar prognosis between patients with advanced MUP and MKP in the current modern treatment era, in a real-world Danish population involving 80 patients with MUP who displayed more MIC stages, which is similar to that observed in our cohort and seems representative to real-world patients with advanced MUP. Similarly, Ludwig et al.³⁶ reported similar outcomes in MUP and MKP patients undergoing ICI therapy in a single-center retrospective study. We did not observe an improved survival in MUP patients, especially those treated with ICI while this population might be particularly sensitive to ICI, considering a favorable biological background.¹³⁻¹⁶ In contrast, a recent pilot study conducted on a small population with better baseline characteristics suggested an improved PFS and a non-significant trend for better response in patients with MUP treated with ICI.¹³

Our results may also be explained by a higher rate of stage IV melanoma cases in our MUP cohort, especially since our multivariate analysis indicated that AJCC stage was a prognostic factor for OS in the total and ICI-treated cohorts of MUP.

Furthermore, Verver et al.³⁷ suggested that first-line ICI therapy compared to first-line TT was a more favorable prognostic factor for OS in patients with MUP. This could be explained by the higher rate of *V600K* mutations in MUP patients, as observed by Beasley et al.³⁸ Indeed, this mutated profile possibly displays a higher mutational load and uses alternative pathways to the ERK pathway, explaining the improved response to ICI and decreased response to TT. Additionally, our study demonstrated that the treatment-related toxicity rate and severity did not differ between advanced MUP and cMKP, regardless of treatment type, especially irAEs in the ICI cohort, which has never been explored in previous studies. Considering the specific biological background of MUP, we can hypothesize that MUP patients would develop more irAES, with a higher risk of grade III-IV AEs.

This study has several limitations, one of which is inherently related to its retrospective design, posing the risk of missing data (e.g., mutation data). Another limitation is the possibility of misclassification bias, given that there is no record of standard diagnostic criteria of MUP used in all participating centers.

Despite these limitations, our study has several strengths, including a large sample size (one of the largest in the MUP literature), multicentric design and long-term follow-up. All data were collected from a common and standardized electronic case report form used across all participating centers. Furthermore, because the proportion of missing data was small, the accuracy of our analysis is high. Finally, the use of propensity score analysis helped us prevent indication bias, which supported the robustness of our data.

VI- CONCLUSION

In conclusion, our results suggest that advanced MUP should be managed with strategies similar to those for advanced cMKP. In our cohort, despite the less favorable baseline prognostic factors in patients with MUP, they benefited from novel therapies as much as patients with cMKP. Exploratory studies investigating mutational burden and host immunity are required to identify the underlying mechanisms.

VII- SUPPLEMENTARY TABLES

Supplementary Table 1. Patient characteristics in whole population, cMKP and MUP cohorts treated with immunotherapy

Baseline Characteristics	Whole population	cMKP	MUP	p-value
Number of patients	1585	1365	220	-
Age				
- Mean, years	64	64	64	0.95
- Median (range), years	66 (20-97)	66 (21-97)	64 (20-92)	0.85
- ≥ 65 years, N (%)	870 (55)	754 (55)	116 (53)	
Sex, N (%)				
Men	954 (60)	814 (60)	140 (64)	0.29
Women	631 (40)	551 (40)	80 (36)	
AJCC 7th edition, N (%)				
III	224 (14)	216 (16)	8 (4)	<0.001
IV	1361 (86)	1149 (84)	212 (96)	
- M1a	162 (10)	137 (10)	25 (11)	
- M1b	267 (17)	248 (18)	19 (8)	
- M1c	932 (59)	764 (56)	168 (76)	
Brain metastasis, N (%)				
Yes	296 (19)	222 (16)	74 (34)	<0.001
Symptomatic	61 (4)	42 (3)	19 (9)	
Liver metastasis, N (%)				
Yes	354 (22)	298 (22)	56 (25)	0.27
Number of disease sites, N (%)				
<3	995 (63)	902 (66)	93 (58)	0.02
≥3	590 (37)	463 (34)	127 (42)	
ECOG PS, N (%)				
0	1117 (70)	978 (72)	139 (63)	0.22
1	340 (22)	284 (21)	56 (26)	
≥2	128 (8)	103 (7)	25 (11)	
Mutations Status, N (%)				
BRAF V600	510 (32)	445 (33)	65 (30)	0.20
LDH, N (%) > ULN ; IC (95%)				
N > ULN	455 (29)	385 (29)	70 (32)	0.22
N > 2 x ULN	125 (8)	98 (7)	27 (12)	0.01
First line treatment, N (%)				
Immune checkpoint inhibitors	1224 (77)	1059 (78)	165 (75)	0.56
- Anti PD1	785 (64)	683 (65)	102 (62)	
- Ipilimumab	183 (15)	162 (15)	21 (13)	
- Ipilimumab + Nivolumab	256 (21)	214 (20)	42 (25)	
Treatment lines received, N (%)				
One line	652 (41)	549 (40)	103 (47)	0.22
Two lines	381 (24)	329 (24)	52 (24)	
Three lines	310 (20)	271 (20)	39 (18)	
Four line and more	242 (15)	216 (16)	26 (12)	

Radiotherapy associated, N (%)				
No	1422 (90)	1228 (90)	194 (88)	0.49
Yes	163 (10)	137 (10)	26 (12)	
Delay between diagnosis and first-line systemic treatment				
- Mean, months	12.6	13	10.7	0.10
- Median [IQR], (months)	2.2 [1-22.7]	2.2 [1-23.2]	2.2 [1.1-11.4]	
Follow-up				
- Mean, months	21.1	21.8	16.8	<0.001
- Median [IQR], months	14.7 [5-31.6]	15.4 [5.6-32.3]	8.8 [3.2-26.0]	

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase

Supplementary Table 2. Patient characteristics in whole population, cMKP and MUP cohorts treated with targeted therapy

Baseline Characteristics	Whole population	cMKP	MUP	p-value
Number of patients	765	668	97	-
Age, years				
- Mean, years	59	59	57	0.41
- Median (range), years	59 (21-94)	60 (21-94)	56 (49-67)	
- ≥ 65 years, N (%)	293 (38)	263 (39)	30 (31)	0.14
Sex, N (%)				
Men	435 (57)	381 (57)	54 (56)	0.89
Women	330 (43)	287 (43)	43 (44)	
AJCC 7th edition, N (%)				
III	68 (9)	67 (10)	1 (1)	0.007
IV	697 (91)	601 (90)	96 (99)	
- M1a	75 (10)	62 (9)	13 (13)	
- M1b	90 (12)	83 (12)	7 (7)	
- M1c	532 (69)	456 (68)	76 (78)	
Brain metastasis, N (%)				
Yes	190 (25)	152 (23)	38 (39)	<0.001
Symptomatic	63 (8)	47 (3)	16 (9)	
Liver metastasis, N (%)				
Yes	225 (29)	197 (29)	28 (29)	0.99
Number of disease sites, N (%)				
<3	400 (52)	352 (53)	48 (49)	0.63
≥3	365 (48)	316 (47)	49 (51)	
ECOG PS, N (%)				
0	526 (69)	458 (69)	68 (70)	0.86
1	158 (21)	139 (20)	19 (20)	
≥2	81 (10)	71 (11)	10 (10)	
Mutations Status, N (%)				
BRAF V600	634 (83)	551 (82)	83 (86)	0.20
LDH, N (%) > ULN ; IC (95%)				
N > ULN	232 (30)	200 (30)	32 (33)	0.62
N > 2 x ULN	80 (10)	70 (10)	10 (10)	1.0
First line treatment, N (%)				
Targeted therapy	574 (75)	488 (73)	86 (89)	
- BRAFi + MEKi*	379 (66)	326 (67)	53 (62)	0.42
- BRAFi**	186 (32)	153 (31)	33 (38)	0.25
- MEKi***	9 (2)	9 (2)	0 (0)	0.37
Treatment lines received, N (%)				
One line	152 (20)	130 (19)	22 (23)	0.01
Two lines	226 (30)	195 (29)	31 (32)	
Three lines	141 (18)	115 (17)	26 (27)	
Four line and more	246 (32)	228 (34)	18 (19)	
Delay between diagnosis and first-line systemic treatment				
- Mean, months	11.8	11.5	13.2	0.51
- Median [IQR], months	2.1 [0.9-18]	2 [0.9-17.6]	2.3 [1-20.6]	

Follow-up				
- Mean, months	22.2	22.2	21.7	0.80
- Median [IQR], months	15.1 [6.2-31]	14.5 [6.2-30.8]	16.8 [6.1-33.7]	

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase

*Vemurafenib + Cobimetinib (N= 51), Dabrafenib + Trametinib (N = 321), Encorafenib + Binimetinib (N= 7); ** Vemurafenib (N= 120), Dabrafenib (N= 66); *** Cobimetinib (N= 9);

Supplementary Table 3. Patient characteristics in whole population, cMKP and MUP cohorts treated with chemotherapy

Baseline Characteristics	Whole population	cMKP	MUP	p-value
Number of patients	355	308	47	-
Age, years (mean)				
- Mean, years	66	65	65	1.0
- Median (range), years	68 (23-94)	68 (23-94)	67 (36-85)	
- ≥ 65 years, N (%)	213 (60)	187 (31)	26 (55)	0.14
Sex, N (%)				
Men	216 (61)	188 (61)	28 (60)	0.98
Women	139 (39)	120 (39)	19 (40)	
AJCC 7th edition, N (%)				
III	30 (8)	29 (9)	1 (2)	0.003
IV	325 (92)	279 (91)	46 (98)	
- M1a	23 (7)	21 (68)	2 (4)	
- M1b	53 (15)	51 (17)	2 (4)	
- M1c	249 (70)	207 (67)	42 (89)	
Brain metastasis, N (%)				
Yes	101 (28)	87 (28)	14 (30)	0.96
Symptomatic	25 (7)	18 (6)	7 (15)	
Liver metastasis, N (%)				
Yes	80 (23)	68 (22)	12 (25)	0.73
Number of disease sites, N (%)				
<3	202 (57)	178 (58)	24 (51)	0.48
≥3	153 (43)	130 (42)	23 (49)	
ECOG PS, N (%)				
0	148 (42)	134 (43)	14 (30)	0.001
1	117 (33)	107 (35)	10 (21)	
≥2	90 (25)	67 (22)	23 (49)	
Mutations Status, N (%)				
BRAF V600	82 (23)	74 (24)	8 (17)	0.49
LDH, N (%) > ULN ; IC (95%)				
N > ULN	119 (34)	102 (29)	17 (5)	0.79
N > 2 x ULN	44 (12)	36 (10)	8 (2)	0.43
First line treatment, N (%)				
Chemotherapy	84 (24)	70 (23)	14 (30)	1.0
- monoCT*	79 (94)	66 (94)	13 (93)	
- polyCT**	5 (6)	4 (6)	1 (7)	
Treatment lines received, N (%)				
One line	27 (8)	19 (6)	8 (17)	0.03
Two lines	91 (26)	76 (25)	15 (32)	
Three lines	101 (28)	91 (30)	10 (21)	
Four line and more	136 (38)	122 (40)	14 (30)	
Delay between diagnosis and first-line systemic treatment				
- Mean, months	11.3	10.6	14.2	0.32
- Median [IQR], months	2.5 [1.1-14.6]	2.7 [1-13.9]	2.4 [1.4-20.4]	
Follow-up				

- Mean, months	11.5	12.5	4.9	<0.001
- Median [IQR], months	5.3 [2.3-11.6]	5.7 [2.5-12.5]	3.5 [1.3-7.7]	

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase

*Dacarbazine (N= 47), Temozolomid (N= 19), Fotemustine (N= 13); **Carboplatin-Paclitaxel (N= 4), Dacarbazine-Temozolomid (N=1)

Supplementary Table 4. Overall survival and progression-free survival at 6 months, 12 months and 24 months in the whole cohort, ICI cohort, TT cohort, and CT cohort, before propensity score

Time (Months)	cMKP (%) (IC95%)	MUP (%) (IC95%)
Whole cohort		
Overall Survival		
6 months	82.1 (80.2 – 84.0)	73.3 (68.0 – 79.0)
12 months	67.4 (65.1 – 69.8)	57.1 (51.2 – 63.7)
24 months	51.2 (48.7 – 53.9)	45.7 (39.6 – 52.7)
Progression-Free Survival		
6 months	47.7 (45.3 – 50.3)	43.0 (37.3 – 49.6)
12 months	33.6 (31.3 – 36.1)	28.2 (23.0 – 34.4)
24 months	23.8 (21.7 – 26.1)	20.6 (15.9 – 26.5)
ICI Cohort		
Overall Survival		
6 months	79.0 (76.9 – 81.3)	68.5 (62.4 – 75.1)
12 months	66.4 (63.9 – 69.1)	53.0 (46.5 – 60.4)
24 months	52.5 (49.7 – 55.4)	45.8 (39.2 – 53.4)
Progression-Free Survival		
6 months	45.6 (42.9 – 48.3)	42.6 (36.3 – 49.8)
12 months	30.6 (28.2 – 33.3)	24.7 (19.4 – 31.5)
24 months	20.2 (18.1 – 22.7)	17.9 (13.2 – 24.2)
TT Cohort		
Overall Survival		
6 months	81.7 (78.8 – 84.8)	79.7 (72.0 – 88.3)
12 months	62.3 (58.6 – 66.2)	63.1 (53.9 – 73.8)
24 months	42.5 (38.7 – 46.7)	47.6 (38.2 – 59.3)
Progression-Free Survival		
6 months	49.2 (45.6 – 53.2)	55.3 (46.1 – 66.4)
12 months	30.7 (27.3 – 34.4)	31.0 (22.9 – 42.1)
24 months	15.9 (13.2 – 19.0)	16.5 (10.3 – 26.6)
CT Cohort		
Overall Survival		
6 months	50.1 (44.7 – 56.0)	34.9 (23.5 – 51.8)
12 months	27.0 (22.4 – 32.5)	6.7 (2.0 – 22.2)
24 months	16.2 (12.5 – 21.1)	3.3 (0.5 – 20.9)
Progression-Free Survival		
6 months	26.3 (21.8 – 31.8)	21.3 (12.3 – 36.9)
12 months	9.9 (7.0 – 13.9)	10.6 (4.6 – 24.4)
24 months	2.6 (1.3 – 5.2)	0.0 (NA – NA)

Supplementary Table 5. Overall survival and progression-free survival at 6 months, 12 months and 24 months in the whole cohort, ICI cohort, TT cohort, and CT cohort, after propensity score

Time (Months)	cMKP (%) (IC95%)	MUP (%) (IC95%)
Whole cohort		
Overall Survival		
6 months	82.0 (81.8 – 82.3)	73.7 (73.1 – 74.3)
12 months	67.6 (67.4 – 67.9)	57.5 (56.8 – 58.2)
24 months	51.4 (51.1 – 51.7)	47.2 (46.4 – 47.9)
Progression-Free Survival		
6 months	46.7 (46.4 – 47.0)	43.3 (42.5 – 44.0)
12 months	33.2 (32.9 – 33.5)	28.2 (27.6 – 28.9)
24 months	23.5 (23.2 – 23.7)	21.5 (20.9 – 22.1)
ICI Cohort		
Overall Survival		
6 months	79.6 (79.4 – 79.9)	69.8 (69.0 – 70.5)
12 months	66.7 (66.4 – 67.0)	54.5 (53.7 – 55.3)
24 months	52.8 (52.4 – 53.1)	47.3 (46.5 – 48.1)
Progression-Free Survival		
6 months	45.4 (45.1 – 45.7)	43.1 (42.3 – 43.9)
12 months	30.9 (30.6 – 31.2)	25.8 (25.1 – 26.5)
24 months	20.4 (20.2 – 20.7)	18.4 (17.8 – 19.1)
TT Cohort		
Overall Survival		
6 months	81.5 (81.1 – 81.9)	79.5 (78.6 – 80.5)
12 months	62.5 (61.3 – 63.7)	62.5 (61.3 – 63.7)
24 months	49.1 (47.9 – 50.4)	49.1 (47.9 – 50.4)
Progression-Free Survival		
6 months	49.5 (49.0 – 50.0)	56.3 (55.2 – 57.6)
12 months	31.0 (30.5 – 31.4)	31.4 (30.3 – 32.6)
24 months	15.6 (15.3 – 16.0)	19.6 (18.6 – 20.6)
CT Cohort		
Overall Survival		
6 months	49.9 (49.3 – 50.6)	37.8 (36.1 – 39.6)
12 months	26.9 (26.3 – 27.5)	6.7 (5.8 – 7.8)
24 months	16.1 (15.6 – 16.6)	3.2 (2.6 – 4.1)
Progression-Free Survival		
6 months	25.1 (24.5 – 25.7)	18.6 (17.2 – 20.0)
12 months	10.5 (10.1 – 11.0)	8.2 (7.3 – 9.3)
24 months	2.4 (2.2 – 2.6)	0.0 (NA – NA)

Supplementary Table 6. Prognostic factors in the whole treatment cohort on:

- overall survival in univariate (A) and multivariate (B) analysis
- progression-free survival in univariate (C) and multivariate (D) analysis

Proportionality over time was studied for all variables.

Supplementary Table 6A

	Variables	HR	IC95%	p-value
All patients	Known/unknown primary	0.80	0.67 – 0.95	0.01
	Sex	0.98	0.87 – 1.12	0.78
	Age	1.11	0.98 – 1.26	0.11
	AJCC	2.04	1.78 – 2.33	< 0.001
	ECOG	2.00	1.76 – 2.28	< 0.001
	LDH level	1.81	1.60 – 2.07	< 0.001
	CNS metastasis	1.78	1.54 – 2.05	< 0.001
	Liver metastasis	1.86	1.63 – 2.13	< 0.001
	BRAF mutation	0.94	0.83 – 1.06	0.30
	Number of metastasis	1.93	1.70 – 2.18	< 0.001
	Treatment type	1.46	1.29 – 1.65	< 0.001
	Neutrophil-to-lymphocyte count	0.91	0.78 – 1.17	0.11
	Auto-immune disease	0.78	0.60 – 1.02	0.07
cMKP	Sex	1.01	0.88 – 1.16	0.86
	Age	1.09	0.95 – 1.25	0.20
	AJCC	1.94	1.68 – 2.23	< 0.001
	ECOG	1.09	0.95 – 1.25	< 0.001
	LDH level	1.73	1.51 – 2.00	< 0.001
	CNS metastasis	1.83	1.55 – 2.15	< 0.001
	Liver metastasis	1.83	1.58 – 2.11	< 0.001
	BRAF mutation	0.96	0.84 – 1.10	0.54
	Number of metastasis	1.88	1.64 – 2.15	< 0.001
	Treatment type	1.49	1.30 – 1.70	< 0.001
	Neutrophil-to-lymphocyte count	0.91	0.78 – 1.17	0.11
	Auto-immune disease	0.80	0.75 – 1.07	0.13
MUP	Sex	0.81	0.58 – 1.12	0.20
	Age	1.23	0.91 – 1.73	0.17
	AJCC	3.01	1.84 – 4.94	< 0.001
	ECOG	1.23	0.91 – 1.73	0.17
	LDH level	2.33	1.68 – 3.23	< 0.001
	CNS metastasis	1.48	1.07 – 2.05	0.02
	Liver metastasis	2.0	1.42 – 2.80	< 0.001
	BRAF mutation	0.83	0.60 – 1.15	0.26
	Number of metastasis	2.11	1.52 – 2.93	< 0.001
	Treatment type	1.26	0.91 – 1.73	0.17
	Neutrophil-to-lymphocyte count	1.08	0.82 – 1.23	0.15
	Auto-immune disease	0.69	0.30 – 1.56	0.37

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 6B

	Variables	HR	IC95%	p-value
All patients	AJCC	1.24	1.03 – 1.48	0.02
	ECOG	1.76	1.54 – 2.01	< 0.001
	LDH level	1.51	1.32 – 1.72	< 0.001
	CNS metastasis	1.40	1.19 – 1.65	< 0.001
	Liver metastasis	1.33	1.13 – 1.56	< 0.001
	Number of metastasis	1.30	1.11 – 1.51	< 0.001
	Treatment type	1.38	1.21 – 1.57	< 0.001
cMKP	AJCC	1.22	1.01 – 1.49	0.04
	ECOG	1.28	1.11 – 1.47	< 0.001
	LDH level	1.51	1.31 – 1.75	< 0.01
	CNS metastasis	1.48	1.23 – 1.77	< 0.001
	Liver metastasis	1.31	1.10 – 1.56	< 0.01
	Number of metastasis	1.31	1.11 – 1.55	< 0.01
	Treatment type	1.43	1.24 – 1.64	< 0.001
MUP	AJCC	2.91	1.77 – 4.76	< 0.001
	LDH level	2.25	1.62 – 3.12	< 0.001

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 6C

	Variables	HR	IC95%	p-value
All patients	Known/unknown primary	0.89	0.76 – 1.02	0.09
	Sex	0.80	0.93 – 1.15	0.52
	Age	1.16	1.04 – 1.29	0.006
	AJCC	1.47	1.32 – 1.64	< 0.001
	ECOG	1.57	1.40 – 1.76	< 0.001
	LDH level	1.54	1.28 – 1.73	< 0.001
	CNS metastasis	1.42	1.25 – 1.61	< 0.001
	Liver metastasis	1.36	1.21 – 1.53	< 0.001
	BRAF mutation	0.73	0.65 – 0.81	< 0.001
	Number of metastasis	1.38	1.24 – 1.54	< 0.001
	Treatment type	0.89	0.80 – 0.99	0.03
	Neutrophil-to-lymphocyte count	1.36	1.22 – 1.51	< 0.001
	Auto-immune disease	0.89	0.72 – 1.11	0.31
cMKP	Sex	1.04	0.93 – 1.17	0.48
	Age	1.12	1.00 – 1.26	0.04
	AJCC	1.45	1.29 – 1.62	< 0.001
	ECOG	1.60	1.41 – 1.81	< 0.001
	LDH level	1.49	1.32 – 1.68	< 0.001
	CNS metastasis	1.45	1.25 – 1.67	< 0.001
	Liver metastasis	1.33	1.17 – 1.51	< 0.001
	BRAF mutation	0.75	0.67 – 0.84	< 0.001
	Number of metastasis	1.36	1.21 – 1.63	< 0.001
Treatment type	0.89	0.79 – 1.00	0.05	

	Neutrophil-to-lymphocyte count	1.33	1.19 – 1.50	0.11
	Auto-immune disease	0.93	0.74 – 1.18	0.57
MUP	Sex	0.97	0.73 – 1.30	0.86
	Age	1.44	1.09 – 1.90	< 0.01
	AJCC	1.61	1.13 – 2.31	< 0.01
	ECOG	1.39	1.04 – 1.86	0.03
	LDH level	1.90	1.42 – 2.53	< 0.001
	CNS metastasis	1.27	0.96 – 1.69	0.09
	Liver metastasis	1.57	1.16 – 2.23	< 0.01
	BRAF mutation	0.59	0.44 – 0.79	< 0.001
	Number of metastasis	1.47	1.11 – 1.94	< 0.01
	Treatment type	1.26	0.91 – 1.73	0.17
	Neutrophil-to-lymphocyte count	1.71	1.23 – 2.36	< 0.01
	Auto-immune disease	0.61	0.29 – 1.30	0.20

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 6D

	Variables	HR	IC95%	p-value
All patients	AJCC	1.21	1.05 – 1.39	< 0.01
	ECOG	1.44	1.29 – 1.62	< 0.001
	LDH level	1.43	1.28 – 1.61	< 0.001
	CNS metastasis	1.27	1.11 – 1.46	< 0.001
	Number of metastasis	1.16	1.02 – 1.32	0.02
	BRAF mutation	0.68	0.61 – 0.76	< 0.001
cMKP	AJCC	1.21	1.04 – 1.40	0.01
	ECOG	1.49	1.32 – 1.69	< 0.001
	LDH level	1.37	1.21 – 1.55	< 0.001
	CNS metastasis	1.27	1.09 – 1.49	< 0.01
	Number of metastasis	1.15	1.00 – 1.33	0.05
	BRAF mutation	0.70	0.62 – 0.78	< 0.001
MUP	LDH level	2.00	1.50 – 2.68	< 0.001
	CNS metastasis	1.49	1.12 – 1.98	< 0.01
	BRAF mutation	0.56	0.42 – 0.75	< 0.001

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 7. Prognostic factors in the ICI cohort on:

- overall survival in univariate (A) and multivariate (B) analysis
- progression-free survival in univariate (C) and multivariate (D) analysis

Proportionality over time was studied for all variables.

Supplementary Table 7A

	Variables	HR	IC95%	p-value
All patients	Known/unknown primary	0.78	0.64 – 0.95	0.01
	Sex	0.97	0.85 – 1.12	0.71
	Age	0.97	0.85 – 1.12	0.68
	AJCC	2.04	1.76 – 2.37	< 0.001
	ECOG	1.92	1.66 – 2.21	< 0.001
	LDH level	1.83	1.59 – 2.12	< 0.001
	CNS metastasis	1.71	1.46 – 2.03	< 0.001
	Liver metastasis	1.70	1.46 – 1.99	< 0.001
	BRAF mutation	1.11	0.96 – 1.28	0.17
	Number of metastasis	1.70	1.48 – 1.96	< 0.001
	Neutrophil-to-lymphocyte count	0.94	0.80 – 1.25	0.19
	Auto-immune disease	0.79	0.59 – 1.01	0.10
cMKP	Sex	0.99	0.85 – 1.16	0.94
	Age	0.97	0.84 – 1.13	0.70
	AJCC	1.94	1.66 – 2.27	< 0.001
	ECOG	2.01	1.71 – 2.35	< 0.001
	LDH level	1.76	1.51 – 2.06	< 0.001
	CNS metastasis	1.81	1.50 – 2.19	< 0.001
	Liver metastasis	1.62	1.37 – 1.92	< 0.001
	BRAF mutation	1.11	0.95 – 1.30	0.19
	Number of metastasis	1.68	1.44 – 1.95	< 0.001
	Neutrophil-to-lymphocyte count	0.93	0.78 – 1.24	0.17
	Auto-immune disease	0.80	0.75 – 1.07	0.13
	MUP	Sex	0.83	0.58 – 1.20
Age		1.00	0.70 – 1.43	0.99
AJCC		2.99	1.74 – 5.14	< 0.001
ECOG		1.44	1.00 – 2.08	0.05
LDH level		2.22	1.54– 3.20	< 0.001
CNS metastasis		1.26	0.87 – 1.83	0.22
Liver metastasis		2.13	1.46 – 3.12	< 0.001
BRAF mutation		1.14	0.78 – 1.67	0.51
Number of metastasis		1.72	1.20 – 2.46	< 0.01
Neutrophil-to-lymphocyte count		0.95	0.82 – 1.28	0.20
Auto-immune disease		0.87	0.28 – 2.74	0.81

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 7B

	Variables	HR	IC95%	p-value
All patients	AJCC	1.53	1.28 – 1.83	< 0.001
	ECOG	1.73	1.50 – 2.00	< 0.001
	LDH level	1.52	1.31 – 1.78	< 0.001
	CNS metastasis	1.34	1.12 – 1.61	< 0.01
	Liver metastasis	1.23	1.03 – 1.47	0.02
cMKP	AJCC	1.57	1.32 – 1.87	< 0.001
	ECOG	1.84	1.57 – 2.15	< 0.001
	LDH level	1.53	1.30 – 1.79	< 0.001
	CNS metastasis	1.37	1.12 – 1.68	< 0.01
MUP	AJCC	2.68	1.55 – 4.62	< 0.001
	LDH level	1.97	1.36 – 2.85	< 0.001

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 7C

	Variables	HR	IC95%	p-value
All patients	Sex	1.00	0.90 – 1.13	0.87
	Age	1.02	0.91 – 1.15	0.62
	AJCC	1.36	1.21 – 1.52	< 0.001
	ECOG	1.44	1.28 – 1.63	< 0.001
	LDH level	1.52	1.35 – 1.72	< 0.001
	CNS metastasis	1.27	1.11 – 1.47	< 0.001
	Liver metastasis	1.30	1.14 – 1.49	< 0.001
	BRAF mutation	0.90	0.80 – 1.01	0.07
	Number of metastasis	1.38	1.23 – 1.55	< 0.001
	Neutrophil-to-lymphocyte count	1.28	1.14 – 1.43	< 0.001
	Auto-immune disease	0.82	0.65 – 1.03	0.09
cMKP	Sex	1.02	0.90 – 1.15	0.74
	Age	1.00	0.89 – 1.13	0.97
	AJCC	1.36	1.20 – 1.54	< 0.001
	ECOG	1.49	1.31 – 1.70	< 0.001
	LDH level	1.46	1.29 – 1.67	< 0.001
	CNS metastasis	1.27	1.09 – 1.49	< 0.01
	Liver metastasis	1.27	1.10 – 1.47	< 0.01
	BRAF mutation	0.92	0.82 – 1.04	0.22
	Number of metastasis	1.33	1.18 – 1.51	< 0.001
	Neutrophil-to-lymphocyte count	1.28	1.13 – 1.45	0.11
	Auto-immune disease	0.85	0.67 – 1.08	0.17
	Sex	0.91	0.67 – 1.24	0.56
	Age	1.20	0.89 – 1.63	0.22
	AJCC	1.28	0.89 – 1.85	0.19
	ECOG	1.17	0.86 – 1.60	0.30
	LDH level	1.97	1.44 – 2.70	< 0.001
	CNS metastasis	1.23	0.90 – 1.69	0.20
	Liver metastasis	1.48	1.05 – 2.07	0.02

MUP	BRAF mutation	0.76	0.55 – 1.05	0.09
	Number of metastasis	1.61	1.19 – 2.17	< 0.01
	Neutrophil-to-lymphocyte count	1.49	1.03 – 2.13	0.03
	Auto-immune disease	0.56	0.21 – 1.50	0.25

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 7D

	Variables	HR	IC95%	p-value
All patients	AJCC	1.18	1.03 – 1.35	0.01
	ECOG	1.38	1.23 – 1.56	< 0.001
	LDH level	1.42	1.25 – 1.60	< 0.001
	Number of metastasis	1.20	1.05 – 1.37	< 0.01
	BRAF mutation	0.84	0.75 – 0.95	< 0.01
cMKP	AJCC	1.57	1.01 – 1.35	0.03
	ECOG	1.84	1.26 – 1.63	< 0.001
	LDH level	1.53	1.20 – 1.56	< 0.001
	Number of metastasis	1.37	1.01 – 1.36	0.03
MUP	LDH level	2.68	1.28 – 2.48	< 0.001
	Number of metastasis	1.38	1.01 – 1.90	0.04

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group

Supplementary Table 8. Prognostic factors in the TT cohort on:

- overall survival in univariate (A) and multivariate (B) analysis
- progression-free survival in univariate (C) and multivariate (D) analysis

Proportionality over time was studied for all variables.

Supplementary Table 8A

	Variables	HR	IC95%	p-value
All patients	Known/unknown primary	1.01	0.77 – 1.33	0.92
	Sex	1.02	0.85 – 1.12	0.84
	Age	1.06	0.88 – 1.26	0.52
	AJCC	2.16	1.74 – 2.33	< 0.001
	ECOG	2.07	1.71 – 2.28	< 0.001
	LDH level	1.62	1.34 – 2.07	< 0.001
	CNS metastasis	1.72	1.40 – 2.05	< 0.001
	Liver metastasis	1.87	1.55 – 2.13	< 0.001
	BRAF mutation	1.06	0.81 – 1.06	0.65
	Number of metastasis	1.77	1.47 – 2.18	< 0.001
	Neutrophil-to-lymphocyte count	0.86	0.75 – 1.17	0.19
	Auto-immune disease	0.81	0.54 – 1.02	0.29
cMKP	Sex	1.04	0.86 – 1.27	0.69
	Age	1.05	0.86 – 1.28	0.65
	AJCC	2.13	1.70 – 2.67	< 0.001
	ECOG	2.19	1.79 – 2.68	< 0.001
	LDH level	1.61	1.31 – 1.98	< 0.001
	CNS metastasis	1.73	1.39 – 2.16	< 0.001
	Liver metastasis	1.89	1.54 – 2.31	< 0.001
	BRAF mutation	1.03	0.77 – 1.37	0.83
	Number of metastasis	1.67	1.68 – 2.03	< 0.001
	Neutrophil-to-lymphocyte count	0.92	0.68 – 1.31	0.28
	Auto-immune disease	0.89	0.59 – 1.36	0.60
	MUP	Sex	0.89	0.54 – 1.49
Age		1.18	0.69 – 2.02	0.55
AJCC		2.62	1.25 – 5.54	0.01
ECOG		1.42	0.84 – 2.42	0.20
LDH level		1.68	1.00 – 2.81	0.05
CNS metastasis		1.85	1.11 – 3.08	0.02
Liver metastasis		1.73	1.02 – 2.96	0.04
BRAF mutation		1.48	0.59 – 3.70	0.41
Number of metastasis		2.63	1.53 – 4.50	< 0.001
Neutrophil-to-lymphocyte count		0.81	0.65 – 1.14	0.23
Auto-immune disease		0.46	0.14 – 1.46	0.19

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 8B

	Variables	HR	IC95%	p-value
All patients	AJCC	1.41	1.05 – 1.81	< 0.01
	ECOG	1.89	1.66 – 2.50	< 0.001
	LDH level	1.31	1.07 – 1.62	< 0.01
	CNS metastasis	1.54	1.22 – 1.96	< 0.001
	Liver metastasis	1.54	1.23 – 1.94	< 0.001
cMKP	AJCC	1.38	1.09 – 1.83	0.02
	ECOG	2.04	1.56 – 2.29	< 0.001
	LDH level	1.35	1.11 – 1.65	0.01
	CNS metastasis	1.52	1.22 – 1.89	< 0.001
	Liver metastasis	1.50	1.21 – 1.85	< 0.001
MUP	Number of metastasis	2.63	1.53 – 4.50	< 0.001

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 8C

	Variables	HR	IC95%	p-value
All patients	Known/unknown primary	1.01	0.77 – 1.33	0.91
	Sex	1.03	0.88 – 1.20	0.73
	Age	1.02	0.88 – 1.20	0.76
	AJCC	1.65	1.39 – 1.96	< 0.001
	ECOG	1.65	1.41 – 1.94	< 0.001
	LDH level	1.46	1.24 – 1.72	< 0.001
	CNS metastasis	1.31	1.10 – 1.57	< 0.01
	Liver metastasis	1.46	1.23 – 1.72	< 0.001
	BRAF mutation	0.93	0.74 – 1.17	0.54
	Number of metastasis	1.34	1.15 – 1.56	< 0.001
	Neutrophil-to-lymphocyte count	1.22	1.04 – 1.43	0.01
	Auto-immune disease	0.90	0.65 – 1.23	0.51
cMKP	Sex	1.09	0.92 – 1.28	0.33
	Age	1.02	0.86 – 1.21	0.81
	AJCC	1.70	1.42 – 2.05	< 0.001
	ECOG	1.66	1.39 – 1.97	< 0.001
	LDH level	1.45	1.21 – 1.72	< 0.001
	CNS metastasis	1.38	1.14 – 1.68	< 0.01
	Liver metastasis	1.47	1.23 – 1.76	< 0.001
	BRAF mutation	0.91	0.72 – 1.16	0.46
	Number of metastasis	1.35	1.15 – 1.59	< 0.001
	Neutrophil-to-lymphocyte count	1.23	1.04 – 1.45	0.01
	Auto-immune disease	1.0	0.71 – 1.41	0.99
	Sex	0.70	0.45 – 1.09	0.11
	Age	1.05	0.65 – 1.69	0.85
	AJCC	1.33	0.77 – 2.30	0.31
	ECOG	1.64	1.01 – 2.65	0.04

MUP	LDH level	1.55	0.98 – 2.46	0.06
	CNS metastasis	1.13	0.72 – 1.77	0.60
	Liver metastasis	1.36	0.84 – 2.20	0.22
	BRAF mutation	1.17	0.50 – 2.72	0.72
	Number of metastasis	1.28	0.82 – 1.99	0.28
	Neutrophil-to-lymphocyte count	1.20	0.72 – 2.00	0.48
	Auto-immune disease	0.48	0.18 – 1.32	0.16

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 8D

	Variables	HR	IC95%	p-value
All patients	AJCC	1.54	1.29 – 1.84	<0.001
	ECOG	1.54	1.31 – 1.82	< 0.001
	LDH level	1.32	1.12 – 1.56	< 0.01
cMKP	AJCC	1.60	1.33 – 1.93	< 0.001
	ECOG	1.55	1.30 – 1.86	< 0.001
	LDH level	1.28	1.06 – 1.52	< 0.01
MUP	ECOG	1.64	1.01 – 2.65	0.04

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group

Supplementary Table 9. Prognostic factors in the CT cohort on:

- overall survival in univariate (A) and multivariate (B) analysis
- progression-free survival in univariate (C) and multivariate (D) analysis

Proportionality over time was studied for all variables.

Supplementary Table 9A

	Variables	HR	IC95%	p-value
All patients	Known/unknown primary	0.58	0.42 – 0.80	< 0.001
	Sex	1.08	0.86 – 1.35	0.53
	Age	0.86	0.60 – 1.01	0.20
	AJCC	2.14	1.65 – 2.77	< 0.001
	ECOG	1.72	1.37 – 2.17	< 0.001
	LDH level	1.45	1.14 -1.83	< 0.01
	CNS metastasis	1.99	1.56 – 2.54	< 0.001
	Liver metastasis	1.53	1.18 – 1.99	< 0.01
	BRAF mutation	1.30	1.01 – 1.68	0.04
	Number of metastasis	1.61	1.29 – 2.02	< 0.001
	Neutrophil-to-lymphocyte count	1.57	1.05 – 1.79	0.04
	Auto-immune disease	0.71	0.45 – 1.13	0.15
cMKP	Sex	1.12	0.88 – 1.44	0.35
	Age	0.89	0.70 – 1.13	0.34
	AJCC	2.03	1.56 – 2.66	< 0.001
	ECOG	1.75	1.36 – 2.23	< 0.001
	LDH level	1.47	1.14 – 1.89	< 0.01
	CNS metastasis	2.06	1.59 – 2.69	< 0.001
	Liver metastasis	1.58	1.20 – 2.10	< 0.01
	BRAF mutation	1.32	1.01 – 1.73	0.04
	Number of metastasis	1.59	1.25 – 2.02	< 0.001
	Neutrophil-to-lymphocyte count	1.51	1.06 – 1.33	0.04
	Auto-immune disease	0.69	0.42 – 1.13	0.14
	MUP	Sex	0.69	0.37 – 1.29
Age		0.68	0.36 – 1.25	0.21
AJCC		2.46	0.75 – 8.06	0.14
ECOG		1.15	0.59 – 2.26	0.68
LDH level		1.17	0.62 – 2.19	0.63
CNS metastasis		1.63	0.84 – 3.14	0.15
Liver metastasis		1.19	0.59 – 2.38	0.62
BRAF mutation		1.59	0.75 – 3.36	0.23
Number of metastasis		1.62	0.88 – 2.97	0.12
Neutrophil-to-lymphocyte count		1.73	0.93 – 3.21	0.08
Auto-immune disease		0.88	0.27 – 2.87	0.83

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 9B

	Variables	HR	IC95%	p-value
All patients	AJCC	1.82	1.37 – 2.41	< 0.01
	ECOG	1.68	1.33 – 2.12	< 0.001
	LDH level	1.36	1.08 – 1.73	0.01
	CNS metastasis	1.51	1.16 – 1.97	< 0.01
cMKP	AJCC	1.72	1.27 – 2.31	< 0.01
	ECOG	1.74	1.36 – 2.23	< 0.001
	LDH level	1.45	1.13 – 1.87	< 0.01
	CNS metastasis	1.60	1.20 – 2.13	< 0.01

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 9C

	Variables	HR	IC95%	p-value
All patients	Known/unknown primary	0.86	0.63 – 1.16	0.32
	Sex	1.03	0.88 – 1.20	1.21
	Age	0.89	0.72 – 1.10	0.28
	AJCC	1.43	1.13 – 1.80	< 0.01
	ECOG	1.33	1.07 – 1.65	0.01
	LDH level	1.25	1.00 – 1.56	0.05
	CNS metastasis	1.31	1.04 – 1.65	0.02
	Liver metastasis	1.20	0.93 – 1.55	0.15
	BRAF mutation	0.75	0.59 – 0.96	0.02
	Number of metastasis	1.35	1.09 – 1.67	< 0.01
	Neutrophil-to-lymphocyte count	1.30	1.05 – 1.61	0.02
	Auto-immune disease	0.91	0.59 – 1.39	0.66
cMKP	Sex	1.28	1.01 – 1.61	0.04
	Age	0.97	0.77 – 1.23	0.81
	AJCC	1.38	1.09 – 1.76	< 0.01
	ECOG	1.34	1.07 – 1.69	0.01
	LDH level	1.22	0.96 – 1.55	0.10
	CNS metastasis	1.32	1.03 – 1.70	0.03
	Liver metastasis	1.25	0.95 – 1.64	0.11
	BRAF mutation	0.78	0.60 – 1.01	0.06
	Number of metastasis	1.35	1.08 – 1.70	0.01
	Neutrophil-to-lymphocyte count	1.35	1.07 – 1.70	0.01
Auto-immune disease	0.86	0.54 – 1.35	0.51	
	Sex	0.79	0.44 – 1.44	0.45
	Age	0.45	0.24 – 0.82	< 0.01
	AJCC	1.72	0.68 – 4.40	0.25
	ECOG	1.06	0.56 – 2.04	0.85
	LDH level	1.32	0.71 – 2.44	0.38
	CNS metastasis	1.25	0.66 – 2.37	0.49
	Liver metastasis	0.87	0.44 – 1.72	0.69

MUP	BRAF mutation	0.60	0.29 – 1.26	0.18
	Number of metastasis	1.27	0.70 – 2.30	0.43
	Neutrophil-to-lymphocyte count	1.73	0.93 – 3.21	0.08
	Auto-immune disease	1.63	0.50 – 5.34	0.42

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 9D

	Variables	HR	IC95%	p-value
All patients	AJCC	1.31	1.02 – 1.70	0.04
	ECOG	1.27	1.02 – 1.59	0.03
	CNS metastasis	1.39	1.05 – 1.83	0.02
	BRAF mutation	0.63	0.48 – 0.82	< 0.001
cMKP	ECOG	1.33	1.05 – 1.67	0.02
	CNS metastasis	1.55	1.18 – 2.05	< 0.01
	BRAF mutation	0.65	0.48 – 0.86	< 0.01
MUP	Age	0.34	0.18 – 0.65	< 0.01
	BRAF mutation	0.41	0.19 – 0.89	< 0.02

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; CNS, Central Nervous System

Supplementary Table 10. Occurrence of AEs of any grade, grade I-II and grade III-IV, categorized according to the different organs/systems involved, across the cMKP and MUP groups

Population Toxicity	MKP adverse events			MUP adverse events		
	All grade N (% patients)	Grade I-II N (% patients)	Grade III- IV N (% patients)	All grade N (% patients)	Grade I- II N (% patients)	Grade III- IV N (% patients)
ALL TREATMENTS (ICI + TT + CT)						
Cutaneous AEs	478 (30)	457 (28)	42 (3)	72 (27)	68 (26)	6 (2)
Endocrine AEs	219 (14)	206 (13)	26 (2)	30 (11)	29 (11)	1 (0)
Gastrointestinal AEs	410 (25)	370 (23)	83 (5)	67 (25)	63 (24)	11 (4)
Hepatic AEs	29 (2)	15 (1)	14 (1)	5 (2)	4 (2)	3 (1)
Pulmonary AEs	88 (5)	77 (5)	19 (1)	11 (4)	9 (3)	3 (1)
Rheumatic AEs	15 (1)	14 (1)	2 (0)	2 (1)	2 (1)	1 (0)
Heart AEs	33 (2)	23 (1)	11 (1)	4 (2)	4 (2)	0 (0)
Eye AEs	86 (5)	80 (5)	6 (0)	17 (6)	16 (6)	1 (0)
Fever/chills AEs	147 (9)	142 (9)	12 (1)	107 (8)	102 (7)	9 (1)
Fatigue AEs	403 (25)	395 (24)	16 (1)	363 (27)	357 (26)	17 (1)
Increased CK AEs	40 (2)	33 (2)	16 (1)	3 (1)	3 (1)	1 (0)
Hematotoxicity AEs	117 (7)	100 (6)	30 (2)	17 (6)	12 (5)	10 (4)
Others	683 (42)	617 (38)	198 (12)	114 (43)	105 (40)	33 (12)
IMMUNOTHERAPY						
Cutaneous irAEs	376 (28)	368 (27)	18 (1)	58 (26)	56 (25)	4(2)
Endocrine irAEs	262 (19)	246 (18)	33 (2)	36 (16)	35 (16)	1 (0)
Gastrointestinal irAEs	371 (27)	330 (24)	81 (6)	63 (29)	59 (27)	5 (2)
Hepatic irAEs	35 (3)	22 (2)	13 (1)	5 (2)	4 (2)	2 (1)
Pulmonary irAEs	94 (7)	83 (6)	17 (1)	13 (6)	12 (5)	1 (0)
Rheumatic irAEs	18 (1)	16 (1)	3 (0)	3 (1)	2 (1)	1 (0)
Heart irAEs	24 (2)	19 (1)	6 (0)	3 (1)	3 (1)	3 (1)
Eye irAEs	50 (4)	45 (3)	5 (0)	13 (6)	12 (5)	1 (0)
Fever/chills irAEs	107 (8)	102 (7)	9 (1)	17 (8)	17 (8)	15 (7)
Fatigue irAEs	363 (27)	357 (26)	17 (1)	51 (23)	49 (22)	2 (1)
Increased CK irAEs	21 (2)	18 (1)	7 (1)	2 (1)	2 (1)	2 (1)
Hematotoxicity irAEs	83 (6)	75 (5)	13 (1)	12 (5)	10 (5)	2 (0)
Others	584 (43)	533 (39)	182 (13)	98 (45)	89 (40)	4 (2)
TARGETED THERAPY						
Cutaneous AEs	261 (39)	244 (37)	40 (6)	29 (30)	26 (27)	5 (5)

Endocrine AEs	28 (4)	25 (4)	6 (1)	4 (4)	4 (4)	1 (1)
Gastrointestinal AEs	207 (31)	191 (29)	35 (5)	22 (23)	22 (23)	2 (2)
Hepatic AEs	10 (1)	6 (1)	4 (1)	4 (4)	3 (3)	1 (1)
Pulmonary AEs	28 (4)	25 (4)	5 (1)	6 (6)	4 (4)	5 (5)
Rheumatic AEs	7 (1)	6 (1)	1 (0)	1 (1)	1 (1)	1 (1)
Heart AEs	32 (5)	20 (3)	14 (2)	4 (4)	3 (3)	1 (1)
Eye AEs	83 (12)	77 (12)	8 (1)	14 (14)	13 (13)	2 (2)
Fever/chills AEs	144 (22)	136 (20)	16 (2)	19 (20)	19 (20)	1 (1)
Fatigue AEs	186 (28)	179 (27)	18 (3)	27 (28)	26 (27)	2 (2)
Increased CK AEs	49 (7)	42 (6)	16 (2)	2 (2)	2 (2)	2 (2)
Hematotoxicity AEs	65 (10)	56 (8)	23 (3)	8 (8)	7 (7)	1 (1)
Others	361 (54)	327 (49)	109 (16)	59 (61)	51 (53)	1 (1)
CHEMOTHERAPY						
Cutaneous AEs	35 (11)	34 (11)	3 (1)	7 (15)	6 (13)	2 (4)
Endocrine AEs	3 (1)	3 (1)	1 (0)	2 (4)	1 (2)	1 (2)
Gastrointestinal AEs	66 (21)	65 (21)	42 (14)	9 (19)	9 (19)	2 (4)
Hepatic AEs	3 (1)	2 (1)	1 (0)	2 (4)	2 (4)	1 (2)
Pulmonary AEs	10 (3)	8 (3)	2 (1)	0 (0)	0 (0)	0 (0)
Heart AEs	1 (0)	1 (0)	0 (0)	1 (2)	1 (2)	0 (0)
Eye AEs	7 (2)	7 (2)	1 (0)	2 (4)	2 (4)	0 (0)
Fever/chills AEs	13 (4)	12 (4)	1 (0)	1 (2)	1 (2)	0 (0)
Fatigue AEs	53 (17)	49 (16)	4 (1)	4 (9)	3 (6)	1 (2)
Increased CK AEs	6 (2)	4 (1)	4 (1)	1 (2)	1 (2)	0 (0)
Hematotoxicity AEs	85 (28)	63 (20)	1 (0)	11 (23)	5 (11)	9 (19)
Others	81 (26)	71 (23)	25 (8)	8 (17)	7 (15)	5 (11)

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Serment d'Hippocrate

« Au moment d'être admise 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 le demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue 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 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 déshonorée et méprisée si j'y manque. »