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The concomitant use of proton pump inhibitors and BRAF/MEK inhibitors in metastatic melanoma

Running head: Proton pump inhibitors and BRAF/MEK inhibitors in metastatic melanoma

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Competing Interests

FL reports reimbursement for travel and/or accommodation expenses for attending medical meetings from Chiesi and Sandoz, outside the submitted work. MD reports reimbursement for travel and/or accommodation expenses for attending medical meetings from BMS, MSD, Novartis and Pierre Fabre Oncology and personal fees from Sanofi, outside the submitted work. TL reports personal fees from BMS, MSD, Novartis and Pierre Fabre Oncology, outside the submitted work. AD reports reimbursement for travel and/or accommodation expenses for attending medical meetings from Sanofi and UCB Pharma, and personal fees from Sanofi outside the submitted work. The other authors have no disclosures.

Author Contributions

Conceptualization, methodology: FP, FL, CT, EO, AD; Data curation, investigation, software: FP, FB; Writing – original draft: FP, AD; Writing – review & editing: All authors; Formal analysis: FP; Funding acquisition: FP, EO, AD; Project administration, resources: FP, FB, EO, AD; Validation, supervision: EO, AD; Visualization: FP.

Data access and cleaning methods

Direct access to the whole database was granted by ANSM to our research consortium. The authors (FP and FB) had full access to all the data that were used to generate the study population. Different metrics were used to check data completeness at population level,

including the number of patients exposed (compared to the expected number) and the stability of reimbursement frequencies over time.

Data Availability

The protocol and the statistical code are available on justified request. Under French law and regulations, databases extracted from the Système National des Données de Santé cannot be made available.

What's already known about this topic?

- Proton-pump inhibitors (PPIs) are commonly used among patients with metastatic melanoma receiving BRAF/MEK inhibitors, although they could reduce the absorption of oral anticancer treatments.
- The Food and Drug Administration and the European Society for Medical Oncology alerted on a potential decreased absorption of the BRAF inhibitor dabrafenib.

What does this study add?

- In a population-based cohort study including 1028 patients with metastatic melanoma receiving BRAF/MEK inhibitors as a first treatment line, we found that concomitant PPI use was not associated with shorter treatment duration or survival.
- We concluded that PPI use does not compromise the efficacy of BRAF/MEK inhibitors. Consistent results were observed when restricting the population to patients receiving dabrafenib.

Summary

Background: Proton-pump inhibitors (PPIs) are commonly used among patients with cancer, although they could reduce the absorption of oral anticancer targeted therapies. The Food and Drug Administration states that the effect of PPIs on the efficacy of dabrafenib among patients with metastatic melanoma is unknown. As a precautionary measure, the European Society for Medical Oncology recommends avoiding PPIs for patients receiving dabrafenib.

Objectives: To determine the effect of the concomitant use of PPIs and BRAF/MEK inhibitors in metastatic melanoma patients.

Methods: Patients with advanced melanoma receiving BRAF/MEK inhibitors as first-line treatments between 2015 and 2017 in France were selected using the French Health Insurance database. We compared time-to-treatment discontinuation (TTD) and overall survival (OS) according to concomitant PPI exposure. We balanced the baseline characteristics of patients exposed and nonexposed to PPIs using an overlap weighting method based on a propensity score.

Results: The metastatic melanoma cohort comprised 1028 patients receiving BRAF/MEK inhibitors, including 361 (32.0%) patients using PPIs. PPI users had more comorbidities and a more severe metastatic disease. After having equally distributed metastatic sites and comorbidities across patients exposed and nonexposed to PPIs, concomitant PPI use was not associated with shorter TTD (weighted hazard ratio [wHR]=1.03, 95% confidence interval [95%CI] 0.86-1.24) or OS (wHR=1.11, 95%CI 0.88-1.39). Consistent results were observed when restricting the population to patients receiving dabrafenib, or when narrowing exposure to PPIs with stronger inhibition of cytochromes.

Conclusion: In a population-based cohort of advanced melanoma patients, the concomitant use of PPIs and BRAF/MEK inhibitors was not associated with worse outcome.

Key words

melanoma ; BRAF inhibitor ; proton pump inhibitors ; drug-drug interactions ; propensity score ; overlap weighting

Introduction

Proton pump inhibitors (PPIs) are commonly used among patients with cancer.^{1,2} With the development of targeted therapies using protein kinase inhibitors, many new anticancer drugs are administered orally, and potential drug-drug interactions between PPIs and oral treatments need to be further characterized. Two mechanisms are involved.^{3,4} First, increasing gastric pH with PPIs potentially modifies the absorption of orally-administered therapeutics if they exhibit pH-dependent solubility, and could also modify the ionized/non-ionized fraction of drugs. Second, PPIs can influence drug metabolism by inhibiting the cytochrome P450 enzyme system, particularly isoenzyme 3A4, leading to an increase in blood concentrations of drugs that are substrates of this cytochrome,^{5,6} which can result in higher toxicity and eventually to dose reduction or discontinuation. Drug-drug interactions may result in a decreased efficacy of anticancer targeted therapies.^{4,7,8} Thus, the concomitant use of PPIs has reduced the absorption of several anticancer tyrosine kinase inhibitors.⁹⁻¹¹ In addition, an increased concentration could lead to higher toxicity and earlier treatment discontinuation. In observational studies, PPI co-administration was associated with shorter survival among cancer patients receiving tyrosine kinase inhibitors.^{12,13}

In metastatic melanoma, targeted therapies using protein kinase inhibitors have significantly improved the prognosis of tumours harbouring the *BRAFV600* mutation.¹⁴⁻¹⁸ BRAF inhibitors (vemurafenib, dabrafenib and encorafenib) have been approved since 2012, and have been combined with MEK inhibitors (cobimetinib, trametinib and binimetinib) since 2015. Little data is available regarding the pharmacokinetics and efficacy of BRAF/MEK inhibitors according to PPI exposure¹⁹⁻²². Therefore, the Food and Drug Administration (FDA) has raised the question of the effect of PPI use on dabrafenib efficacy, and the European Society for Medical Oncology (ESMO) recommend avoiding the combination of BRAF inhibitor dabrafenib with PPIs.^{23,24}

Our aim was to determine the effect of the concomitant use of PPIs and BRAF/MEK inhibitors in metastatic melanoma patients. Treatment duration with BRAF/MEK inhibitor and survival were analysed according to the co-administration of PPIs, using data prospectively collected in the French Health Insurance database.

Material and methods

Data source and study cohorts

This study was conducted using the French National Health Insurance database (SNDS, *Système National des Données de Santé*),^{25,26} and followed the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines.²⁷ The database covers 98.8% of the population living in France (around 66 million inhabitants), and contains exhaustive data on all reimbursements for health-related expenditures, including dispensed drugs with date of dispensation. Information about all hospitalizations in a public or private hospital is also provided, including diagnoses (using ICD-10 codes, International Classification of Diseases, 10th revision). Long-term diseases (including cancers) are recorded, with diagnoses encoded according to ICD-10, because they give entitlement to 100% health insurance coverage.

We previously constructed a national cohort including every new patient receiving a systemic treatment for metastatic melanoma in France between June 2015 and December 2017.^{28,29} The population selection process has been detailed previously.²⁸ Patients receiving BRAF/MEK inhibitors as a first-line treatment for metastatic melanoma were included in the current study.

Ethics approval

The study was approved by the French Data Protection Agency (CNIL, DR-2016-384).

PPI exposure

The time frame used to determine a concomitant PPI exposure was comprised between 1 month before and 3 months after the initiation of BRAF/MEK inhibitors. The concomitant use of PPIs was defined as at least 2 dispensations of PPIs in this time frame. Patients with a single dispensation of PPIs were excluded. Patients exposed and nonexposed to PPIs in this time frame were compared regardless of whether PPIs were continued during follow-up, similarly to an intention-to-treat analysis. In addition, PPI duration was defined for per-protocol analysis, as: number of boxes dispensed * number of units per box * 2 + duration of hospital stays. The duration of hospital stays was added because PPIs dispensed during hospital stays are not recorded in our database, and patients are not allowed to take personal drugs (dispensed by pharmacies) in the hospital; * 2 is the grace period, used in claims databases to allow for some leeway when refilling prescriptions.³⁰

Outcomes

The efficacy of BRAF/MEK inhibitors was evaluated with time-to-treatment discontinuation (TTD), pointing to the duration of the first treatment line, and overall survival (OS). TTD and OS were defined from the date of initiation to the date of discontinuation of BRAF/MEK inhibitors, and date of death, respectively, or until censoring on December 31, 2017. The date of initiation of BRAF/MEK inhibitors was the date of the first dispensation. The treatment was considered as discontinued when a second-line treatment was initiated (date of first infusion of immunotherapy or chemotherapy), or 3 months after the last recorded dispensation of BRAF/MEK inhibitors if no subsequent treatment was initiated. To avoid an immortal-time bias, the landmark method was used.³¹⁻³³ A three-month period was selected as the landmark time to correspond to the end of the PPI exposure time frame. In the 3-month landmark

analysis, patients who discontinued the treatment or died (for TTD and OS respectively), or were censored before the end of the PPI exposure time frame, were excluded. Thus, TTD and OS were measured from the 3-month landmark time after initiation of BRAF/MEK inhibitors.

Sensitivity analyses

In a first sensitivity analysis, we restricted the cohort to patients initiating dabrafenib, alone or combined with trametinib. The FDA and the ESMO paid particular attention to a potential decreased absorption of dabrafenib,^{23,24} which is, furthermore, the only BRAF inhibitor authorized in adjuvant settings. In a second sensitivity analysis, exposure to PPI omeprazole and esomeprazole was compared with no exposure to PPI. Omeprazole and esomeprazole inhibit CYP2C19 and CYP3A4 more strongly than other PPIs, and therefore carry a greater drug-drug interaction potential.^{3,4,34}

Covariates

Numerous patients' characteristics were considered as potential confounders: age, sex, number and location of metastatic sites, previous surgery, stereotactic or external beam radiotherapy, and comorbidities (cardiovascular, neurological, psychiatric disorders, diabetes, respiratory, renal, liver, pancreatic, inflammatory diseases, and cancers other than melanoma). The algorithm used to identify comorbidities on the SNDS database was based on long-term disease diagnoses, hospitalization discharge diagnoses, medical procedures and medications²⁹. In addition, two general indicators of the global multimorbidity burden were assessed, *i.e.* the number of hospitalization days during the PPI exposure time frame, and the total number of drug boxes dispensed (regardless of the drug) during the time frame. Being exposed to corticosteroids was specifically identified as another covariate, because of the frequent prescription of PPIs in patients receiving corticosteroids.

Propensity score and target population

Overlap weighting based on the propensity score was used to create target populations, in which the measured baseline characteristics were exactly balanced between patients exposed and nonexposed to PPI.^{35–38} A multivariate logistic regression was performed to calculate the propensity score for PPI exposure using all covariates with non-zero values. Exposed patients were weighted by the probability of not receiving PPIs ($1 - \text{propensity score}$) and unexposed patients were weighted by the probability of receiving PPIs (propensity score).^{36–39} The exact covariate balance was checked using standardized differences in the target population between the exposed and nonexposed groups.

Statistical analysis

Analyses were first conducted in the original population of patients receiving BRAF/MEK inhibitors as a first-line treatment for metastatic melanoma, according to the concomitant use of PPI. The Kaplan-Meier method and log-rank test were used to estimate TTD and OS from 3 months after initiation of BRAF/MEK inhibitors. Univariate Cox proportional hazards regression models were fitted to assess crude hazard ratios (HRs) and 95% confidence intervals (CIs). Second, analyses were conducted in the target population created to take into account potential confounders in the evaluation of the effect of PPI exposure. Kaplan-Meier curves and weighted log-rank tests were performed in the target population. Propensity score-weighted Cox proportional hazards regression models were used to estimate weighted hazard ratios (wHRs) and 95% confidence intervals (CIs) for TTD and OS. Proportional hazards were assessed by plotting $\log(-\log(\text{survival}))$ versus the log of survival time for categorical covariates, and scaled Schönfeld residuals versus survival time for continuous covariates. Additionally, the per-protocol effect of PPIs was determined by restricting the original

population and the target population to patients who remained adherent to the first allocated group: patients exposed to PPIs were censored when discontinuing PPIs, and patients nonexposed to PPIs were censored when initiating PPIs. Patients were not censored if they had previously discontinued BRAF/MEK inhibitors, as the exposure of interest was the concomitant use of PPIs and BRAF/MEK inhibitors.

Because every individual living in France is included in the SNDS database until death, there was no loss to follow-up. Statistical significance was defined at an a priori value of 0.05. All statistical tests were 2-sided. Statistical analyses were performed using R v3.6.0 software (R Inc, USA).

Results

Patient characteristics

Overall, 1505 patients received BRAF/MEK inhibitors between June 2015 and December 2017 as first-line treatment for metastatic melanoma in France. A total of 1028 and 972 patients receiving BRAF/MEK inhibitors were included for the evaluation of OS and TTD respectively, among whom 361 (32.0%) and 343 (35.3%) were concomitantly exposed to PPIs. The steps are detailed in the flowchart ([Figure 1](#)).

The characteristics of the 1028 patients included in the landmark analysis of OS according to PPI exposure are presented in [Table 1](#). In the original population, patients using PPIs had a higher metastatic burden, including brain (40.2% vs. 14.7%) and liver (30.5% vs. 17.2%) metastases. Nearly all comorbidities were also more prevalent among patients using PPIs ([Table 1](#)). Overlap weighting based on the propensity score was used to create a perfectly-balanced target population regarding all covariates according to PPI exposure ([Table 1](#)).

Standardized mean differences were computed for all covariates and were equal to zero in the

target population (Table S1). Therefore, all the characteristics measured were equally distributed across the groups within the target population.

Association between the concomitant use of PPIs and the outcome

By December 31, 2017, 697 (71.7%) had discontinued BRAF/MEK inhibitors and 471 (45.8%) patients had died. In the original population, PPI exposure was strongly associated with TTD (HR=1.45, 95% CI 1.24-1.69) and OS (HR=1.77, 95% CI 1.47-2.12). The impact of the concomitant use of PPIs and BRAF/MEK inhibitors was evaluated in the target population with an equal distribution of all baseline characteristics. PPI exposure was no more associated with TTD (wHR=1.03, 95% CI 0.86-1.24) or OS (wHR=1.11, 95% CI 0.88-1.39). Weighted log-rank tests were not significant either for TTD ($p=0.70$) or OS ($p=0.37$). These analyses measured the intention-to-treat effect of PPIs. Kaplan-Meier curves with a landmark time of 3 months are shown in Figure 2, panels A and B. Kaplan-Meier curves in the original and target populations were compared in the Figure S1.

Per-protocol analysis

Among the 908 and 961 patients included in the per-protocol analysis of TTD and OS respectively, 279 (30.7%) and 294 (30.6%) were exposed to PPIs. In the original population, HR for TTD was 1.43 (1.18-1.73), and HR for OS was 1.77 (1.41-2.23). In the target population, the concomitant use of PPIs was no more associated with TTD (wHR=1.03, 95% CI 0.82-1.30) or OS (wHR=1.15, 95% CI 0.87-1.51). Kaplan-Meier curves with a landmark time of 3 months are shown in Figure 2, panels C and D.

Sensitivity analyses

As BRAF inhibitor dabrafenib was given particular warning from the FDA and the ESMO, analyses were restricted to patients receiving dabrafenib alone or combined with trametinib as first-line treatment. Among the 571 and 604 patients included in the landmark analysis of TTD and OS respectively, 182 (31.9%) and 194 (32.1%) were exposed to PPIs. In the original population, HR for TTD was 1.47 (1.19-1.82), and HR for OS was 1.73 (1.33-2.25). In the target population, the concomitant use of PPIs was no more associated with TTD (wHR=1.18, 95% CI 0.91-1.54) or OS (wHR=1.10, 95% CI 0.79-1.53) (Figure 3).

Exposure was then restricted to omeprazole and esomeprazole, which carry a greater drug-drug interaction potential due to stronger inhibition of CYP3A4. Among the 868 and 920 patients included in the landmark analysis of TTD and OS respectively, 239 (27.5%) and 253 (27.5%) were exposed to PPIs. In the original population, HR for TTD was 1.47 (1.24-1.75), and HR for OS was 1.94 (1.59-2.37). In the target population, the concomitant use of PPIs was no more associated with TTD (wHR=1.02, 95% CI 0.83-1.26) or OS (wHR=1.11, 95% CI 0.87-1.42) (Figure 3).

Discussion

In this population-based study including 1028 patients receiving targeted therapy with protein kinase inhibitors for metastatic melanoma, the concomitant use of PPIs in 361 patients was not associated with a decreased efficacy of BRAF/MEK inhibitors, as measured with TTD and OS. The association observed in crude analysis in the original population disappeared in the target population obtained by overlap weighting based on the propensity score. Patients using PPIs had more metastases and more comorbidities. Taking into account these confounders allowed the association to be ruled out.

Few pharmacokinetic studies have investigated the effect of the simultaneous use of PPIs and BRAF inhibitors in melanoma. Regarding vemurafenib, mixed results were obtained regarding progression among patients who simultaneously used PPIs.²⁰ However, a retrospective analysis of pooled data from randomized controlled trials on vemurafenib showed unchanged steady-state concentrations of vemurafenib in patients with PPIs, and no significant association between PPI use and survival or disease progression.¹⁹ Regarding dabrafenib, the co-administration of rabeprazole resulted in a 12% decrease in dabrafenib C_{max} . A pharmacokinetics/pharmacodynamics study found a non-significant reduction in the objective function value in patients concomitantly taking dabrafenib and PPIs.²¹ The FDA stated that the effect on dabrafenib efficacy was unknown. However, we did not observe a higher risk of dabrafenib discontinuation or death with the simultaneous use of PPIs. Regarding encorafenib, which was authorized in 2018 (*i.e.* after our study period), a drug interaction study on healthy subjects indicated that encorafenib concentrations were not altered in the presence of PPI rabeprazole. Furthermore, vemurafenib, cobimetinib and dabrafenib are substrates of CYP3A4, and therefore, concomitant administration of moderate and strong CYP3A4 inhibitors or inducers may alter concentrations of BRAF/MEK inhibitors. Omeprazole and esomeprazole are stronger inhibitors of CYP3A4 than other PPIs. However, no shorter time-to-treatment discontinuation or survival was observed when these PPIs were co-administered with BRAF and MEK inhibitors.

Our study has limitations. First, the timing and dosage of PPIs and BRAF/MEK inhibitors were unknown factors. Second, systemic exposure to BRAF/MEK inhibitors was not measured. Third, residual confounding remained. Prognostic factors such as lactate dehydrogenase levels or performance status were lacking in our database. In addition, underestimation of the number of metastatic sites may have occurred for patients with few or

no hospitalization. Fourth, participation in a clinical trial could not be identified in our database, because clinical trials entail no billing to the National Health Insurance. Five, reason for treatment discontinuation was not reported. However, discontinuation of BRAF/MEK inhibitors is mainly due to progression. Discontinuation in case of prolonged response is not recommended because of the risk of resistance induction, and discontinuation for toxicity is reported to occur in 7-17% of patients.^{40,41}

Our study has several strengths. First, we adequately controlled for the indication bias in the target population. Because we identified a large number of comorbidities and metastatic locations in our database, which combines diagnosis-based and medication-based information with considerable historical depth, we were able to minimize the sources of confounding. The overlap weighting method based on the propensity score has been reported to show remarkable performance to avoid confounding (minimum variance of the estimator, exact balance of baseline characteristics between exposed and nonexposed groups). Overlap weighting emphasizes patients at clinical equipoise, *i.e.* with the highest uncertainty regarding drug prescription given their baseline characteristics.³⁹ The significant association observed in the original population disappeared in the target population, suggesting that confounding by indication was handled adequately. Indication bias could have been involved in previous retrospective studies suggesting shorter survival in patients exposed to PPIs. Second, the exhaustiveness of the database, with no loss to follow-up, prevented selection and attrition biases. Third, we used the landmark method to estimate the effect of PPI exposure in an unbiased way. An immortal-time bias would have occurred if the follow-up had started at initiation of BRAF/MEK inhibitors, because the time frame used to determine PPI exposure lasted 3 additional months. Thus, patients who died during these 3 months had a higher probability of being classified as nonexposed to PPIs, and should be excluded.⁴² Fourth, we

emulated a target trial by estimating analogs of both intention-to-treat and per-protocol effects.⁴³ The intention-to-treat effect corresponds to the effect of being assigned to the PPI-exposed group at baseline, regardless of whether the individuals continue following the initial strategy after baseline, and the per-protocol effect corresponds to the effect of concomitant PPI use when the strategy is sustained throughout follow-up. The per-protocol analysis avoids issues arising from exposure-misclassified person-time if the data ceased to be consistent with the initial treatment strategy, but can lead to informative censoring. For example, if PPI initiation occurred in a context of symptomatic worsening of the metastatic disease, or if PPI discontinuation occurred in a context of palliative care or rather of clinical improvement, censoring could affect the treatment effect estimate. Therefore, adjustment for baseline and postbaseline confounders is generally required for the estimation of the per protocol effect.^{44,45} It was not possible in our study to control for postbaseline confounders, as this clinical information was not dated in our database sufficiently precisely. However, in our study, both intention-to-treat and per-protocol effects were similar, which ensured that informative censoring did not bias the per-protocol effect. The intention-to-treat and the per-protocol effects represent different extremes so that, if they lead to the same results, the strength of the conclusion is reinforced. Therefore, we are confident in our study results.

The concomitant use of PPIs and BRAF/MEK inhibitors seemed to be safe in patients with melanoma. Because co-administration is frequent (more than 30% of patients), but is contra-indicated, unveiling a potential risk was crucial. Our results are reassuring for patients and prescribers. When PPIs are needed, our results suggest that concomitant use will not compromise the efficacy of BRAF/MEK inhibitors. Our study highlighted the potential role of indication bias in real-world studies and the importance of measuring a high number of confounders and using the appropriate methodology to control for this bias.

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Tables

Table 1. Characteristics of the original population and the target population according to concomitant PPI exposure

Characteristics, n (%)		Original population		Target population ^a	
		Concomitant use of PPIs ^{bc} N=361	No use of PPIs N=667	Concomitant use of PPIs ^{bc}	No use of PPIs
Treatment	Dabrafenib	110 (30.5)	240 (36.0)	31.0	31.0
	Dabrafenib + trametinib	84 (23.3)	170 (25.5)	24.1	24.1
	Vemurafenib	64 (17.7)	101 (15.1)	17.6	17.6
	Vemurafenib + cobimetinib	103 (28.5)	156 (23.4)	27.3	27.3
Age, years	Mean (sd)	62 (14)	59 (15)	61.5	61.5
Sex	Man	208 (57.6)	397 (59.5)	55.0	55.0
	Woman	153 (42.4)	270 (40.5)	45.0	45.0
Location of metastatic sites ^d					
	Brain	145 (40.2)	98 (14.7)	26.6	26.6
	Lung	171 (47.4)	161 (24.1)	38.8	38.8
	Bone	93 (25.8)	83 (12.4)	18.3	18.3
	Liver	111 (30.5)	115 (17.2)	25.2	25.2
	Digestive system	64 (17.7)	70 (10.8)	15.4	15.4
	Lymph node	185 (51.2)	314 (47.1)	51.6	51.6
	Skin	74 (20.5)	125 (18.7)	19.5	19.5
	Mediastinum	14 (3.9)	10 (1.5)	3.9	3.9
	Urinary tract	36 (10.0)	33 (4.9)	8.2	8.2
	Others	54 (15.0)	70 (10.5)	13.2	13.2
Number of metastatic sites ^d	Mean (sd)	2.6 (1.9)	1.6 (1.6)	2.2	2.2
Previous therapies ^e					
	External beam radiotherapy	33 (9.1)	20 (3.0)	5.2	5.2
	Stereotactic radiotherapy	28 (7.8)	12 (1.8)	3.9	3.9
	Lymphadenectomy	113 (31.3)	260 (39.0)	34.6	34.6
	Surgical resection of distant metastases	52 (14.4)	31 (4.6)	7.3	7.3
Global multimorbidity ^c					
	Duration of hospital stays (days), mean (sd)	18 (18)	8 (12)	12.6	12.6
	Total number of drug boxes dispensed (any drug), mean (sd)	83 (51)	41 (32)	63.7	63.7
Corticosteroid use ^c		57 (15.8)	21 (3.1)	6.6	6.6
Comorbidities ^f					
Cardiovascular and cerebrovascular disease					
	Recent acute ischemic heart disease ^e	6 (1.7)	3 (0.4)	1.0	1.0

Chronic ischemic heart disease	30 (8.3)	24 (3.6)	6.2	6.2
Recent acute ischemic cerebrovascular disease ^e	4 (1.1)	2 (0.3)	0.7	0.7
Recent haemorrhagic stroke ^e	20 (5.5)	5 (0.7)	2.5	2.5
Sequelae or history of cerebrovascular disease	12 (3.3)	9 (1.3)	2.0	2.0
Recent acute heart failure ^e	8 (2.2)	4 (0.6)	1.2	1.2
Chronic heart failure	10 (2.8)	16 (2.4)	2.4	2.4
Cardiac arrhythmia	37 (10.2)	32 (4.8)	6.6	6.6
Cardiac valve disease	13 (3.6)	15 (2.2)	2.6	2.6
Peripheral vascular disease	18 (5.0)	24 (3.6)	4.9	4.9
Respiratory disease				
Chronic respiratory disease (including asthma and chronic obstructive pulmonary disease)	57 (15.8)	46 (6.9)	11.3	11.3
Metabolic disease				
Diabetes	49 (13.6)	64 (9.6)	13.9	13.9
Liver disease				
Mild or moderate liver disease	1 (0.3)	5 (0.7)	0.3	0.3
Severe liver disease	2 (0.6)	4 (0.6)	0.4	0.4
Renal disease				
Chronic renal disease	24 (6.6)	15 (2.2)	3.6	3.6
Inflammatory and systemic disease				
Inflammatory bowel disease	3 (0.8)	1 (0.1)	0.4	0.4
Inflammatory rheumatic disorder or psoriasis requiring immunosuppressive or immunomodulating agents	1 (0.3)	6 (0.9)	0.2	0.2
Connective tissue disease requiring immunosuppressive or immunomodulating agents	2 (0.6)	2 (0.3)	0.4	0.4
Cancer				
Second cancer (other than melanoma)	69 (19.1)	48 (7.2)	12.8	12.8
Neurological disease				
Parkinson's disease and extrapyramidal syndromes	4 (1.1)	8 (1.2)	1.0	1.0
Paralysis	35 (9.7)	18 (2.7)	5.6	5.6
Neuromuscular disease	4 (1.1)	5 (0.7)	1.0	1.0
Epilepsy	27 (7.5)	16 (2.4)	4.7	4.7
Dementia	5 (1.4)	2 (0.3)	0.5	0.5
Mental deficiency	1 (0.3)	2 (0.3)	0.1	0.1
Psychiatric disease				

Hospitalization in a psychiatric hospital	4 (1.1)	12 (1.8)	1.0	1.0
Depression and mood disorders	78 (21.6)	74 (11.1)	16.2	16.2
Schizophrenia and delusional disorders	10 (2.8)	19 (2.8)	2.2	2.2
Alcohol abuse	14 (3.9)	29 (4.3)	4.6	4.6
Substance abuse	2 (0.6)	3 (0.4)	0.7	0.7

^a Target population is obtained using overlap weighting based on the propensity score. Weighted individuals are fictive, and therefore not countable.

^b At least 2 dispensations of PPIs

^c Between 1 month before and 3 months after initiation of BRAF/MEK inhibitors

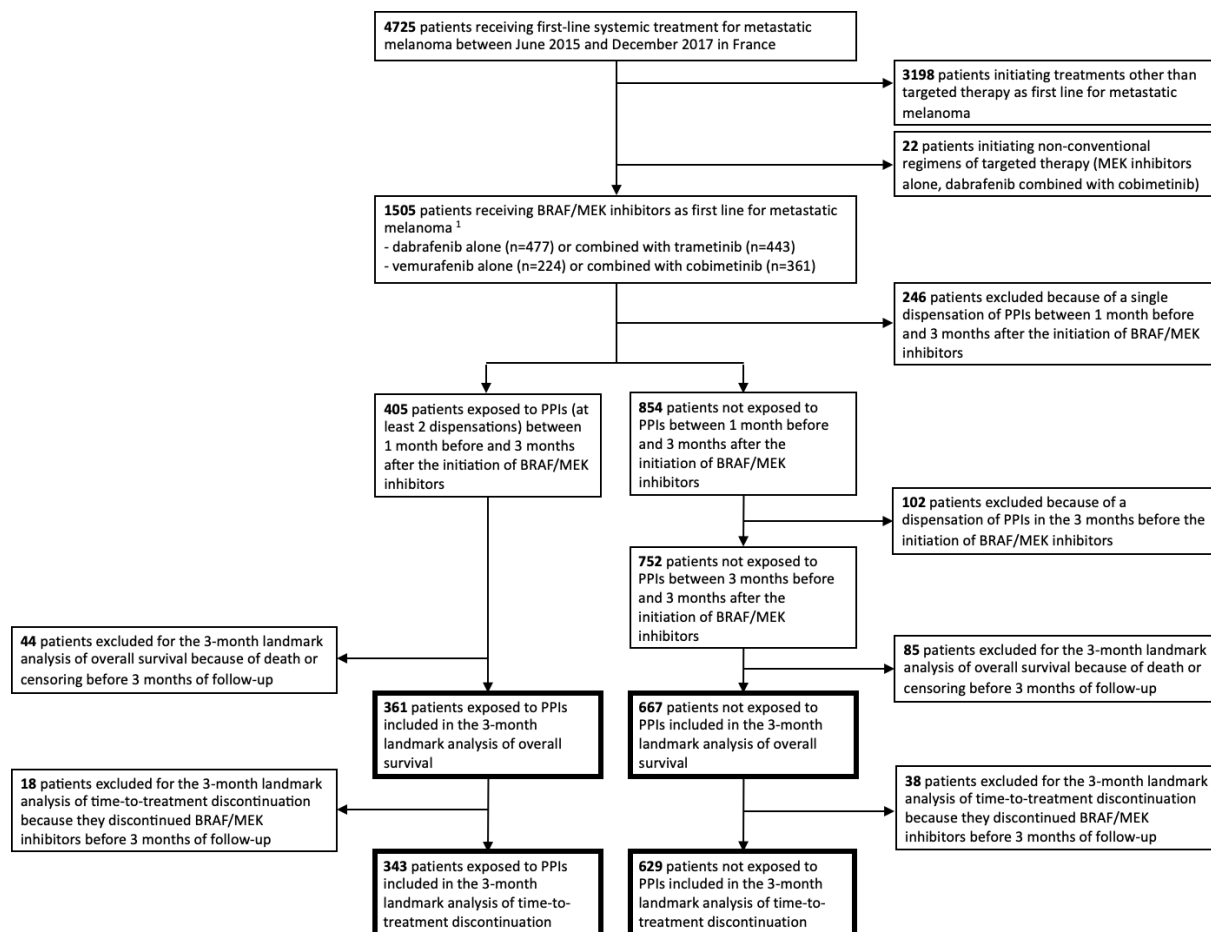
^d Identified from the hospitalization discharge codes between 3 months before and 3 months after initiation of first-line treatment

^e In the 12 months before initiation of the first-line treatment

^f Identified from the hospitalization discharge codes and drug dispensations in the 4 years before initiation of the first-line treatment

Figure legends

Figure 1. Study flowchart



PPI: Proton Pump Inhibitors

¹ BRAF/MEK inhibitors encorafenib and binimetinib were not available at the study period.

Figure 2. Kaplan Meier curves according to concomitant PPI exposure in the target population of patients receiving BRAF/MEK inhibitors as first-line treatment for metastatic melanoma.

The intention-to-treat effect of PPIs is represented in panels A and B, the per-protocol effect of PPIs is represented in panels C and D. Overall survival is shown in panels A and C, time-to-treatment discontinuation in panels B and D. Weighted log-rank tests are provided. The numbers of at-risk individuals are fictive as they correspond to weighted individuals.

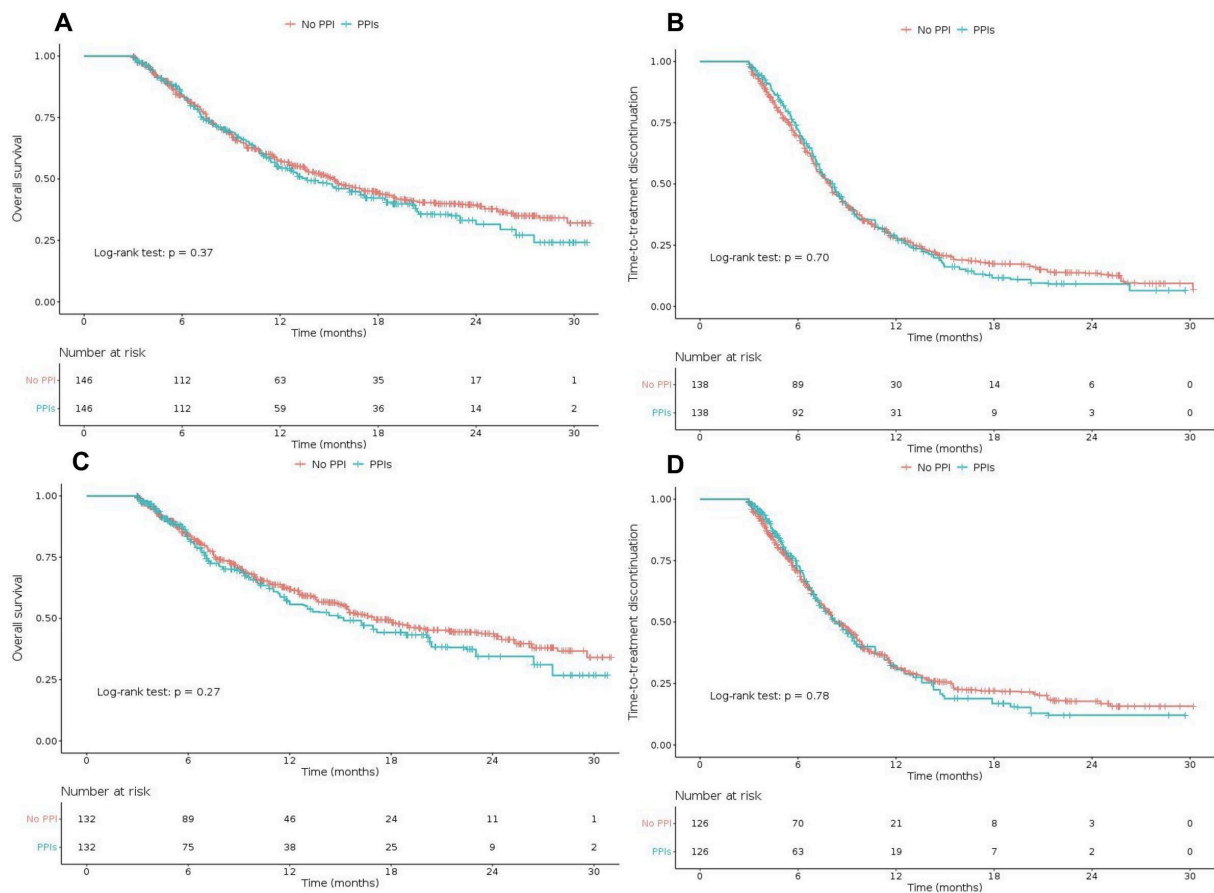
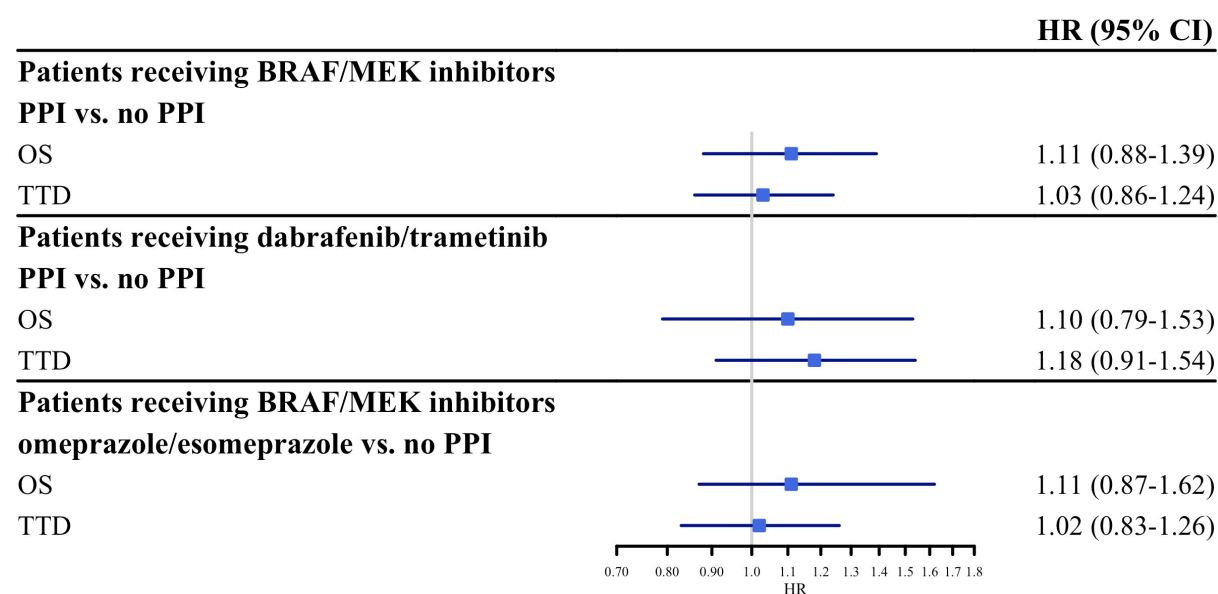


Figure 3. Forest plot summarizing the analyses performed in the target populations of patients receiving BRAF/MEK inhibitors as first-line treatment for metastatic melanoma.

The effect of concomitant use of PPIs in patients receiving BRAF/MEK inhibitors on OS and TTD was analysed. The target population was then restricted to patients receiving dabrafenib alone or combined with trametinib. Exposure was then restricted to omeprazole and esomeprazole, which carry a higher potential for drug-drug interactions due to stronger inhibition of CYP3A4.



CI: confidence interval; HR: hazard ratio; OS: overall survival; PPI: proton pump inhibitor TTD: time-to-treatment discontinuation.