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Louis Gaucher

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Influence des médicaments induisant une dysbiose intestinale et des corticostéroïdes sur la survie globale et la réponse tumorale des patients traités par inhibiteurs de points de contrôle immunitaire

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Liste des abréviations

AINS	anti-inflammatoire non stéroïdien
ATB	antibiotique
AP-1	protéine activatrice 1
AVK	anti-vitamine K
CBNPC	cancer bronchique non à petites cellules
CCR	carcinome à cellules rénales
CHU	centre hospitalo-universitaire
CMH	Complexe majeur d'histocompatibilité
CPA	cellule présentatrice d'antigène
CS	corticostéroïdes
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CU	carcinome urothélial
OMS	Eastern Cooperative Oncology Group
ERK	extracellular signal-regulated kinase
HR	hazard ratio
IC	intervalle de confiance
ICOS	inductible COstimulation receptor
IFN γ	interféron gamma
Ig	immunoglobuline
IL	interleukine
IMC	indice de masse corporelle
IPCI	inhibiteurs de points de contrôle immunitaire
IPP	inhibiteur de la Pompe à Protons
irAEs	immune-related Adverse Events
IRF	interferon regulatory factor
IV	intraveineuse
JNK	C-Jun NH ₂ - terminal kinase
LDH	lactate déshydrogénase
MS	maladie stable
NFAT	facteur nucléaire des lymphocytes T activés
NF-kappaB	nuclear factor-kappa B
NK	natural killer

OMS	organisation mondiale de la santé
OR	odds ratio
PM	progression de la maladie
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
RC	réponse complète
RP	réponse partielle
RCP	résumé des caractéristiques du produit
SG	survie globale
STAT	signal transducer and activator of transcription
SRIS	syndrome de réponse inflammatoire systémique
TCR	T cell receptor
TLR	Toll-like receptor
TMB	tumor mutational burden
TNF α	tumor necrosis factor α

I. INTRODUCTION

A. Historique de l'immunothérapie

L'immunothérapie est définie comme une méthode de traitement destinée à traiter une pathologie par une intervention sur le système immunitaire. Elle est dite « active » quand elle stimule les réponses de l'appareil immunitaire, soit de manière spécifique (vaccination par une bactérie inactivée, vivante ou atténuée, ou par un antigène microbien purifié), soit de manière non spécifique (adjuvant, cytokine immunostimulante telle l'interleukine-2). Elle est dite « passive » lorsqu'elle apporte au receveur des composants de la réponse immunitaire provenant d'individus immunisés (anticorps dans la sérothérapie, traitement par immunoglobulines, cellules lymphoïdes T dans l'immunité « adaptive ») [1].

Les débuts de l'immunothérapie dateraient de l'Égypte Antique. Nombre de rapports médicaux de cette époque décrivent des régressions tumorales consécutives à des épisodes infectieux sans émettre un lien rationnel entre infection et activation du système immunitaire, avec notamment le papyrus d'Edwin Smith daté du XVII^{ème} siècle avant Jésus Christ, qui reste à ce jour l'un des plus anciens traités médicaux [2]. Les tentatives de traitement du cancer par une modulation du système immunitaire, plus tardives, trouvent leurs racines dans la seconde moitié du XIX^{ème} siècle [3].

Ainsi, en Allemagne, deux médecins, Wilhelm Fehleisen et Friedrich Busch, observent indépendamment l'un de l'autre, une régression des tumeurs chez des patients atteints d'érysipèle. En 1868, Fehleisen tente une administration volontaire de bactéries chez un patient cancéreux permettant la diminution de la taille de la tumeur [4]. En 1892, Busch inocule à un patient une souche de *Streptococcus pyogenes* aboutissant au même résultat [5]. En 1893, aux États-Unis, le chirurgien orthopédiste William Bradley Coley se met en tête de trouver un traitement efficace contre les tumeurs à la suite du décès d'une de ses patientes une dizaine de semaines après une amputation pour un sarcome de la main. Après avoir retrouvé dans les archives du *New York Cancer Hospital* la description de régression de sarcomes après un épisode d'érysipèle à *Streptococcus pyogenes*, il procède à l'administration intra-tumorale de souches bactériennes vivantes de *Streptococcus pyogenes*. En dépit de résultats prometteurs, de nombreux patients meurent des suites d'une infection systémique. Coley décide alors d'utiliser un mélange de deux souches bactériennes préalablement

inactivées par la chaleur, *Streptococcus pyogenes* et *Serratia marcescens*. Ce mélange, désigné par la suite sous le terme de « toxines de Coley », commercialisé dès 1899, permet la régression de tumeurs chez près d'un millier de patients. Malgré ce succès, l'absence de mécanisme d'action connu pour les « toxines de Coley » et l'importance du risque d'infection par des bactéries hautement pathogènes chez des patients cancéreux, conduisent les oncologues à abandonner ce protocole, lui préférant la chirurgie et plus encore la radiothérapie au début du XXe siècle [6].

En 1959, la théorie de la surveillance immunitaire, établie par Paul Erlich et décrite par Lewis Thomas et Franck Macfarlane Burnet, permet une avancée dans la compréhension de l'immunité des cancers, le principe étant que le système immunitaire est capable de détecter les cellules tumorales et de les éliminer. Si cette théorie explique la transformation de cellules saines en cellules tumorales sous l'effet de modifications génétiques somatiques, elle n'explique pas l'apparition des tumeurs [7]. C'est ainsi qu'au début des années 2000, elle est remplacée par la théorie des 3E, ou théorie de l'immunoédition en 3 phases : l'élimination qui permet la régulation des cellules tumorales par le système immunitaire, l'équilibre qui est à l'origine d'un contrôle de la croissance des cellules tumorales et l'échappement qui constitue le développement de moyens de détournement de la réponse immunitaire antitumorale par les cellules tumorales à l'origine de la cancérogénèse [8].

Au fil des années, l'immunothérapie continue à se développer : 1^{ère} greffe de moelle allogénique dans le cadre de leucémies et de lymphomes en 1957 [9], BCG-thérapie développée dans les années 1970 pour traiter des hémopathies malignes et certaines tumeurs solides [10], premier traitement par interleukine-2 pour stimuler la prolifération des lymphocytes cytotoxiques en 1985 dans les cancers avancés [11], premier traitement par transfert adoptif de lymphocytes infiltrant les tumeurs associé à l'interleukine-2 en 1988 dans le mélanome métastatique [12].

B. Mécanismes physiologiques de stimulation de la réponse immunitaire

Au début des années 2000, l'avènement des inhibiteurs de points de contrôle immunitaire (IPCI) qui ont un rôle déterminant dans le maintien de l'auto-immunité, ouvre une nouvelle ère dans les traitements des cancers. Lorsque la cellule présentatrice d'antigène (CPA)

présente au lymphocyte T un antigène tumoral *via* le complexe majeur d'histocompatibilité (CMH), un 1^{er} signal appelé « stimulation antigénique » est transduit par le récepteur du lymphocyte T (*T Cell Receptor*, TCR). Une fois intégré, ce 1^{er} signal est ensuite modulé par un ensemble de co-sigaux activateurs et inhibiteurs de l'activation lymphocytaire pour prévenir un emballement immunitaire. La communication du 2nd signal d'activation entre lymphocyte et la CPA, que l'on nomme signal de « co-stimulation », s'établit autour de trois familles : la superfamille des immunoglobulines, les récepteurs du Tumor Necrosis Factor α (TNF α) et les récepteurs aux cytokines.

1. La superfamille des immunoglobulines

La superfamille des immunoglobulines s'articule autour de quatre grandes voies : la voie CD28, l'antigène 4 cytotoxique (CTLA-4), B7-1 (ou CD80), B7-2 (ou CD86), la voie Program Death-1 (PD-1), Program Death-Ligand 1 (PD-L1), Program Death-Ligand 2 (PDL-2), la voie ICOS/ICOSL et la voie B7H3, B7H4, BTLA (**Figure 1**).

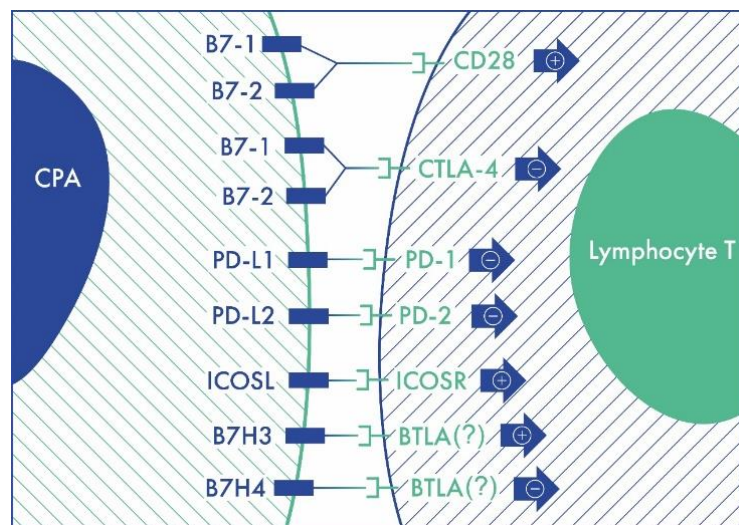


Figure 1: Mécanismes de co-stimulation des lymphocytes T par la superfamille des immunoglobulines. « + », stimulation ; « - », inhibition.

PD-1: program death-1; PD-2 : program death-2 ; PD-L1 : program death ligand 1 ; PD-L2 : program death ligand 2 ; ICOS : inductible costimulatory ; ICOSR : inductible costimulatory receptor.

Le lymphocyte exprime le CTLA-4 qui interagit principalement avec les mêmes ligands que CD28, c'est-à-dire B7-1 et B7-2. Dans ce cas, ce 2nd signal inhibe le lymphocyte T *via* une

diminution de l'expression de *Nuclear Factor of Activated T-cells* induisant une diminution de la transcription de l'IL-2 [13,14].

L'interaction du récepteur PD-1 avec ses ligands est également à l'origine d'une régulation négative de la prolifération et de la différenciation des lymphocytes B et T. Par exemple, la liaison de PD-L1 à PD-1 induit une ubiquitination du TCR (*via* l'ubiquitine ligase E3 CBL-b), réduisant ainsi son expression [15].

2. La famille des récepteurs du TNF α

La famille des récepteurs du TNF α s'articule autour de trois grandes voies : la voie CD40, la voie OX40L, la voie 4-1BB (**Figure 2**) [16–18]. Les réponses de ces voies tendent vers une stimulation lymphocytaire.

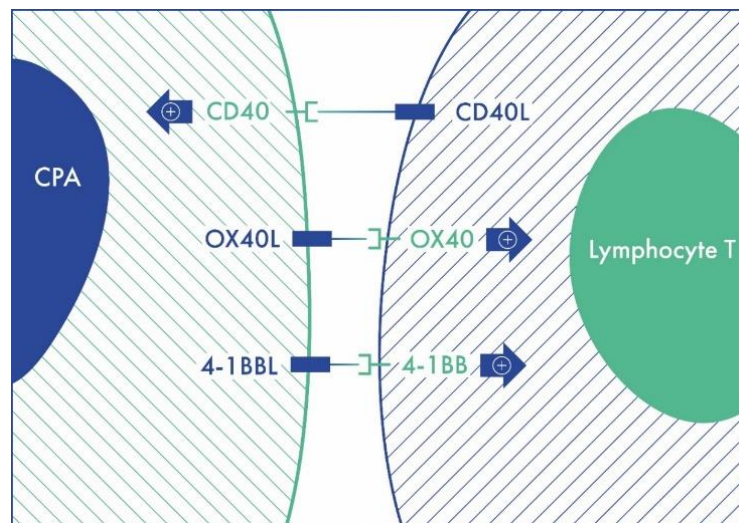


Figure 2: Mécanismes de co-stimulation des lymphocytes T par la famille des récepteurs du TNF α .

« + », stimulation.

3. La famille des récepteurs aux cytokines

La famille des récepteurs aux cytokines est essentiellement représentée par la voie impliquant le CD27 qui est une molécule constitutivement présente sur les lymphocytes T, et dont le

ligand CD27L est inducible par les CPA. Le couple CD27/CD27L, avec la voie du CD28, induit une stimulation lymphocytaire [19].

C. Intérêt des voies de co-stimulation dans la stratégie anti-tumorale

L'expression des protéines des points de contrôle immunitaire peut être dysrégulée par les tumeurs à l'origine d'un mécanisme de résistance immunitaire. Ainsi, les agonistes des récepteurs co-stimulants ou les antagonistes des signaux inhibiteurs des lymphocytes T, aboutissant à l'amplification des réponses lymphocytaires T spécifiques, sont les principaux agents des essais cliniques actuels dans les stratégies antitumorales. Deux récepteurs de points de contrôle immunitaire ont été plus activement étudiés : le CTLA-4 (ou CD156) et le PD-1 (ou CD279).

D. Stratégie médicamenteuse : les inhibiteurs des points de contrôle immunitaire

1. Les anti-CTLA4

En levant le frein de l'inhibition lymphocytaire, les anti-CTLA-4 activent de façon indirecte la réponse anti-tumorale en entraînant la prolifération des lymphocytes et leur infiltration des tumeurs, aboutissant à la mort des cellules tumorales (**Figure 3, Tableau 1**).

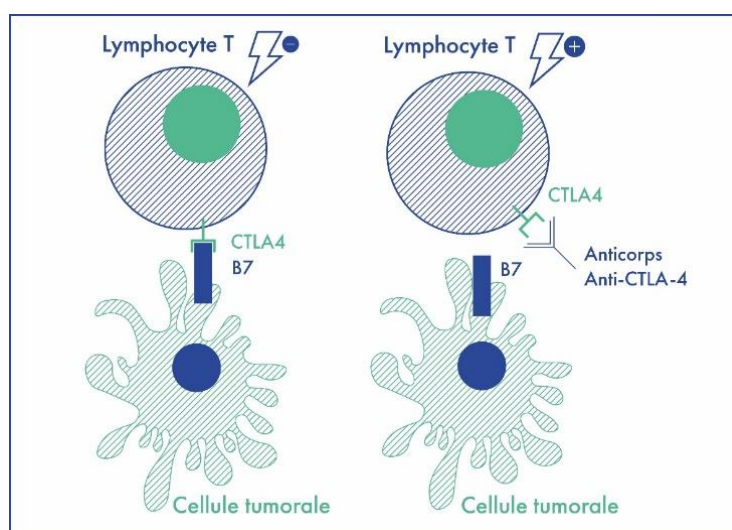


Tableau 1: Caractéristiques et AMM des anticorps monoclonaux humanisés anti-CTLA4.

Figure 3: Mécanisme d'action des anticorps anti-CTLA4.

	Type	AMM	Indications
<i>Ipilimumab</i>	IgG1	2011	<ul style="list-style-type: none"> • Mélanome avancé (âge > 12 ans) en monothérapie ou en association [20] • Cancer bronchique non à petites cellules (CBNPC) en association [20] • Carcinome à cellules rénales (CCR) en association [20]
<i>Tremelimumab</i>	IgG2	Non [21]	Pas d'autorisation de mise sur le marché

CBNPC, cancer bronchique non à petites cellules ; CCR, carcinome à cellules rénales ; CU, carcinome urothélial.

2. Les anti-PD-1 et anti-PD-L1

L'activation de la voie du PD-1 exerce un rétrocontrôle négatif des lymphocytes T dans les tissus périphériques et dans le microenvironnement tumoral. En effet, certaines cellules tumorales expriment le ligand PD-L1 entraînant une diminution de la réponse anti-tumorale des lymphocytes T. Ainsi, le blocage du récepteur ou de son ligand par les anti-PD-1 et les anti-PD-L1 permet de rendre les lymphocytes T de nouveau actifs contre les cellules tumorales (**Figure 4, Tableau 2**).

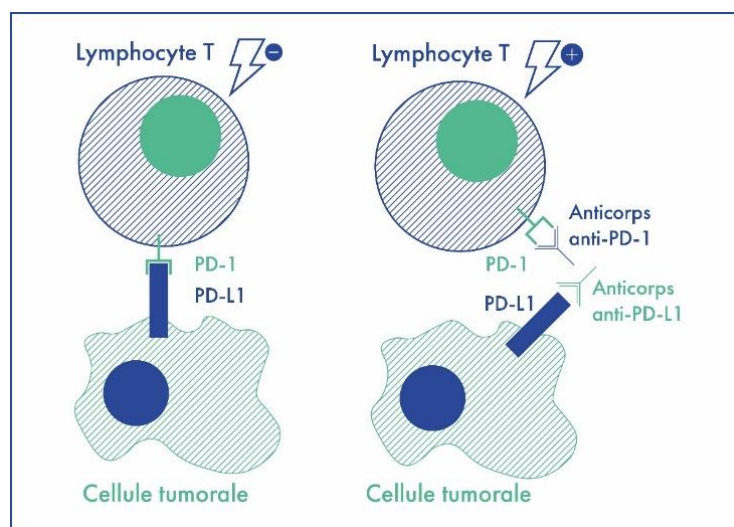


Figure 4: Mécanisme d'action des anticorps anti PD-1 et anti PD-L1.

Tableau 2: Caractéristiques et AMM des anticorps anti-PD-1 et anti-PD-L1.

	Type	AMM	Indications
<i>Nivolumab</i>	Ac anti-PD1 IgG4	2014 (Opdivo®)	<ul style="list-style-type: none"> • Mélanome avancé [22] • CBNPC avancé ou métastatique [22] • CCR avancé [22] • Carcinome urothélial (CU) localement avancé non résecable ou métastatique [22] • Lymphome de Hodgkin classique en rechute ou réfractaire [22] • Carcinome épidermoïde de la tête et du cou en progression [22]
<i>Pembrolizumab</i>	Ac anti-PD1 IgG4	2014 (Keytruda®)	<ul style="list-style-type: none"> • Mélanome avancé [23] • CBNPC métastatique [23] • Lymphome de Hodgkin classique en rechute ou réfractaire [23] • CU avancé ou métastatique [23] • Carcinome épidermoïde de la tête et du cou récidivant ou métastatique [23]
<i>Atezolizumab</i>	Ac monoclonal anti PD-L1 humanisé de type G1 à Fc modifié	2017 (Tecentriq®)	<ul style="list-style-type: none"> • CU localement avancé ou métastatique [24] • CBNPC [24] • Cancer bronchique à petites cellules [24]
<i>Durvalumab</i>	Ac monoclonal PD-L1 de type IgG1 kappa	2018 (Imfinzi®)	<ul style="list-style-type: none"> • CBNPC localement avancé non opérable sans progression après chimio-radiothérapie à base de platine [25] • Cancer bronchique à petites cellules en association avec étoposide et sels de platine en 1ère intention [25]

CBNPC, cancer bronchique non à petites cellules ; CCR, carcinome à cellules rénales ; CU, carcinome urothélial.

E. Mécanisme de résistance aux inhibiteurs de points de contrôle immunitaire

L'utilisation des IPCI chez les patients atteints de cancers cutanés, pulmonaires, rénaux, urothéliaux, ORL et hématologiques, a permis une réduction nette de la morbi-mortalité [26–28]. Cependant, l'échappement tumoral reste encore aujourd'hui un problème majeur dans la prise en charge de ces patients.

Selon les données de la littérature, entre 60% et 80% des patients sont non répondeurs aux IPCI [29]. Les facteurs d'échappement tumoral sous-jacents peuvent être divisés en trois catégories :

- la faible immunogénicité des cellules tumorales (perte des molécules du CMH-1) qui présentent de surcroît des modulations antigéniques et des résistances à la lyse [30,31],
- les facteurs intrinsèques, à savoir l'immunosuppression, l'épuisement des lymphocytes T, l'âge et des facteurs génétiques (HLA, polymorphisme du gène TLR4, mutations des gènes KRAS et BAF) [32],
- les facteurs exogènes, qui dans le cas de l'IPCI, incluent le régime alimentaire, l'exposition prolongée au soleil, les traitements médicamenteux concomitants à l'IPCI et le microbiote intestinal [32].

1. Le microbiote intestinal

a) Définitions et fonctions

Le microbiote intestinal constitue l'ensemble des micro-organismes résidant dans le tube digestif constitué de bactéries, virus, champignons et archées [33]. Il en résulte une interaction hôte-bactéries qui est à l'origine de fonctions métaboliques [34], neurologiques [35,36] et immunologiques, par la formation de peptides microbicides limitant le contact entre bactéries-épithélium et participant au recrutement des cellules de l'immunité innées et adaptatives [37].

b) Composition

Bien que chaque individu possède son propre microbiote il est possible de décrire un état physiologique nommé « normobiose » [38]. A l'inverse, un déséquilibre qualitatif ou quantitatif de l'écosystème bactérien constitue un phénomène de « dysbiose », à l'origine de phénomènes pathologiques (colopathie fonctionnelle, ulcère gastrique, colite à *Clostridium Difficile*, maladie de Crohn, diabète, cancers gastrointestinaux, obésité) [39]. Par ailleurs, il est établi que le microbiote intestinal évolue avec l'âge. Le microbiote intestinal du nouveau-né est essentiellement représenté par *Enterobacteriaceae* et *Staphylococcus* [40]. Dans l'enfance, il est d'abord dominé par *Bifidobacterium* [41], puis se stabilise pour être semblable à celui de l'âge adulte avec essentiellement *Bacteroides*, *Firmicutes* et *Prevotella* [42,43] et, dans une moindre mesure, *Proteobacteria* et *Actinobacteria* [44].

c) Facteurs influençant sa composition

Toutefois, il serait réducteur de juger l'évolution de la composition du microbiote intestinal qu'à travers le prisme de l'âge. Le mode de vie constitue un facteur déterminant dans la composition du microbiote intestinal : la consommation d'alcool [45], de tabac [46], l'activité physique [47], la consommation de médicaments [48,49] et le régime alimentaire [50,51] participent à sa modification.

Parmi les traitements médicamenteux, les antibiotiques apparaissent comme la classe la plus pourvoyeuse de modifications du microbiote. Leur impact sur la composition du microbiote intestinal dépend de plusieurs paramètres :

- Le type d'antibiotique : par exemple, la ceftriaxone et l'ofloxacine tendent respectivement à augmenter et à diminuer la proportion d'*Enterococcus* [52] ;
- La durée de la dysbiose après arrêt de l'antibiothérapie : par exemple, la spiramycine semble affecter le microbiote jusqu'à 28 jours après son arrêt, alors que la pipéracilline a un effet jusqu'à 14 jours [52] (**Tableau 3**).

Tableau 3 : Délai nécessaire à la restauration du microbiote intestinal en fonction des antibiotiques, selon les données de la littérature [52].

<i>Antibiotiques</i>	Délai nécessaire à la restauration du microbiote intestinal (en jours)
<i>Amoxicilline</i>	356
<i>Amoxicilline acide clavulanique</i>	60
<i>Pipéracilline-tazobactam, oracilline, cloxacilline</i>	10
<i>Céphalosporines</i>	40
<i>Macrolides</i>	28
<i>Vancomycine</i>	7
<i>Quinolones</i>	356
<i>Métronidazole</i>	60
<i>Doxycycline</i>	7
<i>Sulfaméthoxazole-triméthoprine</i>	14
<i>Linézolide</i>	28
<i>Aminosides</i>	30

Outre les antibiotiques, d'autres classes de médicaments peuvent induire une dysbiose [49] ; elles sont présentées dans le **Tableau 4**.

Tableau 4: Impact des médicaments (hors antibiotiques) sur le microbiote intestinal.

Médicament	Mécanisme d'action
<i>IPP</i>	Réduction acidité gastrique induisant un afflux de bactéries dans le tractus gastro-intestinal inférieur [53].
<i>Phloroglucinol</i>	Activité bactéricide [54].
<i>AVK</i>	Inconnu
<i>Antiarythmiques</i>	Inconnu
<i>AINS</i>	Perturbation de la vascularisation intestinale [55].
<i>Vitamine D</i>	Rôle protecteur dans l'homéostasie intestinale en assurant une concentration de peptides antimicrobiens et en renforçant les jonctions intercellulaires [56,57].
<i>Statines</i>	Emergence de bactéries capables de diminuer le taux de TNF- α et IL-12 tout en augmentant la concentration d'interleukines anti-inflammatoires comme l'IL10 [58,59].
<i>Metformine</i>	Inhibition du complexe bactérien I conduisant à l'inhibition de la chaîne de transport d'électrons [60].
<i>Opioides</i>	Inhibition de la motricité gastrique et activité bactéricide pour le tramadol [61,62].
<i>Lévothyroxine</i>	L'acide biliaire conjugué et la thyroxine conjuguée conditionnent de manière synergique la composition du microbiote, le déséquilibre de l'un des deux modifierait sa composition [63].
<i>Psychotropes</i>	Les perturbations métaboliques induites (syndrome métabolique, diabète) pourraient être à l'origine d'une altération de la composition du microbiote intestinal[64].

AINS, anti-inflammatoire non stéroïdien ; AVK, anti-vitamine K ; IPP, inhibiteur de la pompe à protons.

d) Lien entre microbiote intestinal et inhibiteurs de points de contrôle immunitaire

Plusieurs études ont mis en évidence un lien entre la dysbiose et l'efficacité des IPCI qui semble être liée à certaines populations bactériennes [65,66]. Ainsi, l'activité anti-CTLA-4 est directement liée à la présence de *Bacteroidetes* et *Proteobacteria* [52]. Une augmentation de la proportion de ces bactéries semble être associée à une plus grande efficacité de l'ipilimumab [67]. De la même façon, l'activité anti-PD-1 est modulée par la présence de *Bacteroidales* (du genre *Bacteroides*), du genre *Bifidobacterium*, du phylum *Actinobacteria*, *Akkermansia muciniphilia*, du phylum *Verrucomicrobia* et du phylum *Firmicutes* [52,65]. D'autres études ont mis en évidence une association entre l'activité anti-PD-L1 et *Bifidobacterium*, *Actinobacteria*, *Collinsella aerofaciens* et *Enterococcus faecium* [52]. Ainsi, les antibiotiques qui influencent la composition du microbiote intestinal peuvent influencer l'efficacité clinique des IPCI (**Tableau 5**).

Tableau 5: Effets des antibiotiques sur l'efficacité des IPCI via les modifications du microbiote intestinal selon les données de la littérature [52,65,67–74].

	Anti-CTLA 4	Anti-PD1	Anti-PDL1
PENICILLINES			
Amoxicilline	+/0	+	+/-
Amoxicilline acide clavulanique	+	+/-	+/-
Piperacilline	0	0	+
Ticarcilline	0	0	+
Tazocilline	NA	NA	NA
Cloxacilline	NA	NA	NA
Oracilline	NA	NA	NA
CEPHALOSPORINES			
Ceftaroline	-	-	-
Ceftriaxone	-	-	+/-
Cefixime	-	-	+/-
Cefuroxime	0	0	+
Ceftazidime	-	-	+/-
MACROLIDES			
Rovamycine	0	0	0
LIPOPEPTIDES			
Vancomycine	+	-	NA
QUINOLONES			
Ciprofloxacin	+/-/0	+/-/0	+/-/0
Ofloxacin	-/0	-	-
Norfloxacin	-/0	-	0
Levofloxacin	0	-	-
IMIDAZOLES			
Metronidazole	NA	NA	NA
CYCLINES			
Doxycycline	0	0	-
AUTRES			
Sulfaméthoxazole triméthoprime	NA	NA	NA

« + », potentialisation de l'activité de l'IPCI ; « - », réduction de l'activité de l'IPCI ; « 0 », sans effet ; NA, effet non connu.

2. Les traitements immunomodulateurs : les corticostéroïdes

a) Mécanisme d'action

Les corticostéroïdes qui sont des agonistes des récepteurs aux glucocorticostéroïdes et aux minéralocorticostéroïdes, sont impliqués dans de nombreux effets physiologiques : métabolisme glucidique [75], métabolisme protéique [76], métabolisme lipidique [77], métabolisme osseux [78], métabolisme hydrosodé [79], activité anti inflammatoire par inhibition des gènes pro inflammatoires (diminution de la synthèse de cytokines), induction de gènes anti-inflammatoires (synthèse de lipocortine responsable de la diminution de la formation de prostaglandines et des leucotriènes) [80,81], effets cutanés [82] et effet immunosuppresseur sur les lymphocytes T se caractérisant par [80] :

- inhibition de la production, de la prolifération et de la différenciation des lymphocytes,
- sélection thymique des populations lymphocytaires T,
- altération du signal induit par le TCR,
- inhibition de la transcription de cytokines pro-inflammatoires, notamment l'interleukine-2,
- inhibition de l'activité T-bet, facteur de transcription de la voie Th1,
- inhibition de l'activité GATA-3, facteur de transcription de la voie Th2.

b) Intérêt et place dans l'IPCI

Les corticostéroïdes peuvent être utilisés au cours d'un traitement par IPCI dans diverses indications : activité antioœdémateuse pour les syndromes de compression et métastases cérébrales [83], activités anti inflammatoire et antalgique pour les métastases osseuses [84], activité immunosuppressive dans le traitement des effets indésirables d'origine immunologique ou « *immune-related adverse events* » (irAEs) induits par les IPCI [85]. Compte-tenu de leur mécanisme d'action les corticostéroïdes pourraient réduire l'efficacité des IPCI, diminuant ainsi la survie globale (SG). Cependant, les données de la littérature divergent en fonction de l'indication de la corticothérapie. Ainsi, l'utilisation des corticostéroïdes pour un irAE ne semble pas être associée à une SG plus courte [86–88]. En revanche, leur utilisation pour une autre indication semble être associée à une diminution de la SG [89–91].

Par ailleurs, les corticostéroïdes inhalés et les dermocorticoïdes présentant un passage systémique n'ont été que très peu évalués quant à leur potentiel effet délétère sur l'efficacité des IPCI. : Une seule publication a étudié les effets des corticostéroïdes inhalés qui semblent être associés à un effet délétère sur l'efficacité des IPCI [92].

F. Objectifs

L'objectif principal est d'évaluer l'association entre l'exposition aux médicaments pouvant influencer l'efficacité des IPCI (ceux modifiant le microbiote intestinal et la corticothérapie par voie systématique, inhalée ou dermocorticoïdes) et la survie globale et la réponse tumorale chez les patients traités par IPCI.

L'objectif secondaire est d'établir un seuil de dose cumulée et un seuil de durée de corticothérapie systémique associés à une mauvaise réponse tumorale.

II. PATIENTS ET METHODES

A. Conception de l'étude

Il s'agit d'une étude rétrospective, observationnelle et monocentrique réalisée entre décembre 2010 et décembre 2019 au CHU Amiens-Picardie.

B. Critères d'éligibilité

1. Critères d'inclusion

- Patients adultes.
- Pris en charge dans les services d'oncologie, de dermatologie, de pneumologie, d'hématologie ou de gastro-entérologie du CHU Amiens-Picardie.
- Traités par anti-CTLA-4 (ipilimumab) et/ou anti-PD-1 (nivolumab ou pembrolizumab).

2. Critères de non-inclusion

Patients déjà inclus dans d'autres essais cliniques, ou recevant une chimiothérapie conventionnelle ou une thérapie ciblée concomitantes durant cette même période.

C. Critères de jugement

1. Evaluation de la survie globale

La survie globale (SG) a été calculée à partir de la date de début de l'IPI (en cas de lignes multiples d'IPI, seule la première ligne était prise en compte dans l'analyse) jusqu'à la date de décès (quelle qu'en soit la cause) ou la date des dernières nouvelles.

2. Evaluation de la réponse tumorale

Sur la base des données recueillies à partir des comptes-rendus de réunions de concertations pluridisciplinaires et des examens d'imagerie, la réponse tumorale a été définie comme une réponse complète (RC), une réponse partielle (RP), une maladie stable (MS) ou une progression de la maladie (PM) selon les critères d'évaluation de la réponse dans les tumeurs solides (RECIST) version 1.1 [93]. La meilleure réponse tumorale sous IPCI a été recueillie. Une RC ou une RP définissait une bonne réponse tumorale, contrairement à une MS ou une PM.

3. Dose cumulée et de durée de la corticothérapie systémique

La dose cumulée (équivalent prednisolone) et la durée de la corticothérapie systémique (voie orale ou intraveineuse) reçue entre le début de l'IPCI et la meilleure réponse tumorale ont été calculées.

D. Autres données recueillies

L'ensemble des données ont été recueillies à partir des dossiers médicaux informatisés.

- Caractéristiques démographiques : âge, sexe, indice de masse corporelle.
- Cancer : type, statut métastatique, nombre de sites métastatiques, score selon l'échelle de l'Organisation Mondiale de la Santé (OMS).
- Chimiothérapies : nombre de lignes et type de chimiothérapie antérieure à l'IPCI (chimiothérapie conventionnelle ou thérapie ciblée), nombre de lignes d'IPCI.
- Comorbidités : statut tabagique (« jamais » ou « actuel/passé »), consommation d'alcool (consommation journalière ou non, quelle que soit la quantité), événements cardiovasculaires (infarctus du myocarde, accident vasculaire cérébral, artériopathie oblitérante des membres inférieurs et/ou thrombose veineuse profonde), diabète (quels que soient le type et la gravité), hypertension artérielle, dyslipidémie, antécédents de cancer autre que celui étudié.
- Antibiotiques : voie d'administration, durée et indication. En cas d'infection, les données suivantes ont été recueillies :

- sévérité de l'infection classée en infection non systémique, syndrome de réponse inflammatoire systémique (SRIS), sepsis, sepsis sévère et choc septique,
 - nécessité d'une hospitalisation,
 - arrêt de l'IPCI.
- Autres médicaments induisant une dysbiose : AINS, antiarythmiques, AVK, IPP, lévothyroxine, metformine, opioïdes, phloroglucinol, statines, cholécalciférol et psychotropes.
 - Corticostéroïdes systémiques, inhalés et dermocorticoïdes. L'indication de la corticothérapie systémique (pour irAE ou autre indication) a également été documentée.

E. Définition des groupes

1. Patients exposés et non exposés aux antibiotiques

Lors de la constitution des groupes, la dysbiose induite par chaque ATB et le temps nécessaire pour la restauration du microbiote intestinal après l'arrêt de l'antibiothérapie ont été pris en compte.

Les patients étaient attribués au groupe exposé à une antibiothérapie (groupe ATB+) s'ils avaient reçu un ou plusieurs antibiotiques :

- avant l'initiation de l'IPCI : dans ce cas, les patients étaient attribués au groupe ATB+ si la durée entre la fin de l'antibiothérapie et l'initiation de l'IPCI était inférieure au délai nécessaire à la restauration du microbiote intestinal après arrêt de l'ATB, et ce pour chaque ATB (**Tableau 3**),

- ou dans les 60 jours après l'initiation de l'IPCI (indépendamment du type d'ATB).

2. Patients exposés et non exposés aux autres médicaments induisant une dysbiose

A ce jour, la littérature ne rapporte pas de données sur la restauration du microbiote intestinal après l'arrêt d'un traitement par IPP, AINS, statines, metformine, opioïdes, cholécalciférol, lévothyroxine, AVK, anti-arythmique, phloroglucinol et psychotropes. Pour cette raison,

lorsqu'un patient était déjà exposé à l'une de ces classes médicamenteuses au moment de l'initiation de l'IPCI ou dans les 60 jours suivants, il était affecté au groupe du médicament correspondant.

3. Patients exposés et non exposés aux corticostéroïdes

Les patients étaient affectés au groupe corticostéroïdes s'ils avaient reçu une corticothérapie par voie systémique (groupe CS+), par voie inhalée (groupe CS+ inhalés) ou des dermocorticoïdes (groupe CS+ dermocorticoïdes) dans les 60 jours suivant l'initiation de l'IPCI.

Concernant la corticothérapie systémique, 2 sous-groupes ont été constitués :

- CS+ irAE : patients exposés à une corticothérapie systémique en raison d'un irAE,
- CS- autre indication : patients exposés à une corticothérapie systémique en raison d'une autre indication.

F. Analyses statistiques

Les variables catégorielles ont été exprimées en nombres (pourcentages). Les variables continues ont été exprimées en termes de moyenne \pm écart-type (ET) ou de médiane [intervalle interquartile] en fonction de leur distribution. Les variables continues entre les groupes ont été comparées à l'aide du test t de Student ou de Wilcoxon (en fonction de la distribution des données). Les variables catégorielles ont été comparées à l'aide d'un test du χ^2 ou d'un test exact de Fisher. La méthode de Kaplan-Meier et un test log-rank ont permis d'apprécier la SG. En analyses multivariées, un modèle de Cox a été réalisé pour évaluer la SG et une régression logistique pour évaluer la réponse tumorale. Les variables avec une valeur $p < 0,2$ en analyse bivariée et les facteurs de risques les plus fréquemment décrits dans la littérature (c'est à dire l'âge, le sexe, l'indice de masse corporelle, le tabagisme actuel ou passé, la consommation d'alcool, les antécédents de maladie cardiovasculaire, la durée du cancer, et le score OMS) ont été inclus dans les modèles de Cox et de régression logistique.

Afin de minimiser le biais d'indication des ATB, plusieurs analyses de sensibilité ont été réalisées :

- SG après exclusion des patients décédés ou perdus de vue dans les 4 semaines suivant l'arrêt de l'ATB (dans l'hypothèse où l'infection est liée décès),
- SG chez les patients qui ont arrêté l'IPCI en raison d'une infection comparativement à ceux qui n'ont pas arrêté leur immunothérapie (dans l'hypothèse où l'arrêt temporaire de l'IPCI peut être associé à une perte d'efficacité),
- SG chez les patients hospitalisés en raison d'une infection comparativement à ceux non hospitalisés,
- SG chez les patients avec une infection non sévère comparativement à ceux avec une infection sévère

Concernant les patients traités par corticostéroïdes systémiques et présentant une mauvaise réponse tumorale (MS ou PM), une dose et une durée seuils ont été déterminées grâce à l'analyse d'une courbe *receiver operating characteristic* (ROC).

Tous les tests statistiques étaient bilatéraux et le seuil de significativité était fixé à $p < 0,05$. Toutes les analyses ont été effectuées à l'aide du logiciel R (version 3.6.0, *R Foundation for Statistical Computing*, Vienne, Autriche).

G. Ethique

Conformément à la législation française sur les analyses rétrospectives de pratique clinique de soins courants, les patients qui n'étaient pas tenus de donner leur consentement éclairé, pouvaient refuser, lors de leur admission à l'hôpital, l'utilisation de leurs données médicales à des fins de recherche.

Ce protocole a été approuvé par la Direction de la Recherche Clinique du CHU Amiens-Picardie et enregistré auprès de la CNIL (référence : PI2018_843_0062).

III. RESULTATS

Entre le 1^{er} décembre 2010 et le 31 décembre 2019, 374 patients ont initié un traitement par ipilimumab, nivolumab ou pembrolizumab, seul ou en association. Deux patients ont été exclus de l'étude en raison de données manquantes.

A. Caractéristiques de la population étudiée

L'âge moyen des patients était de $64,0 \pm 12,1$ ans. L'IPCI le plus prescrit était le nivolumab chez 217 patients (58,3%). Les cancers les plus fréquents étaient le cancer pulmonaire (44,2%) et le mélanome (29,6%). Les caractéristiques de la population étudiée sont détaillées dans le

Tableau 6.

Tableau 6 : Caractéristiques de la population étudiée et des groupes ATB- et ATB+.

	Population totale n = 372	Groupe ATB- n = 260	Groupe ATB+ n = 112	P
Âge (années), moyenne \pm EC	64,0 \pm 12,1	64,8 \pm 12,0	62,1 \pm 12,4	0,048
Sexe				
Homme, n (%)	244 (65,6)	162 (62,3)	82 (73,2)	0,055
Femme, n (%)	128 (34,4)	98 (37,7)	30 (26,8)	
Indice de masse corporelle (kg/m²), moyenne \pm EC	24,8 \pm 5,4	25,3 \pm 5,6	23,7 \pm 5,0	0,009
Tabagisme (actuel ou passé), n (%)	268 (72,0)	177 (68,1)	91 (81,2)	0,013
Consommation d'alcool, n (%)	125 (33,6)	73 (28,1)	52 (46,4)	<0,001
Antécédents cardiovasculaires, n (%)	103 (27,7)	71 (27,3)	32 (28,6)	0,902
Diabète, n (%)	51 (13,7)	38 (14,6)	13 (11,6)	0,542
Hypertension artérielle, n (%)	171 (46,0)	126 (48,5)	45 (40,2)	0,175
Dyslipidémie, n (%)	104 (28,0)	77 (29,6)	27 (24,1)	0,337
Antécédents de cancer, n (%)	67 (18,0)	42 (16,2)	25 (22,3)	0,203
Type de cancer				
Poumon, n (%)	166 (44,6)	104 (40,0)	62 (55,4)	0,009
Mélanome, n (%)	110 (29,6)	94 (36,2)	16 (14,3)	<0,001
Rénal et urothélial, n (%)	27 (7,3)	24 (9,2)	3 (2,7)	0,028
Tête et cou, n (%)	48 (12,9)	25 (9,6)	23 (20,5)	0,006
Lymphome hodgkinien, n (%)	5 (1,3)	1 (0,4)	4 (3,6)	0,030
Digestif, n (%)	4 (1,1)	3 (1,2)	1 (0,9)	1,000
Carcinome épidermoïde, n (%)	1 (0,3)	0	1 (0,9)	0,301
Adénocarcinome de primitif inconnu, n (%)	5 (1,3)	5 (1,9)	0	0,328
Carcinome de primitif inconnu, n (%)	5 (1,3)	4 (1,5)	1 (0,9)	1,000
Porocarcinome, n (%)	1 (0,3)	0	1 (0,9)	0,301
Cancer métastatique, n (%)	276 (74,2)	211 (81,2)	65 (58,0)	<0,001
Nombre de sites métastatiques, médiane [intervalle IQ]	1 [0 – 2]	1 [1 – 2]	1 [0 – 2]	<0,001

Métastase cérébrale, n (%)	29 (7,8)	21 (8,1)	8 (7,1)	0,922
Durée du cancer (mois), médiane [intervalle IQ]	13,7 [6,9 – 33,3]	16,0 [7,6 – 38,8]	10,2 [5,2 – 19,5]	0,001
Score OMS				
0-1, n (%)	295 (79,3)	208 (80,0)	87 (77,7)	0,676
2-4, n (%)	77 (20,7)	52 (20,0)	25 (22,3)	
Chimiothérapie conventionnelle antérieure, n (%)	219 (58,9)	139 (53,5)	80 (71,4)	0,002
Nombre de lignes, médiane [intervalle IQ]	1 [1 – 2]	1 [1 – 2]	1 [1 – 1]	0,289
Chimiothérapie ciblée antérieure, n (%)	66 (17,7)	53 (20,4)	13 (11,6)	0,059
Nombre de lignes, médiane [intervalle IQ]	1 [1 – 1]	1 [1 – 2]	1 [1 – 1]	0,135
IPCI				
Traitement de première ligne, n (%)	372 (100)	260 (100)	112 (100)	1,000
Nivolumab seul, n (%)	217 (58,3)	143 (55,0)	74 (66,1)	0,062
Pembrolizumab, n (%)	130 (34,9)	96 (36,9)	34 (30,4)	0,271
Ipilimumab seul, n (%)	15 (4,0)	14 (5,4)	1 (0,9)	0,046
Nivolumab + ipilimumab, n (%)	10 (2,7)	7 (2,7)	3 (2,7)	1,000
Traitement de deuxième ligne, n (%)	27 (7,3)	24 (9,2)	3 (2,7)	0,028
Nivolumab, n (%) / n'= 27	11 (40,8)	9 (37,5)	2 (66,7)	0,516
Pembrolizumab, n (%) / n'= 27	7 (25,9)	6 (25,0)	1 (33,3)	0,680
Ipilimumab, n (%) / n'= 27	9 (33,3)	9 (37,5)	0	0,062
Traitement de troisième ligne, n (%)	2 (0,5)	2 (0,8)	0	1,000
Nivolumab, n (%) / n'= 2	0	0	0	-
Pembrolizumab, n (%) / n'= 2	1 (50,0)	1 (50,0)	0	-
Ipilimumab, n (%) / n'= 2	1 (50,0)	1 (50,0)	0	-
Facteurs modifiant le microbiote intestinal				
Médicaments concomitants				
AINS, n (%)	23 (6,2)	18 (6,9)	5 (4,5)	0,504
IPP, n (%)	149 (40,1)	103 (39,6)	46 (41,1)	0,883
Statines, n (%)	83 (22,3)	58 (22,3)	25 (22,3)	1,000
Opioides, n (%)	173 (46,5)	119 (45,8)	54 (48,2)	0,749
Metformine, n (%)	17 (4,6)	16 (6,2)	1 (0,9)	0,050
AVKs, n (%)	16 (4,3)	13 (5,0)	3 (2,7)	0,463
Lévothyroxine, n (%)	40 (10,8)	36 (13,8)	4 (3,6)	0,006
Cholécalciférol, n (%)	59 (15,9)	47 (18,1)	12 (10,7)	0,103
Phloroglucinol, n (%)	19 (5,1)	13 (5,0)	6 (5,4)	1,000
Antiarythmique, n (%)	20 (5,4)	11 (4,2)	9 (8,0)	0,214
Corticostéroïdes (systémiques), n (%)	77 (20,7)	57 (21,9)	20 (17,9)	0,454
Utilisation de compléments alimentaires	58 (15,6)	27 (10,4)	31 (27,7)	<0,001

ATB, antibiotique ; AINS, anti-inflammatoire non stéroïdien ; AVK, anti-vitamine K ; EC, écart-type ; IPCI, inhibiteur des points de contrôle immunitaire ; IPP, inhibiteur de la pompe à protons ; IQ, interquartile ; OMS, organisation mondiale de la santé.

B. Analyse de la survie globale et de la réponse tumorale

1. Antibiotiques

a) Description de la population

Cent douze patients (30,1%) sur 374 étaient exposés aux antibiotiques administrés par voie intraveineuse chez 39 d'entre eux (34,8%) et *per os* chez les 73 restants (65,2%). Les pénicillines représentaient la classe d'antibiotique la plus prescrite en 1^{ère} intention (n=75, 70,0%). Il y avait 47 cas d'infections non systémiques (42,0%), 25 cas de SRIS (22,3%), 10 cas de sepsis (8,9%), 3 cas de sepsis sévère (2,7%) et 2 cas de choc septique (1,8%) La durée médiane de traitement était de 14,50 [7,75 – 30,50] jours (**Tableau 7**).

Tableau 7 : Description des infections et des antibiotiques.

	Groupe ATB+ n = 112
Indication de l'antibiothérapie	
Site d'infection	
Poumons, n (%)	46 (41,1)
Peau, n (%)	9 (8,0)
Tractus oropharyngé ou dentaire, n (%)	4 (3,6)
Voies urinaires, n (%)	7 (6,2)
Tube digestif, n (%)	3 (2,7)
Ostéite, n (%)	1 (0,9)
Septicémie, n (%)	18 (16,1)
Antibioprophylaxie, n (%)	4 (3,6)
Indication inconnue, n (%)	20 (17,9)
Gravité de l'infection	
Infection non systémique, n (%)	47 (42,0)
SIRS, n (%)	25 (22,3)
Sepsis, n (%)	10 (8,9)
Sepsis sévère, n (%)	3 (2,7)
Choc septique, n (%)	2 (1,8)
Hospitalisation due à une infection, n (%)	44 (39,3)
Soins intensifs, n (%)	3 (2,7)
ATB	
Voie d'administration	
Intraveineuse, n (%)	39 (34,8)
Orale, n (%)	73 (65,2)
Traitement de première ligne	
n'= 112	
Amoxicilline, n (%)	10 (8,9)
Amoxicilline + métronidazole, n (%)	1 (0,9)

Amoxicilline + clarithromycine + métronidazole, <i>n (%)</i>	1 (0,9)
Amoxicilline – acide clavulanique, <i>n (%)</i>	51 (45,5)
Amoxicilline – acide clavulanique + ciprofloxacine, <i>n (%)</i>	1 (0,9)
Amoxicilline – acide clavulanique + métronidazole, <i>n (%)</i>	1 (0,9)
Azithromycine, <i>n (%)</i>	1 (0,9)
Cefazoline, <i>n (%)</i>	1 (0,9)
Cefpodoxime, <i>n (%)</i>	1 (0,9)
Ceftazidime + ciprofloxacine, <i>n (%)</i>	1 (0,9)
Ceftriaxone, <i>n (%)</i>	4 (3,7)
Ceftriaxone + métronidazole, <i>n (%)</i>	3 (2,8)
Ceftriaxone + spiramycine, <i>n (%)</i>	1 (0,9)
Cefuroxime, <i>n (%)</i>	3 (2,8)
Ciprofloxacine, <i>n (%)</i>	1 (0,9)
Ciprofloxacine + clindamycine, <i>n (%)</i>	1 (0,9)
Ciprofloxacine + Pipéracilline – tazobactam, <i>n (%)</i>	1 (0,9)
Cotrimoxazole, <i>n (%)</i>	3 (2,8)
Daptomycine, <i>n (%)</i>	1 (0,9)
Daptomycine + céfépime, <i>n (%)</i>	1 (0,9)
Doxycycline, <i>n (%)</i>	5 (4,5)
Doxycycline + levofloxacine, <i>n (%)</i>	1 (0,9)
Imipénème – cilastatine + amikacine, <i>n (%)</i>	1 (0,9)
Levofloxacine, <i>n (%)</i>	2 (1,8)
Métronidazole, <i>n (%)</i>	1 (0,9)
Pipéracilline – tazobactam, <i>n (%)</i>	4 (3,7)
Pipéracilline – tazobactam + amikacine, <i>n (%)</i>	2 (1,8)
Pipéracilline – tazobactam + amikacine + spiramycine, <i>n (%)</i>	1 (0,9)
Pipéracilline – tazobactam + gentamicine + Daptomycine, <i>n (%)</i>	1 (0,9)
Pipéracilline – tazobactam + gentamicine + vancomycine, <i>n (%)</i>	1 (0,9)
Pristinamycine, <i>n (%)</i>	3 (2,8)
Roxithromycine, <i>n (%)</i>	1 (0,9)
Traitement de deuxième ligne	<i>n' = 36</i>
Amoxicilline, <i>n (%)</i>	2 (5,5)
Amoxicilline – acide clavulanique, <i>n (%)</i>	11 (30,5)
Amoxicilline – acide clavulanique + vancomycine, <i>n (%)</i>	1 (2,8)
Céfépime, <i>n (%)</i>	1 (2,8)
Céfixime, <i>n (%)</i>	1 (2,8)
Ceftazidime, <i>n (%)</i>	1 (2,8)
Ceftriaxone, <i>n (%)</i>	1 (2,8)
Ceftriaxone + métronidazole, <i>n (%)</i>	1 (2,8)
Ciprofloxacine, <i>n (%)</i>	3 (8,2)
Ciprofloxacine + métronidazole, <i>n (%)</i>	1 (2,8)
Cotrimoxazole, <i>n (%)</i>	1 (2,8)
Imipénème – cilastatine + amikacine, <i>n (%)</i>	1 (2,8)
Linézolide, <i>n (%)</i>	2 (5,5)
Linézolide + Amoxicilline, <i>n (%)</i>	1 (2,8)
Linézolide + imipénème - cilastatine	1 (2,8)
Métronidazole, <i>n (%)</i>	2 (5,5)
Pipéracilline – tazobactam, <i>n (%)</i>	1 (2,8)
Pipéracilline – tazobactam + ciprofloxacine, <i>n (%)</i>	1 (2,8)

Roxithromycine, <i>n</i> (%)	1 (2,8)
Telithromycine, <i>n</i> (%)	1 (2,8)
Vancomycine, <i>n</i> (%)	1 (2,8)
Traitement de troisième ligne	<i>n</i>'= 10
Amoxicilline – acide clavulanique, <i>n</i> (%)	1 (10,0)
Ceftozolane – tazobactam + céfépime, <i>n</i> (%)	1 (10,0)
Ceftriaxone, <i>n</i> (%)	1 (10,0)
Ceftriaxone + spiramycine, <i>n</i> (%)	1 (10,0)
Gentamicine, <i>n</i> (%)	1 (10,0)
Pipéracilline – tazobactam, <i>n</i> (%)	2 (20,0)
Pipéracilline – tazobactam + ciprofloxacine, <i>n</i> (%)	1 (10,0)
Roxithromycine, <i>n</i> (%)	1 (10,0)
Spiramycine	1 (10,0)
Traitement de quatrième ligne	<i>n</i>'= 1
Ceftriaxone + spiramycine, <i>n</i> (%)	1 (100)
Traitement de cinquième ligne	<i>n</i>'= 1
Amikacine + Ceftazidime, <i>n</i> (%)	1 (100)
Arrêt de l'IPCI en raison d'une infection, <i>n</i> (%)	24 (21,4)
Temps entre l'infection et le décès ou perdu de vue	<i>n</i>'= 81
< 4 semaines, <i>n</i> (%)	39 (48,1)
> 4 semaines, <i>n</i> (%)	42 (51,9)

ATB, antibiotiques ; IPCI, inhibiteur des points de contrôle immunitaire ; SRIS, syndrome de réponse inflammatoire systémique.

b) Survie globale

Quatre-vingt-un patients (72,3%) sont décédés dans le groupe ATB+ contre 146 (56,2%) dans le groupe ATB-. La durée médiane de la SG était significativement plus faible dans le groupe ATB+ (durée médiane de la SG [IC 95%] : 39,3 [30,9 – 54,1] vs. 96,9 [64,1 – 152,4] semaines ; hazard ratio (HR) brut [IC 95%] : 1,75 [1,33 – 2,30], $p < 0,001$; **Figure 5**). La durée de l'antibiothérapie n'influçait pas la SG (durée médiane de la SG [IC 95%] : 39,8 [30,9 – 71,1] semaines chez les patients avec une antibiothérapie < 14,5 jours vs. 39,3 [26,0 – 56,9] semaines chez les patients avec une antibiothérapie > 14,5 jours ; HR brut [IC 95%] : 0,99 [0,64 – 1,53], $p = 1,000$; **Figure 6**). Une administration intraveineuse d'antibiotiques était associée à une SG plus courte comparée à une administration *per os* (durée médiane de la SG [IC 95%] : 31,1 [21,7 – 53,6] vs. 42,7 [33,1 – 75,3] ; HR brut [IC 95%] : 1,59 [1,02 – 2,49], $p = 0,040$; **Figure 7**).

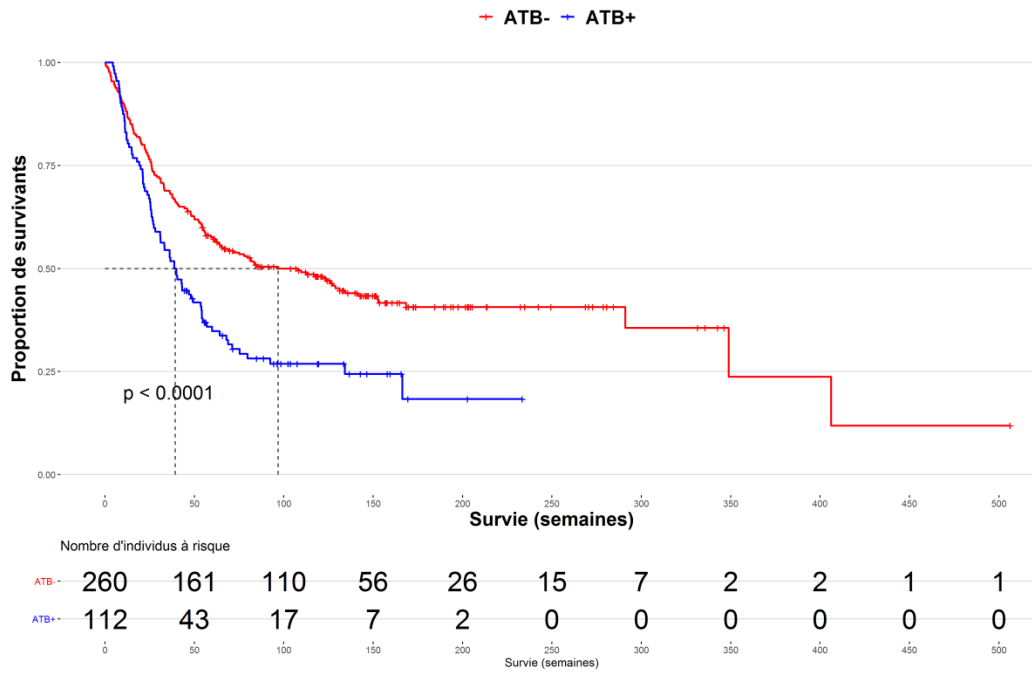


Figure 5 : Survie globale en fonction de l'utilisation d'antibiotiques.

ATB, antibiotiques.

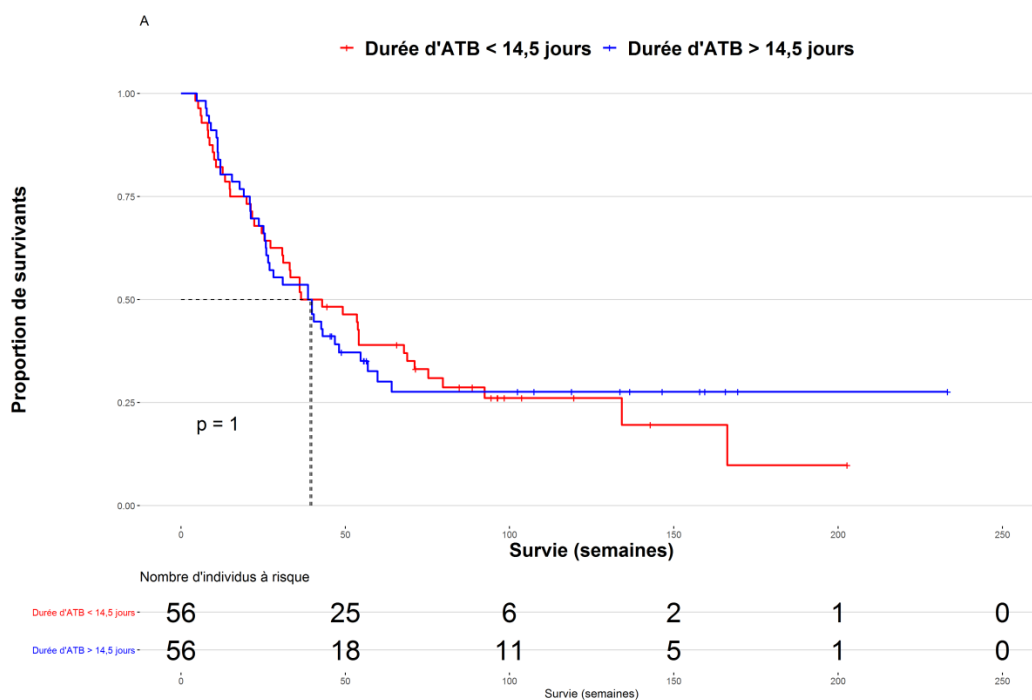


Figure 6 : Survie globale selon la durée de l'antibiothérapie.

ATB, antibiotiques.

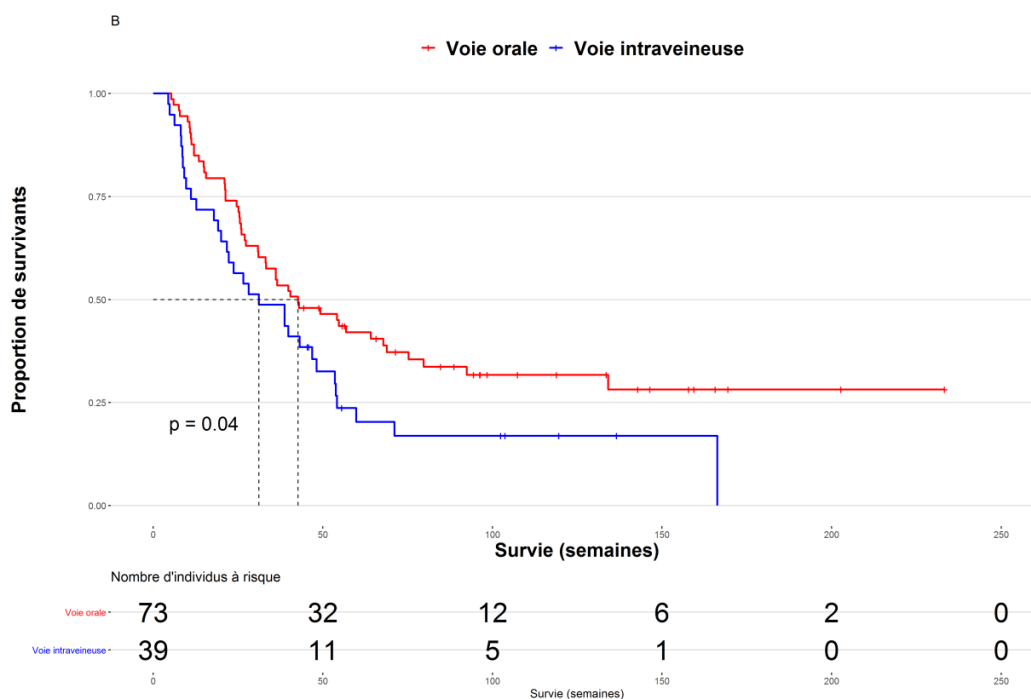


Figure 7: Survie globale selon la voie d'administration de l'antibiothérapie.

La SG était significativement plus courte dans le groupe ATB+ vs groupe ATB- (HR ajusté [IC 95%] : 1,38 [1,00 – 1,90], $p=0,048$) en analyse multivariée. Un score OMS élevé était associé à une SG plus courte (HR ajusté [IC 95%] : 2,73 [1,92 – 3,89], $p<0,001$; **Tableau 8**).

Tableau 8 : Analyses univariée et multivariée de la survie globale (modèle de Cox).

	N (%)	Modèle brut		Modèle ajusté	
		HR [IC 95%]	p	HR [IC 95%]	p
Âge	372 (100)	1,00 [0,99 - 1,01]	0,556	1,01 [0,99 - 1,02]	0,307
Indice de masse corporelle	372 (100)	0,95 [0,93 - 0,98]	<0,001	0,99 [0,95 - 1,02]	0,402
Sexe					
Homme	244 (65,6)	Référence		Référence	
Femme	128 (34,4)	0,80 [0,60 – 1,06]	0,100	0,80 [0,57 - 1,10]	0,172
Tabagisme					
Jamais	104 (28,0)	Référence		Référence	
Actuel ou passé	268 (72,0)	1,65 [1,22 – 2,26]	0,001	0,98 [0,65 - 1,49]	0,936
Consommation d'alcool					
Non	247 (66,4)	Référence		Référence	
Oui	125 (33,6)	1,57 [1,20 – 2,06]	<0,001	1,20 [0,85 - 1,70]	0,303
Antécédents de maladies cardiovasculaires					
Non	269 (72,3)	Référence		Référence	
Oui	103 (27,7)	1,10 [0,82 - 1,46]	0,500	0,85 [0,62 - 1,16]	0,299

Type de cancer						
Poumon	166 (44,6)	Référence		Référence		
Mélanome	110 (29,6)	0,45 [0,32 – 0,63]	< 0,001	1,14 [0,61 - 2,15]		0,677
Rénal et urothélial	27 (7,3)	0,76 [0,45 – 1,28]	0,306	0,89 [0,38 - 2,11]		0,789
Tête et cou	48 (12,9)	1,05 [0,70 – 1,57]	0,824	0,69 [0,43 - 1,12]		0,129
Lymphome hodgkinien	5 (1,3)	0,45 [0,11 – 1,81]	0,260	0,47 [0,11 - 2,07]		0,318
Digestif	4 (1,1)	6,08 [2,19 – 16,85]	<0,001	4,03 [1,22 - 13,37]		0,023
Carcinome cutané de cellules squameuses	1 (0,3)	3,27 [0,45 – 23,58]	0,240	5,70 [0,69 - 49,80]		0,105
Adénocarcinome de primaire inconnue	5 (1,3)	0,46 [0,11 – 1,86]	0,275	0,66 [0,16 - 2,79]		0,572
Carcinome de site primitif inconnu	5 (1,3)	0,86 [0,27 – 2,70]	0,794	0,34 [0,10 - 1,16]		0,084
Porocarcinome	1 (0,3)	2,11 [0,29 – 15,15]	0,459	2,80 [0,33 - 23,69]		0,343
Durée du cancer	372 (100)	1,00 [0,99 – 1,00]	0,081	1,00 [0,99 – 1,00]		0,337
Score OMS						
0-1	295 (79,3)	Référence		Référence		
2-4	77 (20,7)	2,90 [2,15 – 3,90]	< 0,001	2,73 [1,92 - 3,89]		<0,001
Cancer métastatique						
Non	96 (25,8)	Référence		Référence		
Oui	276 (74,2)	0,74 [0,55 – 0,98]	0,040	0,89 [0,62 - 1,28]		0,538
Métastase cérébrale						
Non	343 (92,2)	Référence		Référence		
Oui	29 (7,8)	1,13 [0,70 – 1,83]	0,600	1,25 [0,70 – 2,23]		0,453
Chimiothérapie conventionnelle antérieure						
Non	153 (41,1)	Référence		Référence		
Oui	219 (58,9)	1,72 [1,30 – 2,28]	<0,001	1,53 [0,95 - 2,46]		0,081
Chimiothérapie ciblée antérieure						
Non	306 (82,3)	Référence		Référence		
Oui	66 (17,7)	1,17 [0,83 – 1,63]	0,400	1,27 [0,78 - 2,07]		0,338
IPCI						
Nivolumab	217 (58,3)	Référence		Référence		
Pembrolizumab	130 (34,9)	0,58 [0,43 – 0,77]	<0,001	0,64 [0,44 - 0,94]		0,023
Ipilimumab (Ipilimumab)	15 (4,0)	0,36 [0,17 – 0,78]	0,009	0,46 [0,18 - 1,15]		0,096
Nivolumab + Ipilimumab	10 (2,7)	0,56 [0,21 – 1,50]	0,247	1,07 [0,36 – 3,24]		0,900
Utilisation d'ATB						
Non	260 (69,9)	Référence		Référence		
Oui	112 (30,1)	1,75 [1,33 – 2,30]	<0,001	1,38 [1,00 - 1,90]		0,048
Utilisation d'IPP						
Non	223 (59,9)	Référence		Référence		
Oui	149 (40,1)	0,84 [0,54 – 1,29]	0,150	0,80 [0,60 - 1,08]		0,148
Utilisation d'opioïdes						
Non	199 (53,5)	Référence		Référence		
Oui	173 (46,5)	1,82 [1,40 – 2,37]	<0,001	1,33 [0,99 - 1,79]		0,057
Utilisation de metformine						
Non	355 (95,4)	Référence		Référence		
Oui	17 (4,6)	0,77 [0,40 – 1,51]	0,500	0,75 [0,36 – 1,58]		0,455
Utilisation de lévothyroxine						
Non	332 (89,2)	Référence		Référence		
Oui	40 (10,8)	0,83 [0,54 – 1,29]	0,400	1,06 [0,65 – 1,72]		0,822
Utilisation de corticostéroïdes pour un irAE						
Non	351 (94,4)	Référence		Référence		

Oui	21 (5,6)	1,25 [0,53 – 1,71]	0,900	1,04 [0,56 - 1,95]	0,902
Utilisation de corticostéroïdes pour une autre indication					
Non	316 (84,9)	Référence		Référence	
Oui	56 (15,1)	1,35 [0,96 – 1,90]	0,087	1,34 [1,05 – 2,03]	0,046

ATB, antibiotiques ; AINS, anti Inflammatoires non stéroïdiens ; AVK, anti-vitamine K ; IPCI, inhibiteurs des points de contrôles immunitaires ; IPP, inhibiteur de la pompe à protons ; OMS, organisation mondiale de la santé.

c) Réponse tumorale

La proportion de répondeurs était significativement plus élevée dans le groupe ATB- (33,1% vs. 8,1%, $p=0,001$; **Figure 8**).

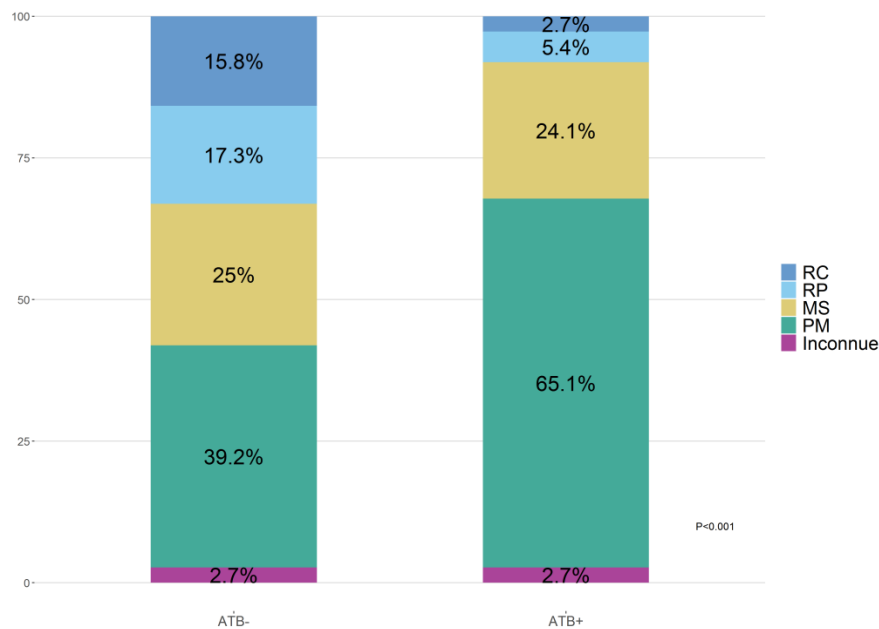


Figure 8: Réponse tumorale en fonction de l'utilisation d'antibiotiques.

ATB, antibiotiques ; MS, maladie stable, PM, progression de la maladie RC, réponse complète ; RP, réponse partielle.

Après ajustement sur les facteurs de confusion, la régression logistique confirmait ces résultats (OR ajusté [IC 95%] : 6,06 [2,80 – 14,53], $p < 0,001$). De plus, un score OMS élevé était associé à une mauvaise réponse tumorale (OR ajusté [IC 95%] : 2,71 [1,17 – 6,93], $p = 0,026$; **Tableau 9**).

Tableau 9 : Analyses univariée et multivariée (régression logistique) de la réponse tumorale (comparaison des non-répondeurs avec les répondeurs, selon les critères RECIST 1.1).

	N (%)	Modèle brut		Modèle ajusté	
		OR [IC 95%]	p	OR [IC 95%]	p
Âge	362 (100)	1,00 [0,99 - 1,02]	0,640	1,01 [0,99 - 1,04]	0,307
Indice de masse corporelle	362 (100)	0,94 [0,90 - 0,98]	0,003	1,00 [0,94 - 1,05]	0,867
Sexe					
Homme	237 (65,5)	Référence		Référence	
Femme	125 (34,5)	0,73 [0,45 - 1,18]	0,193	0,68 [0,36 - 1,30]	0,241
Tabagisme					
Jamais	101 (27,9)	Référence		Référence	
Actuel ou passé	261 (72,1)	1,78 [1,07 - 2,93]	0,025	0,75 [0,35 - 1,62]	0,471
Consommation d'alcool					
Non	239 (66,0)	Référence		Référence	
Oui	123 (34,0)	1,51 [0,91 - 2,57]	0,115	0,87 [0,42 - 1,78]	0,693
Antécédents de maladies cardiovasculaires					
Non	263 (72,7)	Référence		Référence	
Oui	99 (27,3)	1,45 [0,85 - 2,57]	0,183	1,08 [0,55 - 2,16]	0,824
Type de cancer					
Poumon	158 (543,6)	2,27 [1,39 - 3,80]	0,001	0,80 [0,19 - 2,73]	0,738
Mélanome	108 (29,3)	0,28 [0,17 - 0,46]	<0,001	0,77 [0,16 - 3,25]	0,730
Rénal et urothélial	27 (7,5)	1,61 [0,64 - 4,94]	0,347	2,10 [0,29 - 14,73]	0,457
Tête et cou	48 (13,3)	1,22 [0,62 - 2,63]	0,574	0,54 [0,10 - 2,40]	0,429
Durée du cancer	362 (100)	0,99 [0,99 - 1,00]	0,045	0,99 [0,99 - 1,00]	0,055
Score OMS					
0-1	288 (79,6)	Référence		Référence	
2-4	74 (20,4)	3,57 [1,73 - 8,35]	0,001	2,71 [1,17 - 6,93]	0,026
Cancer métastatique					
Non	95 (26,2)	Référence		Référence	
Oui	267 (73,8)	0,87 [0,50 - 1,47]	0,600	1,23 [0,59 - 2,56]	0,580
Métastase cérébrale					
Non	335 (92,5)	Référence		Référence	
Oui	27 (7,5)	1,27 [0,52 - 3,54]	0,622	1,86 [0,55 - 6,98]	0,334
Chimiothérapie conventionnelle antérieure					
Non	151 (41,7)	Référence		Référence	
Oui	211 (58,3)	2,60 [1,62 - 4,22]	<0,001	1,82 [0,76 - 4,35]	0,175
Chimiothérapie ciblée antérieure					
Non	296 (81,8)	Référence		Référence	
Oui	66 (18,2)	1,03 [0,57 - 1,94]	0,921	0,95 [0,39 - 2,40]	0,917
IPI					
Nivolumab	209 (57,7)	Référence		Référence	
Pembrolizumab	128 (35,4)	0,48 [0,29 - 0,80]	0,004	0,73 [0,34 - 1,56]	0,408
Ipilimumab	15 (4,1)	0,49 [0,16 - 1,64]	0,212	1,23 [0,28 - 5,69]	0,780
Nivolumab + Ipilimumab	10 (2,8)	0,16 [0,04 - 0,60]	0,007	0,24 [0,04 - 1,31]	0,107
Utilisation d'ATB					
Non	253 (69,9)	Référence		Référence	
Oui	109 (30,1)	5,72 [2,90 - 12,67]	<0,001	6,06 [2,80 - 14,53]	<0,001

Utilisation d'IPP					
Non	217 (59,4)	Référence		Référence	
Oui	145 (40,6)			1,57 [0,85 – 2,91]	0,150
Utilisation d'opioïdes					
Non	195 (53,9)	Référence		Référence	
Oui	167 (46,1)	2,60 [1,59 – 4,34]	<0,001	1,63 [0,88 - 3,06]	0,123
Utilisation de metformine					
Non	345 (95,3)	Référence		Référence	
Oui	17 (4,7)			0,51 [0,14 – 1,76]	0,283
Utilisation de lévothyroxine					
Non	323 (89,2)	Référence		Référence	
Oui	39 (10,8)	0,89 [0,44 - 1,95]	0,768	1,44 [0,58 - 3,71]	0,434
Utilisation de compléments alimentaires					
Non	304 (84,0)	Référence		Référence	
Oui	58 (16,0)	5,77 [2,28 - 19, 45]	0,001	3,40 [1,14 – 13,09]	0,045
Utilisation de corticostéroïdes pour un irAE					
Non	341 (94,2)	Référence		Référence	
Oui	21 (5,8)	0,88 [0,35 – 2,54]	0,803	1,69 [0,52 – 6,56]	0,413
Utilisation de corticostéroïdes pour une autre indication					
Non	311 (85,9)	Référence		Référence	
Oui	51 (14,1)	2,48 [1,14 – 6,21]	0,033	2,04 [1,07 – 5,80]	0,039

ATB, antibiotique ; IPCI, Inhibiteurs des Points de Contrôles Immunitaires ; IPP, inhibiteur de la pompe à protons. ; irAE, effet indésirable d'ordre immunologique ; OMS : organisation mondiale de la santé.

Par ailleurs, il n'y avait pas de différence significative concernant la SG entre :

- les patients ayant arrêté l'IPCI pour une infection et ceux n'ayant pas arrêté l'IPCI (**Figure 9B**),
- les patients hospitalisés pour une infection et ceux non hospitalisés (**Figure 9C**),
- les patients avec une infection grave et ceux avec une infection modérée (**Figure 9D**).

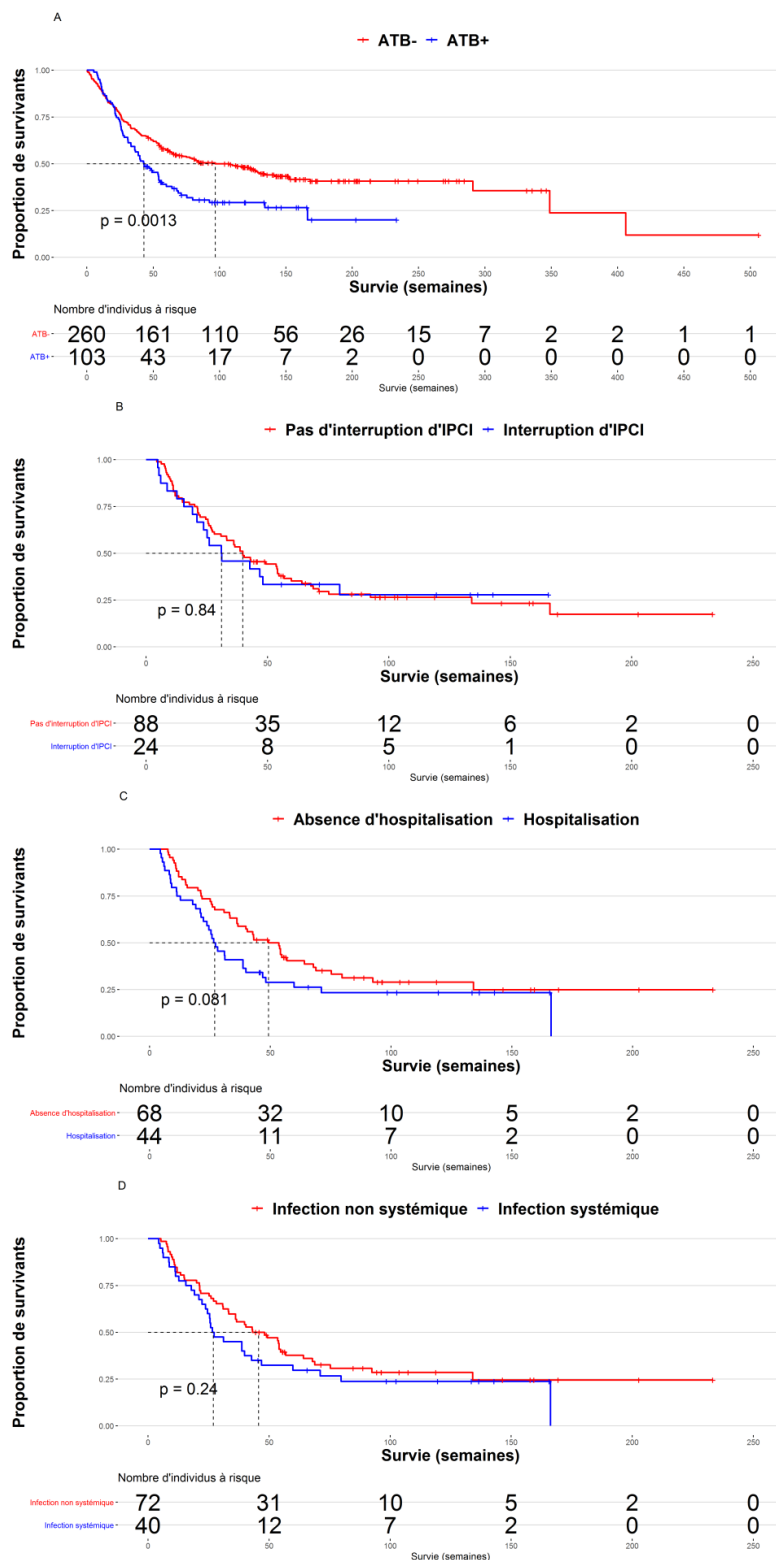


Figure 9 : Survie globale (A) selon l'utilisation de l'ATB après exclusion des patients décédés dans les 4 semaines suivant l'arrêt de l'ATB, (B) selon l'interruption de l'IPCI en raison d'une infection dans le groupe ATB+, (C) selon une hospitalisation pour l'infection dans le groupe ATB+ et (D) selon la gravité de l'infection dans le groupe ATB+.

ATB, antibiotiques.

2. Autres médicaments induisant une dysbiose

Dans le groupe de patients exposés aux opioïdes, la SG était significativement plus courte que chez les patients non exposés (durée médiane de la SG [IC 95%] : 36,6, [26,6 – 48,1] vs 126,4 [77,7 – 168,4] semaines ; HR brut [IC 95%] : 1,82 [1,40 – 2,37], $p < 0,001$; **Figure 10**) avec une réponse tumorale plus faible (16,2% vs. 33,7%, $p = 0,002$; **Figure 11**). Dans les analyses bivariées, les patients traités par opioïdes avait un pronostic significativement plus défavorable, avec à la fois une prévalence du tabac (82,1% vs. 63,3% ; $p < 0,001$) de l'alcool (39,3% vs 28,6%, $p = 0,039$) et d'un score OMS (31,2% vs. 11,4%, $p < 0,001$) plus élevés. Cette tendance n'était plus significative après ajustement sur les facteurs de confusion.

Concernant les autres traitements, en analyse bivariée, la réponse tumorale était moins bonne chez les patients traités par IPP (18,8% vs. 30,1%, $p = 0,036$) et meilleure chez ceux traités par metformine (47,1% vs. 24,5%, $p = 0,020$; **Figure 11**). Ces différences n'étaient plus significatives en analyse multivariée (**Tableau 9**).

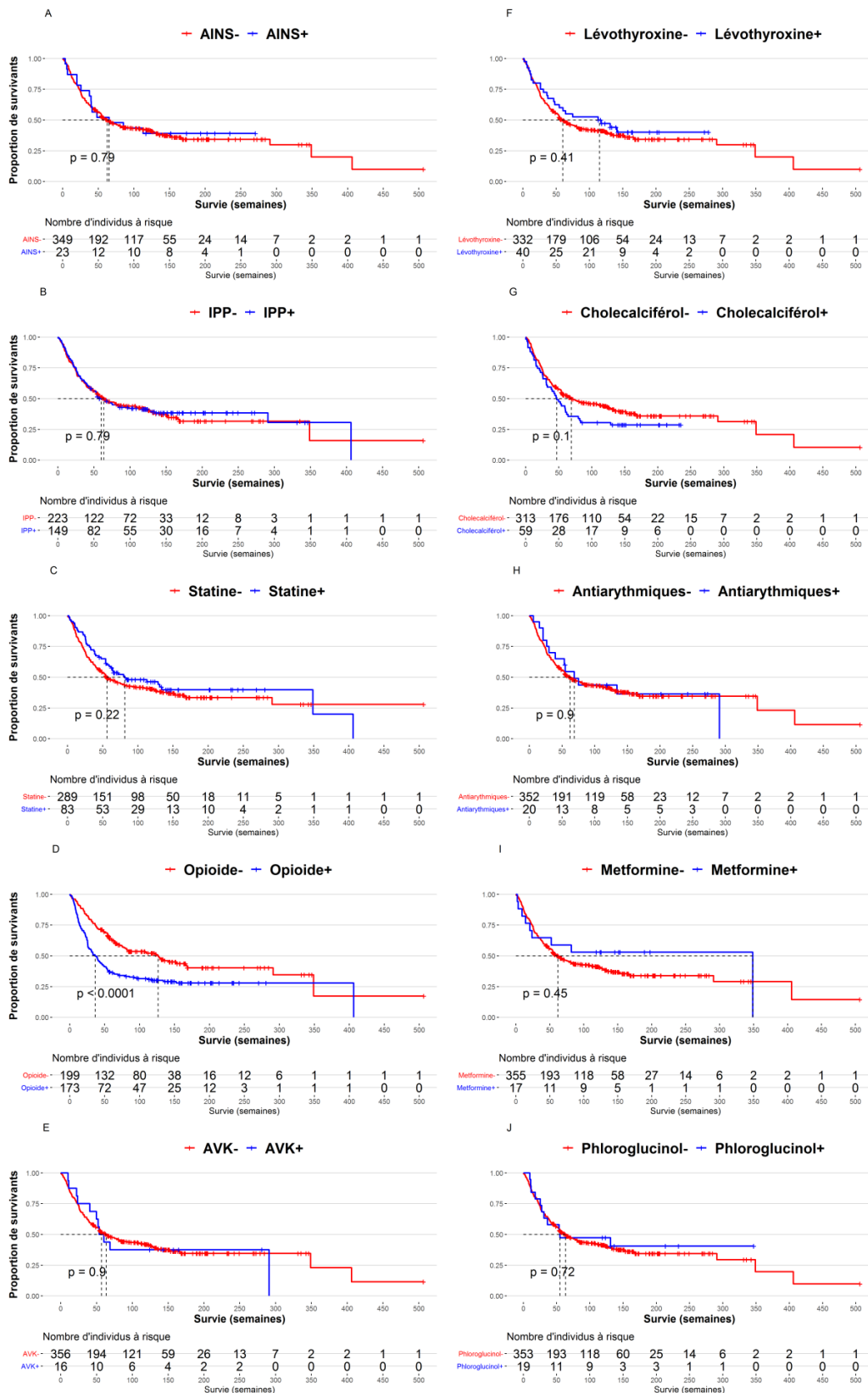


Figure 10: Survie globale selon l'utilisation de (A) AINS, (B) IPP, (C) statine, (D) opioïde, (E) AVK, (F) lévothyroxine, (G) cholécalférol, (H) antiarythmiques, (I) metformine et (J) phloroglucinol.

AINS, anti-inflammatoires non stéroïdiens ; AVK, anti-vitamine K ; IPP, inhibiteurs de la pompe à protons.

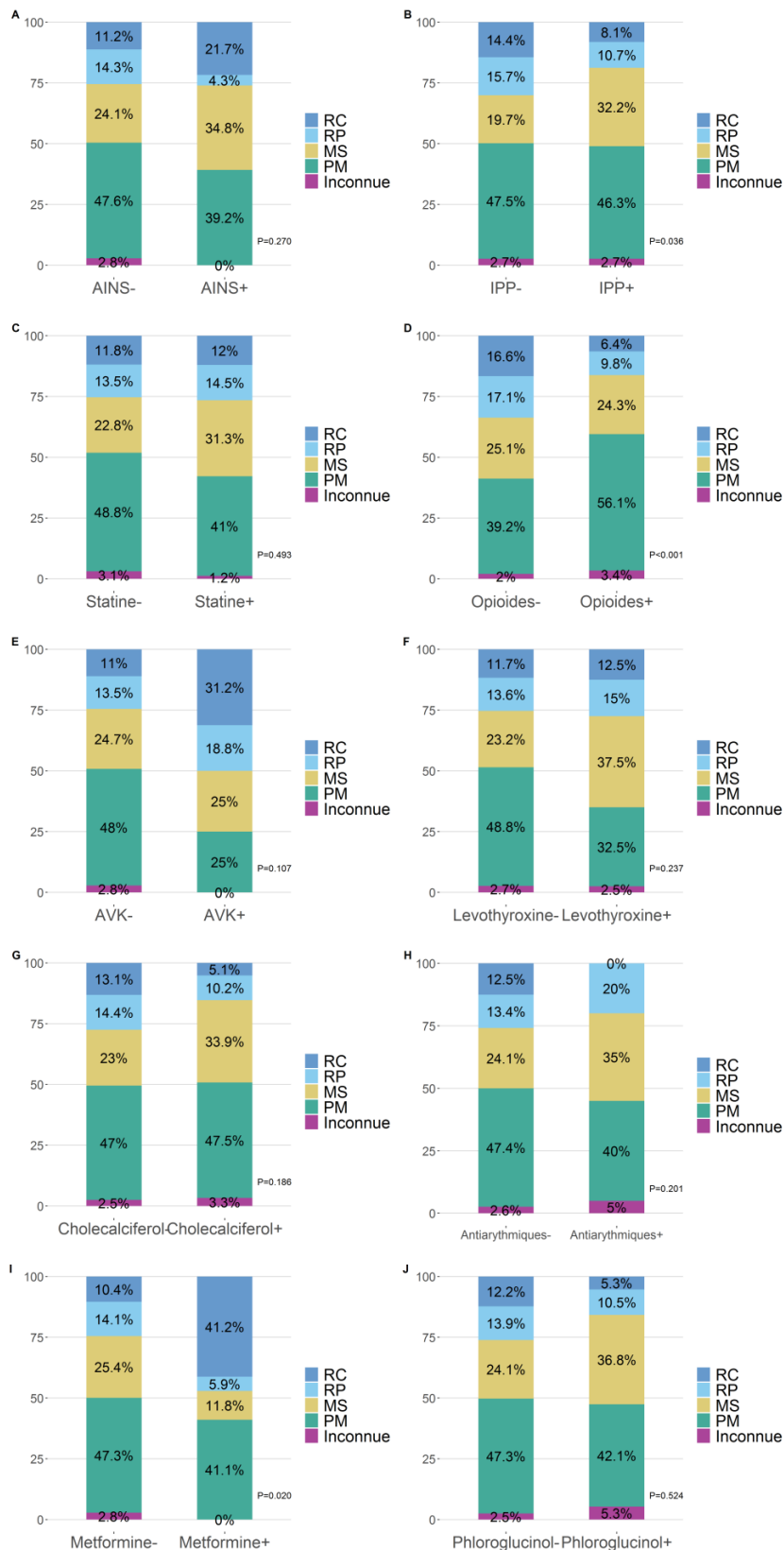


Figure 11: Réponse tumorale selon l'utilisation de (A) AINS, (B) IPP, (C) statine, (D) opioïde, (E) AVK, (F) lévothyroxine, (G) cholécalférol, (H) antiarythmiques, (I) metformine et (J) phloroglucinol.

AINS, anti-inflammatoires non stéroïdiens ; AVK, anti-vitamine K ; IPP, inhibiteurs de la pompe à protons ; MS, maladie stable, PM, progression de la maladie RC, réponse complète ; RP, réponse partielle.

3. Corticostéroïdes systémiques

a) Description de la population

Soixante-dix-sept (20,7%) patients étaient exposés aux corticostéroïdes administrés par voie systémique. Les caractéristiques de la population étudiée sont détaillées dans le **Tableau 10**.

Tableau 10 : Caractéristiques de l'ensemble de la population étudiée et des groupes CS- et CS+.

	Population totale n = 372	Groupe CS- n = 295	Groupe CS+ n = 77	P
Âge(années), moyenne \pm SD	64,0 \pm 12,1	64,8 \pm 12,2	60,5 \pm 11,4	0,005
Sexe				
Homme, n (%)	244 (65,6)	203 (68,8)	41 (53,2)	0,015
Femme, n (%)	128 (34,4)	92 (31,2)	36 (46,8)	
Indice de masse corporelle (kg/m ²), moyenne \pm SD	24,8 \pm 5,4	24,6 \pm 5,6	25,4 \pm 4,9	0,245
Tabagisme (actuel ou passé), n (%)	268 (72,0)	209 (70,8)	59 (76,6)	0,388
Consommation d'alcool, n (%)	125 (33,6)	106 (35,9)	19 (24,7)	0,084
Antécédents cardiovasculaires, n (%)	103 (27,7)	79 (26,8)	24 (31,2)	0,533
Diabète, n (%)	51 (13,7)	45 (15,3)	6 (7,8)	0,131
Hypertension artérielle, n (%)	171 (46,0)	136 (46,1)	35 (45,5)	1,000
Dyslipidémie, n (%)	104 (28,0)	83 (28,1)	21 (27,3)	0,994
Antécédents de cancer, n (%)	67 (18,0)	50 (16,9)	17 (22,1)	0,381
Type de cancer				
Poumon, n (%)	166 (44,6)	122 (41,4)	44 (57,1)	0,019
Mélanome, n (%)	110 (29,6)	88 (29,8)	22 (28,6)	0,40
Rénal et urothélial, n (%)	27 (7,3)	24 (8,1)	3 (3,9)	0,322
Tête et cou, n (%)	48 (12,9)	45 (15,3)	3 (3,9)	0,007
Lymphome hodgkinien, n (%)	5 (1,3)	5 (1,7)	0	0,588
Digestif, n (%)	4 (1,1)	3 (1,0)	1 (1,3)	1,000
Carcinome cutané à cellules squameuses, n (%)	1 (0,3)	0	1 (1,3)	0,207
Adénocarcinome de primitif inconnu, n (%)	5 (1,3)	3 (1,0)	2 (2,6)	0,277
Carcinome de primitif inconnu, n (%)	5 (1,3)	4 (1,4)	1 (1,3)	1,000
Porocarcinome, n (%)	1 (0,3)	1 (0,3)	0	1,000
Cancer métastatique, n (%)	276 (74,2)	204 (69,2)	72 (93,5)	<0,001
Nombre de sites métastatiques, médiane [intervalle IQ]	1 [0 – 2]	1 [0 – 2]	2 [1 - 2]	<0,001
Métastase cérébrale, n (%)	29 (7,8)	12 (4,1)	17 (22,1)	<0,001
Durée du cancer (mois), médiane [intervalle IQ]	13,7 [6,9 – 33,3]	13,5 [7,1 – 35,0]	14,9 [6,7 – 27,5]	0,584
Score OMS				
0-1, n (%)	295 (79,3)	236 (80,0)	59 (76,6)	0,529
2-4, n (%)	77 (20,7)	59 (20,0)	18 (23,4)	
Chimiothérapie conventionnelle antérieure, n (%)				
Nombre de lignes, médiane [intervalle IQ]	1 [1 – 2]	1 [1 – 2]	1 [1 – 2]	0,913
Chimiothérapie ciblée antérieure, n (%)				
Nombre de lignes, médiane [intervalle IQ]	1 [1 – 1]	1 [1 – 1]	1 [1 – 1]	0,649
IPCI				
Traitement de première ligne	372 (100)	295 (100)	77 (100)	1,000

Nivolumab, n (%)	217 (58,3)	175 (59,3)	42 (45,5)	0,531
Pembrolizumab, n (%)	130 (34,9)	104 (35,3)	26 (33,8)	0,913
Ipilimumab, n (%)	15 (4,0)	11 (3,7)	4 (5,2)	0,524
Nivolumab + ipilimumab, n (%)	10 (2,7)	5 (1,7)	5 (6,5)	0,036
Traitement de deuxième ligne, n (%)	27 (7,3)	16 (5,4)	11 (14,3)	0,013
Nivolumab, n (%) / n'= 27	11 (40,8)	5 (31,2)	6 (54,5)	0,013
Pembrolizumab, n (%) / n'= 27	7 (25,9)	5 (31,2)	2 (18,2)	0,638
Ipilimumab, n (%) / n'= 27	9 (33,3)	6 (37,5)	3 (27,3)	0,400
Traitement de troisième ligne, n (%)	2 (0,5)	1 (0,3)	1 (1,3)	0,372
Nivolumab, n (%) / n'= 2	0	0	0	-
Pembrolizumab, n (%) / n'= 2	1 (50,0)	0	1 (50,0)	-
Ipilimumab, n (%) / n'= 2	1 (50,0)	1 (50,0)	0	-
Facteurs modifiant le microbiote intestinal				
Médicaments concomitants				
AINS, n (%)	23 (6,2)	19 (6,4)	4 (5,2)	0,890
IPP, n (%)	149 (40,1)	112 (38,0)	37 (48,1)	0,140
Statines, n (%)	83 (22,3)	69 (23,4)	14 (18,2)	0,410
Opioides, n (%)	173 (46,5)	131 (44,4)	42 (54,5)	0,144
Metformine, n (%)	17 (4,6)	16 (5,4)	1 (1,3)	0,216
AVK, n (%)	16 (4,3)	14 (4,7)	2 (2,6)	0,541
Lévothyroxine, n (%)	40 (10,8)	34 (11,5)	6 (7,8)	0,462
Cholécalférol, n (%)	59 (15,9)	44 (14,9)	15 (1,5)	0,423
Phloroglucinol, n (%)	19 (5,1)	16 (5,4)	3 (3,9)	0,802
Antiarythmique, n (%)	20 (5,4)	18 (6,1)	2 (2,6)	0,352
ATB, n (%)	112 (30,1)	92 (31,2)	20 (26,0)	0,454
Utilisation de compléments alimentaires	58 (15,6)	50 (16,9)	8 (10,4)	0,216

ATB, antibiotique ; IPCI, Inhibiteurs des Points de Contrôles Immunitaires ; IPP, inhibiteur de la pompe à protons. ; irAE, événement indésirable lié au système immunitaire ; OMS : Organisation Mondiale de la Santé.

La dose cumulée médiane d'équivalent prednisolone était de 1520 [365 – 4080] mg. Les indications des corticostéroïdes systémiques étaient des irAEs chez 21 patients (27,3%), des métastases cérébrales chez 21 patients (27,3%), des arthralgies sans lien avec un effet indésirable d'ordre immunologique chez 7 patients (9,1%), une infection ORL chez 5 patients (6,5%), une masse médiastinale compressive chez 2 patients (2,6%) et une réaction allergique chez 1 patient (1,3%). L'indication des corticostéroïdes n'était pas connue chez 20 patients (25,9%) qui étaient par ailleurs tous atteints d'un cancer pulmonaire.

b) Survie globale

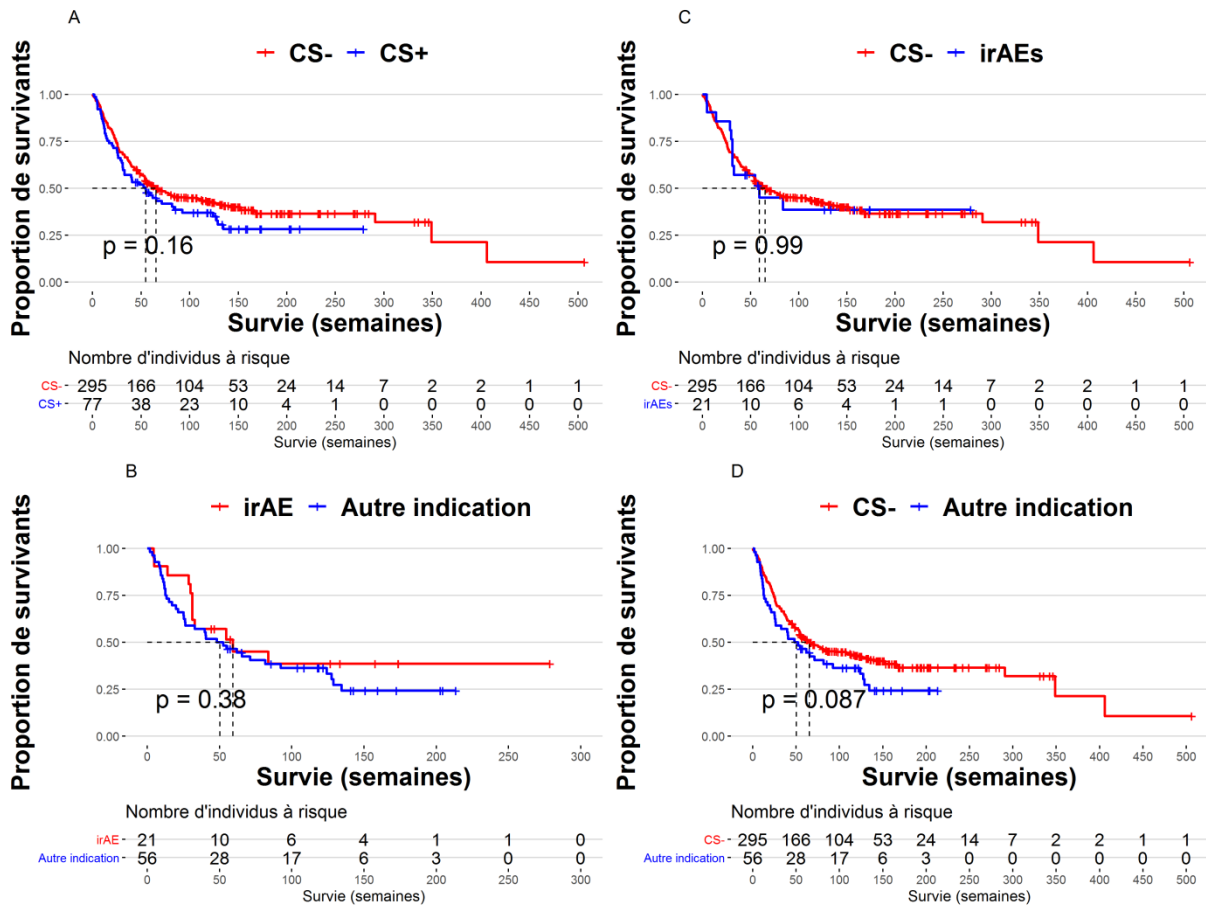


Figure 12 : Survie globale (A) dans les groupes CS+ (quelle que soit l'indication) et CS-, (B) groupes CS+ (irAE) et CS-, (C) groupes CS+ (irAE) et CS+ (autre indication), et (D) groupes CS+ (autre indication) et CS-.

CS, corticostéroïdes, irAEs ; événement indésirable lié au système immunitaire.

La SG était plus faible chez les patients CS+ comparé au groupe CS- (**Figure 12A**). Les analyses stratifiées sur l'indication montraient une SG identique chez les patients CS+ irAE vs. les patients CS- (durée médiane de la SG [IC 95%] : 59,3 [31,1 – NA] vs. 65,3 [54,1 – 113] semaines, HR brut [IC 95%] : 1,01 [0,56 – 1,80], $p=0,990$; **Figure 12C**), et une SG diminuée chez les patients CS+ pour une autre indication vs. les patients CS- (durée médiane de la SG [IC 95%] : 50,4 [26,1 – 124] vs. 65,3 [54,1 – 113] semaines, HR brut [IC 95%] : 1,35 [0,96 – 1,91], $p=0,087$; **Figure 12D**).

En analyse multivariée, l'exposition aux corticostéroïdes pour un irAE n'était pas associée de façon significative à une SG plus courte, contrairement à l'exposition aux corticostéroïdes pour une autre indication (HR ajusté [IC 95%] : 1,34 [1,05 – 2,03], $p=0,046$; **Tableau 8**).

c) Réponse tumorale

La proportion de patients répondeurs était significativement inférieure dans le groupe CS+ comparé au groupe CS- (16,9% vs. 27,8%, $p=0,025$). L'analyse stratifiée par indications montrait l'absence de différence significative entre la proportion de patients répondeurs dans le groupe CS+ irAE comparé au groupe CS-. La proportion de patients répondeurs était significativement inférieure dans le groupe CS+ pour une autre indication comparée au groupe CS- (12,5% vs. 27,8%, $p=0,008$; **Figure 13**).



Figure 13: Réponse tumorale selon l'utilisation de corticostéroïdes dans les(A) groupes CS- et CS+ (indépendamment de l'indication), (B) groupes CS- et CS+ (irAE), (C) groupes CS- et CS+ (autres indications).

CS, corticostéroïdes, irAEs ; événement indésirable lié au système immunitaire ; MS, maladie stable, PM, progression de la maladie RC, réponse complète ; RP, réponse partielle.

Après ajustement sur les facteurs de confusion, l'administration de corticostéroïdes systémiques pour un irAE n'était pas associée à une mauvaise réponse tumorale, alors que leur utilisation pour une indication autre qu'un irAE était significativement associée à une mauvaise réponse tumorale (OR ajusté [IC 95%] : 2,04 [1,07 – 5,80], $p=0,039$). Un score OMS élevé était associé à une mauvaise réponse tumorale (OR ajusté [IC 95%] : 2,61 [1,15 – 6,57], $p=0,029$; **Tableau 9**).

d) Seuils de dose cumulée et de durée associée à une mauvaise réponse tumorale

L'analyse ROC retrouvait des seuils différents en termes de durée et de dose cumulée selon l'indication de la corticothérapie chez les patients présentant une mauvaise réponse tumorale :

- un seuil de durée de 114 jours (spécificité : 61,5%, sensibilité : 82,8%) et un seuil de dose cumulée de 3215 mg d'équivalent prednisolone indépendamment de l'indication (spécificité : 53,8%, sensibilité : 67,2% ; **Figures 14, A et B**),
- un seuil de durée de 132 jours (spécificité : 71,4%, sensibilité : 89,8%) et un seuil de dose cumulée de 3215 mg d'équivalent prednisolone pour une indication irAE (spécificité : 71,4%, sensibilité : 65,3% ; **Figures 14, C et D**),
- un seuil de durée de 114 jours (spécificité : 50,0% ; sensibilité : 73,3%) et un seuil de dose cumulée de 1138,75 mg d'équivalent prednisolone pour une indication autre qu'un irAE (spécificité : 83,3%, sensibilité : 60,0% ; **Figures 14, C et D**).

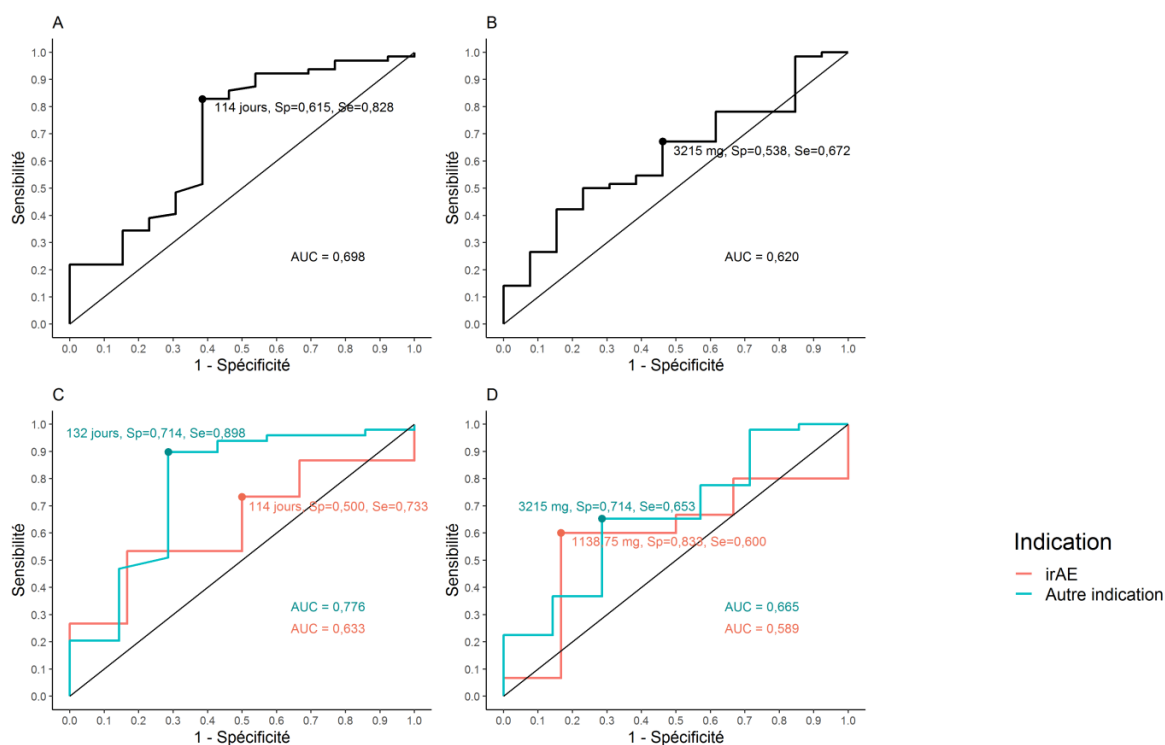


Figure 14 : Courbes ROC : relation entre la mauvaise réponse tumorale (maladie stable ou progression de la maladie) et (A) la durée de l'utilisation de corticostéroïdes systémiques (indépendamment de l'indication), (B) la dose cumulée de corticostéroïdes systémiques (indépendamment de l'indication), (C) la durée de l'utilisation de corticostéroïdes systémique pour un irAE et les autres indications et (D) la dose cumulée de corticostéroïdes systémiques pour un irAE et les autres indications.

AUC, aire sous la courbe ; irAEs ; événement indésirable lié au système immunitaire.

4. Dermocorticoïdes

Vingt-trois patients (6,2%) ont reçu des dermocorticoïdes pour une durée médiane de 34 [26,9 – 49,1] semaines. Les indications des dermocorticoïdes étaient des irAEs dermatologiques chez 17 patients (73,9%), un psoriasis chez 4 patients (17,4%), un prurigo chez un patient (4,3%) et un exanthème maculopapuleux chez un seul patient (4,3%). La SG était plus élevée chez les patients qui avaient reçu des dermocorticoïdes (durée médiane de la SG [IC 95%] : NA [124,1 – NA] vs. 55 [48,1-75,3] semaines ; HR brut [IC 95%] : 0,42 [0,22 – 0,83]), $p=0,010$). Après stratification par indications, la SG chez les patients exposés aux dermocorticoïdes pour un irAE dermatologique était plus élevée comparée aux patients exposés aux dermocorticoïdes pour une autre indication (durée médiane de la SG [IC 95%] : 141,4 [71,9 – NA] vs. 55,7 [48,3 – 77,7] semaines ; HR brut [IC 95%] : 0,54 [0,26 – 0,98], $p=0,029$; **Figure 15**).

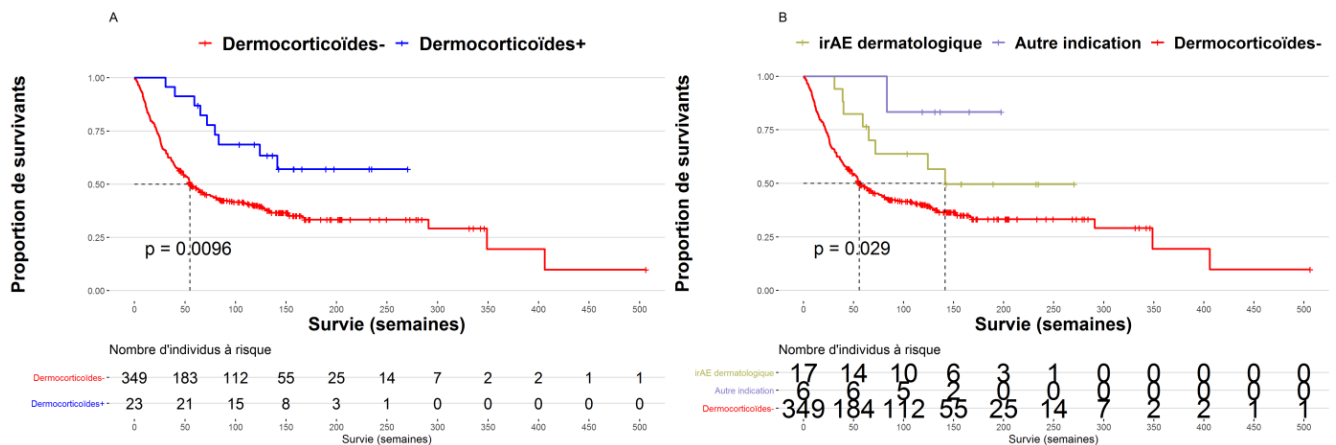


Figure 15: Survie globale dans les (A) groupes Dermocorticoïdes+ (quelle que soit l'indication) et Dermocorticoïdes-, et (B) groupes Dermocorticoïdes + (stratifiés par indication) et groupe Dermocorticoïdes-.

5. Corticostéroïdes inhalés

Vingt-deux (5,9%) patients ont reçu un traitement par corticostéroïdes inhalés au long cours, dont les indications étaient une bronchopneumopathie chronique obstructive chez 21 patients et un asthme chez 1 patient. Parmi ces 22 patients, 16 avaient un cancer du poumon, 3 avaient un mélanome et 1 avait un carcinome urothélial. La SG était similaire dans le groupe

exposé aux corticostéroïdes inhalés (CS inhalé+) et dans le groupe non exposé (CS inhalé-) (Figure 16).

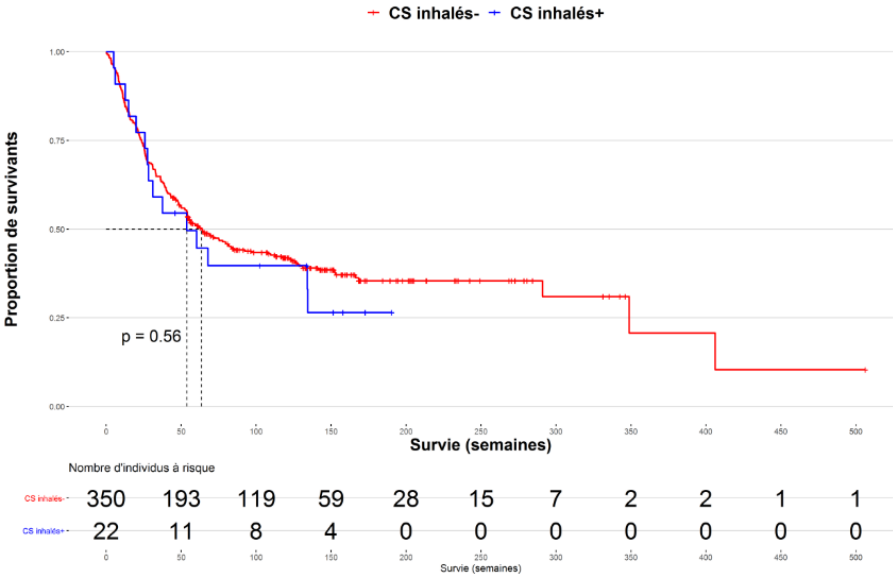


Figure 16 : Survie globale des groupes CS inhalé+ et groupe CS inhalé-.

CS, corticostéroïdes.

IV. DISCUSSION

A. Antibiotiques

Nos résultats montrent que dans une population de patients traités par IPCI (n=372), l'exposition aux ATB était associée à une SG plus faible (HR ajusté : 1,38 [1,00 – 1,90], $p=0,048$) ainsi qu'à une mauvaise réponse tumorale (OR ajusté : 6,06 [2,80 – 14,53], $p<0,001$). Ces résultats corroborent certaines données récentes de la littérature [73,74,94–96]. En revanche, d'autres études n'ont pas trouvé d'association entre l'exposition aux ATB et la SG et/ou la réponse tumorale [97–99]. Ces résultats contradictoires ont plusieurs explications. Premièrement, il est difficile de définir un seuil optimal de durée pendant laquelle l'ATB a encore, ou non, un effet sur l'efficacité de l'IPCI. L'étude de Derosa *et al.* [96] a établi que la SG chez les patients exposés aux ATB dans les 60 jours avant le début de l'IPCI était meilleure comparativement à ceux exposés dans les 30 jours avant le début de l'IPCI [96]. Ainsi, il semble pertinent de prendre en compte le temps nécessaire à la restauration du microbiote intestinal après arrêt de l'antibiothérapie (**Tableau 5**) [52]. Deuxièmement, la nature de la dysbiose est différente selon le type d'ATB utilisé. Par exemple, la vancomycine semble avoir un effet boost sur les IPCI anti-CTLA-4 en augmentant la proportion de *Bacteroidales* [100]. Ce paramètre a également été pris en compte dans notre étude, à partir des données de la littérature [52]. Troisièmement, à la différence de notre étude, les précédentes études n'ont pas pris en compte le biais d'indication (c'est-à-dire un décès en lien avec une infection bactérienne pour laquelle une antibiothérapie a été initiée) [73,74,95–99]. Dans le groupe ATB+ de notre étude, il n'y avait pas de différence significative entre les patients hospitalisés pour une infection et ceux non hospitalisés, entre les patients qui présentaient une infection sévère comparativement à ceux qui présentaient une infection non sévère, ou bien entre les patients qui ont arrêté l'IPCI en raison d'une infection et les autres patients. Par conséquent, ces facteurs n'expliquaient pas la faible SG dans le groupe ATB+, renforçant l'hypothèse que l'utilisation d'ATB a pu diminuer l'efficacité des IPCI.

B. Autres médicaments induisant une dysbiose

L'exposition aux autres médicaments connus pour induire une dysbiose intestinale, n'était pas associée à une SG plus courte, excepté pour les opioïdes. Le faible impact de ces médicaments sur le microbiote intestinal peut expliquer ces résultats.

L'utilisation d'IPP est associée à une augmentation de la concentration en *Bifidobacterium* et à une inhibition de l'alpha diversité du microbiote intestinal, ce qui pourrait augmenter l'efficacité des IPCI [101,102]. Ces changements de la composition du microbiote intestinal seraient dus à la diminution de l'acidité de l'estomac [49,102,103]. Néanmoins, les résultats de la littérature divergent à ce sujet. Alors que certaines études rétrospectives ont montré une association négative entre l'exposition aux IPP et la SG et/ou la réponse tumorale chez les patients traités par IPCI [104], d'autres ont observé une absence d'association [97,99], et certaines ont trouvé une association positive (meilleure SG lors d'un traitement par IPP) [105,106]. Notre travail n'a pas pu mettre en évidence une association entre l'utilisation d'IPP et la SG. Cependant, les analyses *post hoc* d'essais contrôlés randomisés, avec une population plus importante, ont montré un impact négatif des IPP sur la SG et sur la survie sans progression chez les patients traités par IPCI pour un CU ou un CBNPC, en comparaison aux patients traités par une chimiothérapie conventionnelle [107,108]. Plusieurs hypothèses peuvent expliquer ces résultats contradictoires. Tout d'abord, la petite taille d'échantillon des études rétrospectives aboutit à une faible puissance des tests statistiques, empêchant la mise en évidence d'associations [97,99,104–106]. Deuxièmement, l'hétérogénéité de la population dans ces études rétrospectives (qu'il s'agisse du type de cancers, du nombre de lignes de chimiothérapies, de l'IPCI prescrit et/ou des caractéristiques de la population étudiée) ne peut être prise en compte dans des analyses multivariées, engendrant un biais de confusion. En effet, les essais randomisés de Hopkins *et al.* [108] et Chalabi *et al.* [107], portant respectivement sur des patients atteints de CU et de CBNPC, qui étaient naïfs de chimiothérapie ou avaient été traités par un ou deux agents cytotoxiques avant l'introduction de l'IPCI (un anti-PD-L1, l'atezolizumab) alors que la population de notre étude était constituée de patients ayant reçus de nombreuses lignes de traitements, incluant des thérapies ciblées. Il semblerait que la dysbiose induite par les IPP ait un effet plus prononcé sur l'efficacité des IPCI lors des premières lignes de traitement, dans la mesure où les cellules tumorales développent des capacités d'échappement au système immunitaire à un stade avancé du

cancer, engendrant une perte d'efficacité des IPCI indépendamment du microbiote intestinal [109].

L'utilisation d'opioïdes semble affecter la composition du microbiote intestinal *via* l'activation des récepteurs opioïdes qui réduit la motilité intestinale [110]. Le tramadol a également une activité bactéricide *in vitro* [111]. Nos résultats ont montré que les opioïdes étaient associés à une faible SG en analyse bivariée mais pas en analyse multivariée. Dans notre population, les patients traités par opioïdes avaient un score OMS plus élevé, reflétant un pronostic défavorable, comparativement à ceux qui n'en avaient pas reçu. Nos résultats sont contradictoires avec ceux de l'étude d'Iglesias-Santamaría [99] qui a montré que l'utilisation d'opioïdes était associée à une SG plus faible en analyses multivariées (HR ajusté [IC 95%] : 3,63 [1,92 – 6,85], $p < 0,001$). Ces résultats incohérents peuvent être expliqués par le fait que l'étude d'Iglesias-Santamaría n'a pas pris en compte le score OMS dans le modèle de Cox.

Notre travail s'est également intéressé à l'effet de l'exposition aux statines, AINS, AVK, cholécalférol, phloroglucinol et anti arythmiques. Ces médicaments sont tous connus pour induire des dysbioses [49,102,113–116]. Nos résultats ne retrouvent aucune association entre ces médicaments et la SG possiblement expliqué par le fait que ces médicaments ont un impact moins important que celui des ATB sur le microbiote intestinal. Toutefois, nous ne pouvons exclure le fait que notre faible nombre de patients prenant des AINS, des AVK, du phloroglucinol, de la metformine et/ou des anti arythmiques, ait empêché la mise en évidence d'associations. Concernant la metformine et les statines qui semblent avoir un rôle protecteur sur le microbiote intestinal [59,105], l'exposition à ces médicaments n'avait pas d'influence sur la SG ou la réponse tumorale (excepté une meilleure réponse tumorale chez les patients traités par metformine en analyse bivariée) dans notre étude, comme il a également été rapporté par Failing *et al.* [105]. Cette absence d'association pourrait être expliquée par le faible nombre de patients traités par metformine dans notre cohorte et également par un biais d'indication (comorbidités plus importantes chez les patients diabétiques).

C. Corticostéroïdes

Nos résultats ont montré que l'utilisation de corticostéroïdes par voie systémique pour une indication autre qu'un irAE était associée à une SG plus courte (HR ajusté [IC 95%] : 1,34 [1,05

– 2,03], $p=0,046$) et à une réponse tumorale défavorable (OR ajusté [IC 95%] :2.04 [1.07 – 5.80], $p=0,039$). De plus, il n’y avait pas de différence significative en termes de SG ou de réponse tumorale entre les patients qui recevaient des corticostéroïdes pour un irAE et ceux qui ne recevaient pas de corticostéroïdes. Ces résultats peuvent être expliqués par le fait que la survenue d’un irAE est associée à une meilleure survie et à une meilleure réponse tumorale [117–119]. Par ailleurs, plusieurs études ont montré que l’utilisation de corticostéroïdes pour une indication autre qu’un irAE à l’instauration d’un IPCI est associée à une SG plus courte à une mauvaise réponse tumorale [89–91], et que l’utilisation de corticostéroïdes pour un irAE n’affecte pas la SG [86–88]. Par conséquent, il est possible que dans ce contexte la survie soit liée à l’indication de la corticothérapie puisque les corticostéroïdes n’affectent pas la SG lorsqu’ils sont utilisés pour un irAE.

L’analyse ROC a montré qu’une valeur seuil de 132 jours de traitement par corticostéroïdes systémique pour une indication autre qu’un irAE et une dose seuil de 3215mg (équivalent de prednisolone) sont associées à une progression de la maladie. Ainsi, une attention particulière devrait être apportée lorsque ces seuils sont atteints.

Notre travail a montré que les dermocorticoïdes étaient associés à une SG plus longue (HR brut [IC 95%] : 0,42 [0,22 – 0,83], $p=0,010$). L’indication la plus fréquente des dermocorticoïdes était un irAE dermatologique ce qui peut expliquer pourquoi la SG était plus longue chez ces patients, dans la mesure où les irAE dermatologiques sont associés à une meilleure SG [117–119].

Enfin, concernant les corticostéroïdes inhalés, notre étude n’a pas pu mettre en évidence de différence significative de SG entre le groupe exposé et le groupe non exposé. L’étude de Mingjila *et al.* [92] avait identifié un effet péjoratif des corticoïdes inhalés chez les patients sous IPCI. Ces résultats contradictoires avec les nôtres peuvent être expliqués par le faible nombre de patients inclus dans notre étude.

D. Limites de l’étude

Notre étude comporte plusieurs limites, principalement en raison de son caractère rétrospectif, à savoir un biais de confusion résiduel malgré les analyses ajustés et un biais de classification possible. De plus, même si nous avons tenté de minimiser le biais d’indication

(exclusion des patients décédés dans les 4 semaines après la fin de l'antibiothérapie, stratifications sur la sévérité de l'infection dans le groupe ATB+), celui-ci ne peut être maîtrisé qu'en présence d'un groupe contrôle non traité par IPCI. Par ailleurs, la taille de notre échantillon a pu empêcher la mise en évidence de certaines associations en raison d'un manque de puissance. Le caractère monocentrique de notre étude ne permet pas de généraliser nos résultats. De plus, certains facteurs pronostiques n'ont pas été pris en compte dans cette étude, tels que le score de Clark ou l'indice de Breslow pour le mélanome. Enfin, le microbiote intestinal des patients n'a pas été directement étudié.

V. Conclusion

Notre étude a permis de mettre en évidence des résultats susceptibles d'avoir un impact dans la prise en charge des patients traités par IPCI. L'utilisation d'ATB, en fonction de leur période d'exposition, semble être associée à une SG plus courte et à une mauvaise réponse tumorale chez les patients traités par IPCI. Une vigilance particulière devrait être adoptée quant à leur utilisation dans cette population. Concernant les autres médicaments pouvant induire une dysbiose, nous n'avons pas mis en évidence d'association entre leur utilisation et une SG plus courte ou une mauvaise réponse tumorale. Pour certaines classes de médicaments, tels que les IPP, des études complémentaires sont nécessaires compte-tenu des données divergentes. Quant aux corticostéroïdes administrés par voie systémique, leur utilisation n'affecte ni la SG ni la réponse tumorale lorsqu'ils sont utilisés pour traiter un irAE, contrairement à une utilisation dans une autre indication, avec un seuil de durée de 132 jours et un seuil de dose cumulée de 3215 mg d'équivalent prednisolone. Le passage systémique est dermocorticoïdes et des corticoïdes inhalés ne semble pas affecter la SG ou la réponse tumorale.

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VI. ANNEXES

Associations between dysbiosis-inducing drugs, overall survival and tumor response in patients treated with immune checkpoint inhibitors

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Abstract

Background: There are conflicting data on the effects of dysbiosis-inducing drugs, and especially antibiotics (ATBs), on clinical outcomes in patients treated with immune checkpoint inhibitors (ICIs). There is a particular lack of data for patients with melanoma.

Methods: We performed a single-center retrospective study of the associations between ATBs and other drugs known to modify the gut microbiota (proton pump inhibitors, nonsteroidal anti-inflammatory drugs, statins, opioids, anti-vitamin K, levothyroxine, vitamin D3, antiarrhythmics, metformin and phloroglucinol), overall survival (OS) and tumor response in consecutive cancer patients (particularly those with melanoma) treated with an ICI (ipilimumab, nivolumab or pembrolizumab) over a 9-year period.

Results: A total of 372 patients were included. The mean \pm standard deviation age was 64.0 ± 12.1 years. The most frequently prescribed ICI was nivolumab (in 58.3% of patients) and the most frequent indications were lung cancer (44.6%) and melanoma (29.6%). Overall, 112 patients (30.1%) had received ATBs. ATB use was associated with (1) shorter OS in the study population as a whole [adjusted hazard ratio (95% confidence interval (CI)): 1.38 (1.00–1.90), $p=0.048$] and in patients with melanoma [adjusted hazard ratio (95% CI): 2.60 (1.06–6.39), $p=0.037$], and (2) a lower response rate in the study population as a whole [8.1%, versus 31.1% in patients not treated with ATBs; adjusted odds ratio (95% CI): 6.06 (2.80–14.53), $p < 0.001$] and in patients with melanoma [adjusted odds ratio (95% CI): 4.41 (1.04–22.80), $p=0.045$].

Sensitivity analyses that minimized the indication bias did not reveal an association between OS and the presence of an infection requiring ATBs (quantified as the severity of infection, hospitalization for an infection, or ICI discontinuation). Other dysbiosis-inducing drugs were not associated with a difference in OS.

Conclusion: Unlike other dysbiosis-inducing drugs, ATBs were associated with poorer clinical outcomes in ICI-treated patients overall and in the subset of patients with melanoma.

Keywords: antibiotic, drug-induced dysbiosis, dysbiosis, immune checkpoint inhibitor, melanoma

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Introduction

In the early 2000s, the advent of immune checkpoint inhibitors (ICIs) led to a new era in cancer treatment. By targeting inhibitory receptors (CTLA-4 and PD-1) or a ligand (PD-L1)

expressed on the surface of lymphocytes,^{1,2} ICIs promote the immune-mediated control of tumor growth. The use of ICIs by patients with skin, lung, kidney, ear nose and throat and hematological cancers has led to marked reductions in morbidity

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and mortality.³⁻⁵ However, tumor escape is still a major problem.

According to the literature, between 60% and 80% of patients fail to respond to ICIs.⁶ The factors underlying escape from ICIs can be divided into three classes: tumor-related factors, host factors, and environmental factors.⁷ The latter include infectious agents, diet, prolonged exposure to the sun, concomitant drug treatments (including exposure to corticosteroids and the indications requiring treatment with corticosteroids),⁸ and the gut microbiota (i.e. all the microorganisms in the digestive tract, primarily bacteria but also viruses, fungi, and archaea). Interaction with the microbiota (mainly the bacteria) influences the host's digestive, metabolic, neurological and immunological functions.⁹

A number of studies have highlighted a link between dysbiosis (i.e. a quantitative and/or qualitative imbalance in the microbiota) and the patient's response to ICIs.^{10,11} For example, the treatment success rate is directly related to the proportions of certain bacteria.¹² Thus, anti-CTLA-4 activity is directly related to the presence of certain Bacteroidetes (the Bacteroidales) and Proteobacteria (the Burkholderiales).¹³ In fact, an increase in the proportion of these bacteria seems to be associated with greater effectiveness of ipilimumab.¹⁴ Similarly, anti-PD-1 activity is modulated by the presence of the order Bacteroidales (the genus *Bacteroides*), the genus *Bifidobacterium*, the phylum Actinobacteria, *Akkermansia muciniphilia*, the phylum Verrucomicrobia, and the phylum Firmicutes.^{10,13} Other studies have highlighted an association between anti-PD-L1 activity and *Bifidobacterium*, Actinobacteria, *Collinsella aerofaciens*, and *Enterococcus faecium*.¹³

Drugs that influence the composition of the gut microbiota [e.g. antibiotics (ATBs)] can influence the clinical effectiveness of drugs. To date, studies of the effectiveness of ICIs have not considered the impact of individual ATBs on the gut microbiota.^{10,15-21} In fact, it is known that the impact on the microbiome differs from one ATB to another. For example, treatments with ceftriaxone and ofloxacin tend to increase and reduce the proportion of *Enterococcus*, respectively.¹³ The duration of dysbiosis after ATB discontinuation also differs from one compound to another. Thus, spiramycin seems to affect the microbiota for up

to 28 days after discontinuation, whereas piperacillin has an effect for up to 14 days.¹³ Hence, the change in the microbiota induced by a particular ATB can influence the interaction with ICIs. For example, the use of amoxicillin and amoxicillin/clavulanic acid might boost the effectiveness of ICIs by increasing the number of *Bacteroides*.¹³

Retrospective studies of the association between ATB use and overall survival (OS) in patients treated with ICIs have generated conflicting results: some have shown a negative association,^{16,17,19,22} while others did not observe an association.^{15,20,21} As described by Derosa *et al.*,²² the timeframe of exposure to ATBs before ICI initiation appears to be a determinant factor; the clinical outcomes in patients exposed to ATBs 60 days before ICI initiation were better than in patients exposed for just 30 days before initiation. Furthermore, most of these studies focused on patients with renal cell carcinoma, urothelial carcinoma (UC) or nonsmall-cell lung carcinoma (NSCLC) but not on those with melanoma. Moreover, the researchers did not determine whether the severity of the infection influenced the association between ATB use and worse OS. Lastly, recent *post hoc* analyses of randomized trials of patients with UC and NSCLC showed worse OS and progression-free survival in individuals in the ICI arm (the anti-PD-L1 atezolizumab) receiving ATBs but not in those in the control arm (conventional chemotherapy) receiving ATBs.^{23,24}

Along with ATBs, a number of other drug classes can induce dysbiosis: proton pump inhibitors (PPIs), drugs for functional gastrointestinal disorders (particularly phloroglucinol), anti-vitamin K (AVK) anticoagulants, antiarrhythmics, non-steroidal anti-inflammatory drugs (NSAIDs), vitamin D3 (known for its protective role in intestinal homeostasis),²⁵ metformin (which stimulates the gut microbiota and the immune system),²⁶ opioids, statins (which appear to be associated with an anti-inflammatory gut microbiotic profile),²⁷ levothyroxine, and psychotropics.²⁸⁻³⁵

The objective of the present study was to evaluate the associations between ATBs (especially amoxicillin and amoxicillin/clavulanic acid) and other drugs known to modify gut microbiota on one hand and OS and the tumor response in patients treated with ICIs (particularly patients with melanoma) on the other.

Methods

Study design

We performed a retrospective, observational study of all consecutive adult patients (aged 18 years and over) treated with an anti-CTLA-4 agent (ipilimumab) and/or an anti-PD-1 agent (nivolumab or pembrolizumab) in the departments of oncology, dermatology, pulmonology, hematology and gastroenterology from December 2010 to December 2019 at Amiens University Medical Center (Amiens, France). Patients enrolled in clinical trials or receiving concomitant chemotherapy or targeted therapy were not included.

Collection of patients' baseline characteristics

Demographic characteristics (age and sex), body mass index (BMI), and comorbidities were collected: smoking status (defined as 'never' or 'current/past'), alcohol consumption (defined as daily consumption or not, regardless of the dose), a history of cardiovascular disease (including myocardial infarction, stroke, obliterating arteriopathy of the lower limbs, and deep vein thrombosis), the presence or absence of diabetes mellitus (regardless of the severity), the presence or absence of high blood pressure, the presence or absence of dyslipidemia, and a history of cancer. The type of current cancer, its metastatic status, the number of metastatic sites (including brain metastases, if present), and the Eastern Cooperative Oncology Group (ECOG) performance status were collected. Any conventional and targeted chemotherapies prior to ICI initiation were recorded. The first-line treatment of ICIs was considered in the analyses, and subsequent lines (if applicable) were also described.

Evaluation of the tumor response and overall survival

On the basis of data gathered from multidisciplinary team meeting reports and imaging reports, the best overall response was defined as a complete response (CR), partial response (PR), stable disease (SD) or disease progression (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1).³⁶ A good response was defined as CR or PR status. OS was calculated from the date of ICI initiation to the time of death from any cause or to the date of the last follow-up examination.

Collection of data on drug use and definitions of patient groups

Antibiotics. When defining the patient groups, we took account of the dysbiosis caused by each ATB,¹³ the influence of dysbiosis on the ICI's effectiveness^{10,14,37,38} and the time needed for recovery of the gut microbiota after ATB discontinuation.¹³ Patients with a documented tumor response at least 3 months after the initiation of ICI treatment were assigned to the 'ATB+' group if they had received amoxicillin in the year preceding ICI initiation, amoxicillin/clavulanic acid in the preceding 60 days, piperacillin-tazobactam, cloxacillin or oracillin in the preceding 10 days, any cephalosporin in the preceding 40 days, any macrolide in the preceding 28 days, vancomycin (only for patients treated with an anti-PD-1 agent) in the preceding 7 days, any quinolone in the preceding year, metronidazole in the preceding 60 days, doxycycline in the preceding 7 days, sulfamethoxazole-trimethoprim in the preceding 14 days, linezolid in the preceding 28 days, any aminoglycoside in the preceding 30 days, or any type of ATB in the 60 days following the initiation of ICI treatment. The ATB's administration route was documented, along with the treatment duration, the indication, the severity of the confirmed or suspected infection (classified as systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock,³⁹ or a nonsystemic infection), hospitalization prompted by an infection, and ICI discontinuation prompted by an infection.

Other dysbiosis-inducing drugs. Given the lack of literature data on the gut microbiota's recovery after the discontinuation of PPIs, NSAIDs, statins, metformin, opioids, cholecalciferol, levothyroxine, AVK anticoagulants, antiarrhythmic, phloroglucinol and psychotropics, patients were assigned to the corresponding drug class group if they received this drug class upon initiation of ICI treatment or in the following 60 days. For each drug class, the indication was documented.

Steroids. Given that systemic treatment with corticosteroids is known to lower the effectiveness of ICIs,⁴⁰⁻⁴² the use of oral corticosteroids in the 60 days following the initiation of ICI treatment, together with the indication [an immune-related adverse event (irAE) or another indication], and the dose level were documented.

Ethical approval and informed consent statements

In line with the French legislation on retrospective analyses of routine clinical practice, patients were not required to give their informed consent. On admission to hospital, however, patients could refuse the use of their medical data for research purposes. The present study protocol was approved by an institutional committee with competency for studies not requiring approval by an independent ethics committee (Clinical Research Directorate, Amiens University Medical Center, Amiens, France) and was registered with the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés, Paris, France; reference: PI2018_843_0062, dated 11 November 2018).

Statistical analyses

In our descriptive analysis, categorical variables were expressed as the number (percentage). Continuous variables were expressed as the mean \pm standard deviation (SD), the median (interquartile range), or the median (range), depending on the data distribution. In a bivariate analysis comparing patients receiving the drug of interest with those not receiving it, continuous variables were compared using Student's *t* test or a Wilcoxon's rank-sum test (depending on the data distribution), and categorical variables were compared using a Chi-square test or Fisher's exact test. OS in the ATB+ and ATB- groups was assessed using the Kaplan–Meier method and a log-rank test. The groups' tumor response rates (according to the RECIST 1.1 criteria) were also compared. In multivariate analyses, a Cox proportional hazards model was built for OS and a logistic regression model was built for the tumor response (with a worse tumor response defined as SD or PD status). Variables with a *p*-value < 0.2 in the bivariate analysis and the predictors of death most frequently described in the literature (i.e. age, sex, BMI, current or past smoking, alcohol consumption, a history of cardiovascular disease, cancer duration, and ECOG performance status) were included in the models, together with other drugs associated with better or poorer OS or a better or worse tumor response in bivariate analyses. A Cox proportional hazards model and a logistic regression including diabetes, hypertension, dyslipidemia, number of metastatic sites (as a binary variable: at least two metastatic sites *versus* fewer than two metastatic sites) and the line of treatment of ICI were also applied.

In sensitivity analyses, the same analyses were performed in (1) patients exposed to ATBs in the 30 days preceding or following the initiation of ICI (the 'ATB+30' group) *versus* those who were not (the 'ATB-30' group) and (2) patients exposed to ATBs in the 60 days preceding or following the initiation of ICI (the 'ATB+60' group) *versus* those who were not (the 'ATB-60' group).

We also analyzed the subsets of patients in the ATB+ and ATB- groups with melanoma. For these subgroups, prognosis factors [i.e. brain metastasis, levels of lactate dehydrogenase (LDH) known at ICI initiation, and ulceration as a histological characteristic of the melanoma]⁴³ were included in the multivariate analyses (Cox proportional hazards model and logistic regression).

Moreover, we evaluated OS and the tumor response in patients having received amoxicillin and/or amoxicillin/clavulanic acid *versus* patients having received other ATBs and patients having not received ATBs. In order to minimize indication bias, several sensitivity analyses were performed: (1) patients who died or were lost to follow-up within 4 weeks of ATB discontinuation; (2) OS in patients who discontinued the ICI due to an infection *versus* those who did not, (3) OS in hospitalized patients requiring systemic ATB therapy *versus* patients not hospitalized, and (4) OS in patients with a clinical infection *versus* those with sepsis.

All statistical tests were two-sided, and the threshold for statistical significance was set to $p < 0.05$. All analyses were performed using R software (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 374 patients started treatment with ipilimumab, nivolumab or pembrolizumab (alone or in combination) between 1 December 2010, and 31 December 2019. Overall, 2 patients were excluded because of missing data and so 372 patients were included in the analysis. The mean \pm SD age was 64.0 ± 12.1 years. The most frequently prescribed ICI [in 217 patients (58.3%)] was nivolumab. The most frequent cancers were lung cancers (44.6%) and melanoma (29.6%). The study population's demographic and clinicopathological characteristics are summarized in Table 1.

Table 1. Characteristics of the overall study population and the ATB- and ATB+ groups.

	Overall population <i>n</i> =372	ATB- group <i>n</i> =260	ATB+ group <i>n</i> =112	<i>p</i> -value
Age (years), mean \pm SD	64.0 \pm 12.1	64.8 \pm 12.0	62.1 \pm 12.4	0.048
Sex				
Male, <i>n</i> (%)	244 (65.6)	162 (62.3)	82 (73.2)	0.055
Female, <i>n</i> (%)	128 (34.4)	98 (37.7)	30 (26.8)	
Body mass index (kg/m ²), mean \pm SD	24.8 \pm 5.4	25.3 \pm 5.6	23.7 \pm 5.0	0.009
Smoking (current or past), <i>n</i> (%)	268 (72.0)	177 (68.1)	91 (81.2)	0.013
Alcohol consumption, <i>n</i> (%)	125 (33.6)	73 (28.1)	52 (46.4)	<0.001
Cardiovascular history, <i>n</i> (%)	103 (27.7)	71 (27.3)	32 (28.6)	0.902
Diabetes mellitus, <i>n</i> (%)	51 (13.7)	38 (14.6)	13 (11.6)	0.542
High blood pressure, <i>n</i> (%)	171 (46.0)	126 (48.5)	45 (40.2)	0.175
Dyslipidemia, <i>n</i> (%)	104 (28.0)	77 (29.6)	27 (24.1)	0.337
History of cancer, <i>n</i> (%)	67 (18.0)	42 (16.2)	25 (22.3)	0.203
Tumor type				
Lung, <i>n</i> (%)	166 (44.6)	104 (40.0)	62 (55.4)	0.009
Melanoma, <i>n</i> (%)	110 (29.6)	94 (36.2)	16 (14.3)	<0.001
Renal and urothelial, <i>n</i> (%)	27 (7.3)	24 (9.2)	3 (2.7)	0.028
Head and neck, <i>n</i> (%)	48 (12.9)	25 (9.6)	23 (20.5)	0.006
Hodgkin lymphoma, <i>n</i> (%)	5 (1.3)	1 (0.4)	4 (3.6)	0.030
Digestive, <i>n</i> (%)	4 (1.1)	3 (1.2)	1 (0.9)	1.000
Cutaneous squamous cell carcinoma, <i>n</i> (%)	1 (0.3)	0	1 (0.9)	0.301
Adenocarcinoma of unknown primary, <i>n</i> (%)	5 (1.3)	5 (1.9)	0	0.328
Squamous cell carcinoma of unknown primary, <i>n</i> (%)	5 (1.3)	4 (1.5)	1 (0.9)	1.000
Porocarcinoma, <i>n</i> (%)	1 (0.3)	0	1 (0.9)	0.301
Metastatic cancer, <i>n</i> (%)	276 (74.2)	211 (81.2)	65 (58.0)	<0.001
Number of metastatic sites, med (IQR)	1 (0–2)	1 (1–2)	1 (0–2)	<0.001
Brain metastasis, <i>n</i> (%)	29 (7.8)	21 (8.1)	8 (7.1)	0.922
Cancer duration (months), med (IQR)	13.7 (6.9–33.3)	16.0 (7.6–38.8)	10.2 (5.2–19.5)	0.001
ECOG performance status				
0–1, <i>n</i> (%)	295 (79.3)	208 (80.0)	87 (77.7)	0.676
2–4, <i>n</i> (%)	77 (20.7)	52 (20.0)	25 (22.3)	
Prior conventional chemotherapy, <i>n</i> (%)	219 (58.9)	139 (53.5)	80 (71.4)	0.002
Number of lines, med (IQR)	1 (1–2)	1 (1–2)	1 (1–1)	0.289

(Continued)

Table 1. (Continued)

	Overall population <i>n</i> =372	ATB- group <i>n</i> =260	ATB+ group <i>n</i> =112	<i>p</i> -value
Prior targeted chemotherapy, <i>n</i> (%)	66 (17.7)	53 (20.4)	13 (11.6)	0.059
Number of lines, med (IQR)	1 (1-1)	1 (1-2)	1 (1-1)	0.135
ICIs				
First-line treatment, <i>n</i> (%)	372 (100)	260 (100)	112 (100)	1.000
Nivolumab alone, <i>n</i> (%)	217 (58.3)	143 (55.0)	74 (66.1)	0.062
Pembrolizumab, <i>n</i> (%)	130 (34.9)	96 (36.9)	34 (30.4)	0.271
Ipilimumab alone, <i>n</i> (%)	15 (4.0)	14 (5.4)	1 (0.9)	0.046
Nivolumab + ipilimumab, <i>n</i> (%)	10 (2.7)	7 (2.7)	3 (2.7)	1.000
Second-line treatment, <i>n</i> (%)	27 (7.3)	24 (9.2)	3 (2.7)	0.028
Nivolumab, <i>n</i> (%) / <i>n</i> ' = 27	11 (40.8)	9 (37.5)	2 (66.7)	0.516
Pembrolizumab, <i>n</i> (%) / <i>n</i> ' = 27	7 (25.9)	6 (25.0)	1 (33.3)	0.680
Ipilimumab, <i>n</i> (%) / <i>n</i> ' = 27	9 (33.3)	9 (37.5)	0	0.062
Third-line treatment, <i>n</i> (%)	2 (0.5)	2 (0.8)	0	1.000
Nivolumab, <i>n</i> (%) / <i>n</i> ' = 2	0	0	0	-
Pembrolizumab, <i>n</i> (%) / <i>n</i> ' = 2	1 (50.0)	1 (50.0)	0	-
Ipilimumab, <i>n</i> (%) / <i>n</i> ' = 2	1 (50.0)	1 (50.0)	0	-
Factors modifying the gut microbiota				
Concomitant medications				
NSAIDs, <i>n</i> (%)	23 (6.2)	18 (6.9)	5 (4.5)	0.504
PPIs, <i>n</i> (%)	149 (40.1)	103 (39.6)	46 (41.1)	0.883
Statins, <i>n</i> (%)	83 (22.3)	58 (22.3)	25 (22.3)	1.000
Opioids, <i>n</i> (%)	173 (46.5)	119 (45.8)	54 (48.2)	0.749
Metformin, <i>n</i> (%)	17 (4.6)	16 (6.2)	1 (0.9)	0.050
AVKs, <i>n</i> (%)	16 (4.3)	13 (5.0)	3 (2.7)	0.463
Levothyroxine, <i>n</i> (%)	40 (10.8)	36 (13.8)	4 (3.6)	0.006
Cholecalciferol, <i>n</i> (%)	59 (15.9)	47 (18.1)	12 (10.7)	0.103
Phloroglucinol, <i>n</i> (%)	19 (5.1)	13 (5.0)	6 (5.4)	1.000
Antiarrhythmic drug, <i>n</i> (%)	20 (5.4)	11 (4.2)	9 (8.0)	0.214
Corticosteroids, <i>n</i> (%)	77 (20.7)	57 (21.9)	20 (17.9)	0.454
Use of food supplements, <i>n</i> (%)	58 (15.6)	27 (10.4)	31 (27.7)	<0.001
ATB, antibiotic; AVK, anti-vitamin K; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; IQR, interquartile range; NSAID: nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SD standard deviation.				

Overall survival and tumor response as a function of concomitant medications

Antibiotics

The study population as a whole. Overall, 112 patients (30.1%) were exposed to ATBs, with intravenous administration in 39 patients (34.8%) and oral administration in 73 (65.2%). The most frequently prescribed first-line drug class was penicillin ($n=75$, 70.0%). A total of 36 patients (32.1%) received two courses of ATB for the same infection or for separate infections, 10 patients (8.9%) received three courses, and 1 patient (2.0%) received five courses. In 88 of the patients (78.6%), ATBs were prescribed for a pre-existing infection. There were 47 cases of nonsystemic infection (42.0%), 25 cases of systemic inflammatory response syndrome (22.3%), 10 cases of sepsis (8.9%), 3 cases of severe sepsis (2.7%), and 2 cases of septic shock (1.8%). The median (interquartile range) cumulative duration of all ATB treatments for all lines was 14.50 (7.75–30.50) days. A total of 44 of the 88 patients with a pre-existing infection (50.0%) had been hospitalized for that reason (Table 2).

The ATB+ and ATB- groups differed with regard to several prognostic factors at baseline. Patients in the ATB+ group were younger than those in the ATB- group (mean \pm SD age: 62.1 ± 12.4 versus 64.8 ± 12.0 years, respectively; $p=0.048$). Relative to the ATB- group, the ATB+ group had a higher proportion of patients with alcohol consumption (28.1% versus 46.4%, respectively; $p<0.001$) and a higher proportion of patients with lung cancer (40.0% versus 55.4%, respectively; $p=0.009$). However, the proportion of patients with metastatic cancer was higher in the ATB- group than in the ATB+ group (81.2% versus 58.0%, respectively; $p<0.001$), and the duration of cancer was longer in the ATB- group than in the ATB+ group [median (interquartile range): 16.0 (7.6–38.8) versus 10.2 (5.2–19.5) months respectively; $p=0.001$, Table 1]. With regard to factors that could have modified the gut microbiota, the two groups were well balanced for the use of medications other than ATBs, except for levothyroxine (3.6% in the ATB- group versus 13.8% in the ATB+ group; $p=0.006$, Table 1). Furthermore, the use of food supplements was more frequently reported in the ATB+ group than in the ATB- group (27.7% versus 10.4%, respectively; $p<0.001$, Table 1).

Of the 112 patients in the ATB+ group and the 260 patients in the ATB- group, respectively 81

(72.3%) and 146 (56.2%) died during the study period. The median (95% CI) OS time was significantly lower in the ATB+ group than in the ATB- group [39.3 (30.9–54.1) versus 96.9 (64.1–152.4) weeks, respectively; crude hazard ratio (HR) (95% CI): 1.75 (1.33–2.30); $p<0.001$ in a log-rank test; Figure 1]. The duration of ATB administration did not influence OS [median (95% CI) OS time: 39.8 (30.9–71.1) weeks in patients with an ATB duration <14.5 days versus 39.3 (26.0–56.9) weeks in patients with an ATB duration >14.5 days; crude HR (95% CI): 0.99 (0.64–1.53), $p=1.000$ in a log-rank test, Supplementary Figure S1]. Intravenous ATB administration was associated with poorer OS than oral ATB administration [median (95% CI) OS time: 31.1 (21.7–53.6) versus 42.7 (33.1–75.3) respectively; crude HR (95% CI): 1.59 (1.02–2.49), $p=0.040$ in a log-rank test, Supplementary Figure S2]. The results of the multivariate analysis confirmed these trends; OS was significantly shorter in the ATB+ group than in the ATB- group [adjusted HR (95% CI): 1.38 (1.00–1.90); $p=0.048$]. Furthermore, a higher ECOG performance status was associated with a shorter survival time [adjusted HR (95% CI): 2.73 (1.92–3.89), $p<0.001$], as was the use of corticosteroids for an indication other than an irAE [adjusted HR (95% CI): 1.33 (1.04–2.19), $p=0.046$] but not for an irAE [adjusted HR (95% CI): 1.03 (0.55–1.94), $p=0.926$, Table 3].

The proportion of responders was higher in the ATB- group than in the ATB+ group (33.1% versus 8.1% respectively; $p<0.001$, Figure 2). After adjustment for confounding variables, the logistic regression analysis confirmed this trend [adjusted OR (95% CI): 6.06 (2.80–14.53), $p<0.001$]. Furthermore, a higher ECOG performance status was associated with a worse tumor response [adjusted OR (95% CI): 2.71 (1.17–6.93), $p=0.026$], as was the use of corticosteroids for an indication other than an irAE [adjusted OR (95% CI): 1.90 (1.03–5.45), $p=0.048$] but not for an irAE [adjusted HR (95% CI): 1.57 (0.48–6.05), $p=0.480$, Table 4].

Regarding ATB use, the results were similar when adding the variables diabetes mellitus, hypertension, dyslipidemia, the number of metastatic sites and the number of lines of ICI treatment to the models [adjusted HR (95% CI): 1.34 (1.05–1.85), $p=0.045$ for OS, Supplementary Table S1; adjusted OR (95% CI): 5.97 (2.70–14.57), $p<0.001$ for the tumor response, Supplementary Table S2].

Table 2. Description of infections and ATBs.

	ATB therapy group <i>n</i> = 112
Indication for ATBs	
Infection site	
Lungs, <i>n</i> (%)	46 (41.1)
Skin, <i>n</i> (%)	9 (8.0)
Oropharyngeal tract or dental, <i>n</i> (%)	4 (3.6)
Urinary tract, <i>n</i> (%)	7 (6.2)
Digestive tract, <i>n</i> (%)	3 (2.7)
Osteitis, <i>n</i> (%)	1 (0.9)
Sepsis, <i>n</i> (%)	18 (16.1)
Prophylactic ATB therapy, <i>n</i> (%)	4 (3.6)
Unknown indication, <i>n</i> (%)	20 (17.9)
Severity of infection	
Nonsystemic infection, <i>n</i> (%)	47 (42.0)
SIRS, <i>n</i> (%)	25 (22.3)
Sepsis, <i>n</i> (%)	10 (8.9)
Severe sepsis, <i>n</i> (%)	3 (2.7)
Septic shock, <i>n</i> (%)	2 (1.8)
Hospitalization due to infection, <i>n</i> (%)	44 (39.3)
Intensive care, <i>n</i> (%)	3 (2.7)
ATBs	
Administration route	
Intravenous, <i>n</i> (%)	39 (34.8)
Oral, <i>n</i> (%)	73 (65.2)
First-line treatment	<i>n</i> = 112
Amoxicillin, <i>n</i> (%)	10 (8.9)
Amoxicillin + metronidazole, <i>n</i> (%)	1 (0.9)
Amoxicillin + clarithromycin + metronidazole, <i>n</i> (%)	1 (0.9)
Amoxicillin/clavulanic acid, <i>n</i> (%)	51 (45.5)
Amoxicillin/clavulanic acid + ciprofloxacin, <i>n</i> (%)	1 (0.9)
Amoxicillin/clavulanic acid + metronidazole, <i>n</i> (%)	1 (0.9)
Azithromycin, <i>n</i> (%)	1 (0.9)
Cefazolin, <i>n</i> (%)	1 (0.9)
Cefpodoxime, <i>n</i> (%)	1 (0.9)
Ceftazidime + ciprofloxacin, <i>n</i> (%)	1 (0.9)

(Continued)

Table 2. (Continued)

	ATB therapy group <i>n</i> = 112
Ceftriaxone, <i>n</i> (%)	4 (3.7)
Ceftriaxone + metronidazole, <i>n</i> (%)	3 (2.8)
Ceftriaxone + spiramycin, <i>n</i> (%)	1 (0.9)
Cefuroxime, <i>n</i> (%)	3 (2.8)
Ciprofloxacin, <i>n</i> (%)	1 (0.9)
Ciprofloxacin + clindamycin, <i>n</i> (%)	1 (0.9)
Ciprofloxacin + piperacillin/tazobactam, <i>n</i> (%)	1 (0.9)
Cotrimoxazole, <i>n</i> (%)	3 (2.8)
Daptomycin, <i>n</i> (%)	1 (0.9)
Daptomycin + cefepime, <i>n</i> (%)	1 (0.9)
Doxycycline, <i>n</i> (%)	5 (4.5)
Doxycycline + levofloxacin, <i>n</i> (%)	1 (0.9)
Imipenem/cilastatin + amikacin, <i>n</i> (%)	1 (0.9)
Levofloxacin, <i>n</i> (%)	2 (1.8)
Metronidazole, <i>n</i> (%)	1 (0.9)
Piperacillin/tazobactam, <i>n</i> (%)	4 (3.7)
Piperacillin/tazobactam + amikacin, <i>n</i> (%)	2 (1.8)
Piperacillin/tazobactam + amikacin + spiramycin, <i>n</i> (%)	1 (0.9)
Piperacillin/tazobactam + gentamicin + daptomycin, <i>n</i> (%)	1 (0.9)
Piperacillin/tazobactam + gentamicin + vancomycin, <i>n</i> (%)	1 (0.9)
Pristinamycin, <i>n</i> (%)	3 (2.8)
Roxithromycin, <i>n</i> (%)	1 (0.9)
Second-line treatment	<i>n</i> = 36
Amoxicillin, <i>n</i> (%)	2 (5.5)
Amoxicillin/clavulanic acid, <i>n</i> (%)	11 (30.5)
Amoxicillin/clavulanic acid + vancomycin, <i>n</i> (%)	1 (2.8)
Cefepime, <i>n</i> (%)	1 (2.8)
Cefixime, <i>n</i> (%)	1 (2.8)
Ceftazidime, <i>n</i> (%)	1 (2.8)
Ceftriaxone, <i>n</i> (%)	1 (2.8)
Ceftriaxone + metronidazole, <i>n</i> (%)	1 (2.8)
Ciprofloxacin, <i>n</i> (%)	3 (8.2)

(Continued)

Table 2. (Continued)

	ATB therapy group <i>n</i> = 112
Ciprofloxacin + metronidazole, <i>n</i> (%)	1 (2.8)
Cotrimoxazole, <i>n</i> (%)	1 (2.8)
Imipenem/cilastatin + amikacin, <i>n</i> (%)	1 (2.8)
Linezolid, <i>n</i> (%)	2 (5.5)
Linezolid + amoxicillin, <i>n</i> (%)	1 (2.8)
Linezolid + imipenem/cilastatin	1 (2.8)
Metronidazole, <i>n</i> (%)	2 (5.5)
Piperacillin/tazobactam, <i>n</i> (%)	1 (2.8)
Piperacillin/tazobactam + ciprofloxacin, <i>n</i> (%)	1 (2.8)
Roxithromycin, <i>n</i> (%)	1 (2.8)
Telithromycin, <i>n</i> (%)	1 (2.8)
Vancomycin, <i>n</i> (%)	1 (2.8)
Third-line treatment	<i>n</i> = 10
Amoxicillin/clavulanic acid, <i>n</i> (%)	1 (10.0)
Ceftozolane/tazobactam + cefepime, <i>n</i> (%)	1 (10.0)
Ceftriaxone, <i>n</i> (%)	1 (10.0)
Ceftriaxone + spiramycin, <i>n</i> (%)	1 (10.0)
Gentamicin, <i>n</i> (%)	1 (10.0)
Piperacillin/tazobactam, <i>n</i> (%)	2 (20.0)
Piperacillin/tazobactam + ciprofloxacin, <i>n</i> (%)	1 (10.0)
Roxithromycin, <i>n</i> (%)	1 (10.0)
Spiramycin	1 (10.0)
Fourth-line treatment	<i>n</i> = 1
Ceftriaxone + spiramycin, <i>n</i> (%)	1 (100)
Fifth-line treatment	<i>n</i> = 1
Amikacin + ceftazidime, <i>n</i> (%)	1 (100)
Discontinuation of ICI due to infection, <i>n</i> (%)	24 (21.4)
Time between infection and death or loss to follow-up	<i>n</i> = 88
<4 weeks, <i>n</i> (%)	9 (10.2)
>4 weeks, <i>n</i> (%)	79 (89.8)

ATB, antibiotic; ICI, immune checkpoint inhibitor; SIRS, systemic inflammatory response syndrome.

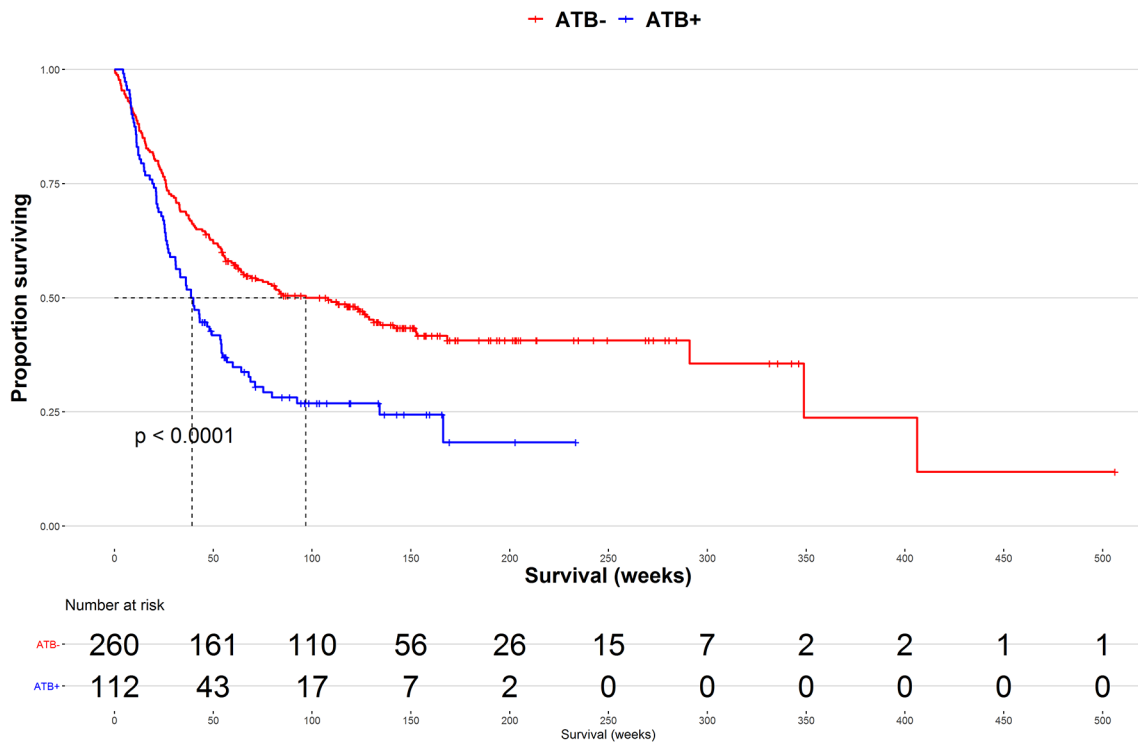


Figure 1. OS as a function of ATB use (the ATB- group *versus* the ATB+ group). ATB, antibiotic; OS, overall survival.

The results of sensitivity analyses of patients exposed to ATBs in the 30 or 60 days preceding or following ICI initiation confirmed these trends. The median OS time was shorter (1) in the ATB+30 group than in the ATB-30 group [36.1 (26.0–46.9) *versus* 83.3 (63.6–131.1) respectively, crude HR (95% CI): 1.87 (1.38–2.53), $p < 0.001$ in a log-rank test, Supplementary Figure S3(a)] and (2) in the ATB+60 group than in the ATB-60 group [37.6 (27.3–49.3) *versus* 96.9 (63.6–141.4) weeks respectively; crude HR (95% CI): 1.79 (1.35–2.37), $p < 0.001$ in a log-rank test, Supplementary Figure S3(b)]. In Cox proportional hazards models, ATB exposure within 30 days was still associated with poorer OS [adjusted HR (95% CI): 1.67 (1.17–2.38), $p = 0.004$, Supplementary Table S3], as was ATB exposure in the 60 days [adjusted HR (95% CI): 1.47 (1.05–2.04), $p = 0.022$, Supplementary Table S4]. The proportion of responders was lower (1) in the ATB+30 group than in the ATB-30 group [10.5% *versus* 29.4% *versus* respectively; $p = 0.003$, Supplementary Figure S4(a)] and (2) in the ATB+60 group than in the ATB-60 group [9.0% *versus* 31.6%, respectively; $p < 0.001$, Supplementary Figure S4(b)]. The

results of multivariate analyses showed that ATB exposure within 30 days was still associated with a worse tumor response [adjusted OR (95% CI): 3.11 (1.37–7.92), $p = 0.011$, Supplementary Table S5] as well as ATB exposure in the 60 days [adjusted OR (95% CI): 4.21 (1.95–10.05), $p < 0.001$, Supplementary Table S6].

In a sensitivity analysis that excluded patients who died within 4 weeks of ATB discontinuation ($n = 9$), OS was shorter in the ATB+ group than in the ATB- group [median (95% CI) OS time: 43.0 (36.1–56.9) *versus* 96.9 (64.1–152.4) weeks, respectively; crude HR (95% CI): 1.59 (1.19–2.12); $p = 0.001$ in a log-rank test; Supplementary Figure S5(a)]. There was no significant difference in OS between (1) patients having discontinued the ICI due to the infection and those not having discontinued the ICI [median (95% CI) OS time: 31.1 (23.7–NA) *versus* 39.9 (30.9–54.7) weeks, respectively; crude HR (95% CI): 1.06 (0.62–1.81), $p = 0.840$ in a log-rank test, Supplementary Figure S5(b)], (2) patients hospitalized for an infection and those not hospitalized [median (95% CI) OS time: 26.9 (22.3–46.9) *versus* 49.3 (36.1–68.9) weeks, respectively;

Table 3. Univariate and multivariate analysis of overall survival (Cox regression model).

	N (%)	Crude model		Adjusted model	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	372 (100)	1.00 (0.99–1.01)	0.556	1.01 (0.99–1.02)	0.307
Body mass index	372 (100)	0.95 (0.93–0.98)	<0.001	0.99 (0.95–1.02)	0.402
Sex					
Male	244 (65.6)	Reference		Reference	
Female	128 (34.4)	0.80 (0.60–1.06)	0.100	0.80 (0.57–1.10)	0.172
Smoking					
Never	104 (28.0)	Reference		Reference	
Current or past	268 (72.0)	1.65 (1.22–2.26)	0.001	0.98 (0.65–1.49)	0.936
Alcohol consumption					
No	247 (66.4)	Reference		Reference	
Yes	125 (33.6)	1.57 (1.20–2.06)	<0.001	1.20 (0.85–1.70)	0.303
History of cardiovascular disease					
Absence of cardiovascular disease	269 (72.3)	Reference		Reference	
Presence of cardiovascular disease	103 (27.7)	1.10 (0.82–1.46)	0.500	0.85 (0.62–1.16)	0.299
Type of cancer					
Lung	166 (44.6)	Reference		Reference	
Melanoma	110 (29.6)	0.45 (0.32–0.63)	<0.001	1.14 (0.61–2.15)	0.677
Renal and urothelial	27 (7.3)	0.76 (0.45–1.28)	0.306	0.89 (0.38–2.11)	0.789
Head and neck	48 (12.9)	1.05 (0.70–1.57)	0.824	0.69 (0.43–1.12)	0.129
Hodgkin lymphoma	5 (1.3)	0.45 (0.11–1.81)	0.260	0.47 (0.11–2.07)	0.318
Digestive	4 (1.1)	6.08 (2.19–16.85)	<0.001	4.03 (1.22–13.37)	0.023
Cutaneous squamous cell carcinoma	1 (0.3)	3.27 (0.45–23.58)	0.240	5.70 (0.69–49.80)	0.105
Adenocarcinoma of unknown primary	5 (1.3)	0.46 (0.11–1.86)	0.275	0.66 (0.16–2.79)	0.572
Squamous cell carcinoma of unknown primary	5 (1.3)	0.86 (0.27–2.70)	0.794	0.34 (0.10–1.16)	0.084
Porocarcinoma	1 (0.3)	2.11 (0.29–15.15)	0.459	2.80 (0.33–23.69)	0.343
Cancer duration	372 (100)	1.00 (0.99–1.00)	0.081	1.00 (0.99–1.00)	0.337
ECOG performance status					
0–1	295 (79.3)	Reference		Reference	
2–4	77 (20.7)	2.90 (2.15–3.90)	<0.001	2.73 (1.92–3.89)	<0.001

(Continued)

Table 3. (Continued)

	N (%)	Crude model		Adjusted model	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Metastatic cancer					
No	96 (25.8)	Reference		Reference	
Yes	276 (74.2)	0.74 (0.55–0.98)	0.040	0.89 (0.62–1.28)	0.538
Brain metastasis					
No	343 (92.2)	Reference		Reference	
Yes	29 (7.8)	1.13 (0.70–1.83)	0.600	1.25 (0.70–2.23)	0.453
Prior conventional chemotherapy					
No	153 (41.1)	Reference		Reference	
Yes	219 (58.9)	1.72 (1.30–2.28)	<0.001	1.53 (0.95–2.46)	0.081
Prior targeted chemotherapy					
No	306 (82.3)	Reference		Reference	
Yes	66 (17.7)	1.17 (0.83–1.63)	0.400	1.27 (0.78–2.07)	0.338
ICIs					
Nivolumab	217 (58.3)	Reference		Reference	
Pembrolizumab	130 (34.9)	0.58 (0.43–0.77)	<0.001	0.64 (0.44–0.94)	0.023
Ipilimumab	15 (4.0)	0.36 (0.17–0.78)	0.009	0.46 (0.18–1.15)	0.096
Nivolumab + ipilimumab	10 (2.7)	0.56 (0.21–1.50)	0.247	1.07 (0.36–3.24)	0.900
ATB use					
No	260 (69.9)	Reference		Reference	
Yes	112 (30.1)	1.75 (1.33–2.30)	<0.001	1.38 (1.00–1.90)	0.048
PPI use					
No	223 (59.9)	Reference		Reference	
Yes	149 (40.1)	0.84 (0.54–1.29)	0.150	0.80 (0.60–1.08)	0.148
Opioid use					
No	199 (53.5)	Reference		Reference	
Yes	173 (46.5)	1.82 (1.40–2.37)	<0.001	1.33 (0.99–1.79)	0.057
Metformin use					
No	355 (95.4)	Reference		Reference	
Yes	17 (4.6)	0.77 (0.40–1.51)	0.500	0.75 (0.36–1.58)	0.455

(Continued)

Table 3. (Continued)

	N (%)	Crude model		Adjusted model	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Levothyrox use					
No	332 (89.2)	Reference		Reference	
Yes	40 (10.8)	0.83 (0.54–1.29)	0.400	1.06 (0.65–1.72)	0.822
Oral corticosteroid use for an irAE					
No	351 (94.4)	Reference		Reference	
Yes	21 (5.6)	1.25 (0.53–1.71)	0.900	1.03 (0.55–1.94)	0.926
Oral corticosteroid use for another indication					
No	316 (84.9)	Reference		Reference	
Yes	56 (15.1)	1.35 (0.96–1.90)	0.087	1.33 (1.04–2.19)	0.046
Use of food supplements					
No	314 (84.4)	Reference		Reference	
Yes	58 (15.6)	1.58 (1.13–2.22)	0.007	1.00 (0.68–1.47)	0.990

ATB, antibiotic; AVK, anti-vitamin K; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; NSAID: nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

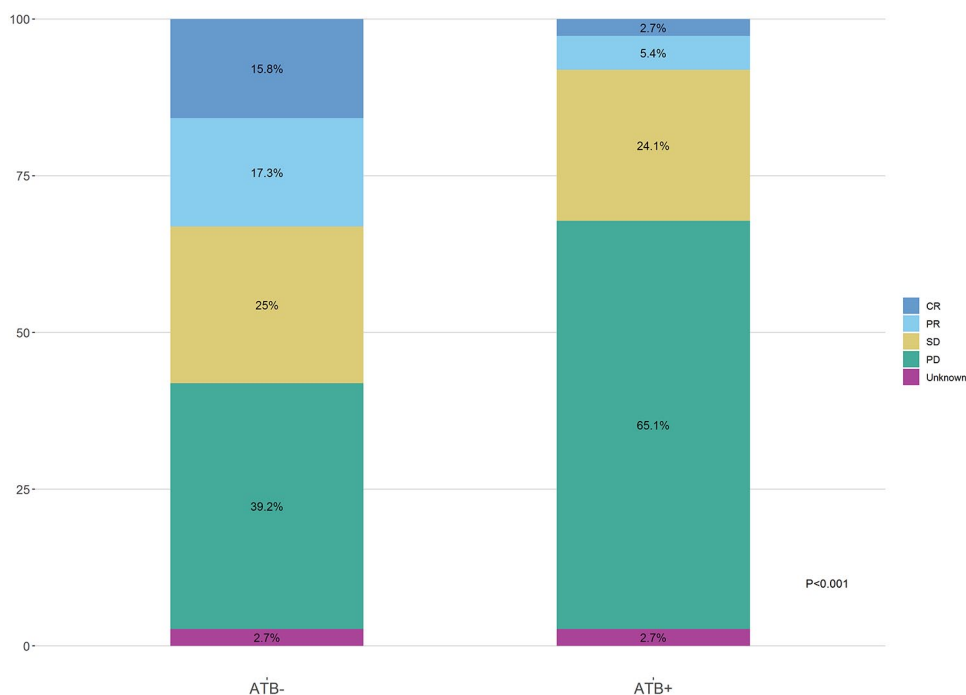


Figure 2. The best overall tumor response as a function of ATB use (the ATB- group versus the ATB+ group). ATB, antibiotic; CR, complete response; PD, progression of disease; PR, partial response; SD, stable disease.

Table 4. Univariate and multivariate analysis (logistic regression) of the tumor response (comparison of nonresponders with responders, according to the RECIST 1.1 criteria).

	N (%)*	Crude model		Adjusted model	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age	362 (100)	1.00 (0.99–1.02)	0.640	1.01 (0.99–1.04)	0.307
Body mass index	362 (100)	0.94 (0.90–0.98)	0.003	1.00 (0.94–1.05)	0.867
Sex					
Male	237 (65.5)	Reference		Reference	
Female	125 (34.5)	0.73 (0.45–1.18)	0.193	0.68 (0.36–1.30)	0.241
Smoking					
Never	101 (27.9)	Reference		Reference	
Current or past	261 (72.1)	1.78 (1.07–2.93)	0.025	0.75 (0.35–1.62)	0.471
Alcohol consumption					
No	239 (66.0)	Reference		Reference	
Yes	123 (34.0)	1.51 (0.91–2.57)	0.115	0.87 (0.42–1.78)	0.693
History of cardiovascular disease					
Absence of cardiovascular disease	263 (72.7)	Reference		Reference	
Presence of cardiovascular disease	99 (27.3)	1.45 (0.85–2.57)	0.183	1.08 (0.55–2.16)	0.824
Type of cancer					
Lung	158 (43.6)	2.27 (1.39–3.80)	0.001	0.80 (0.19–2.73)	0.738
Melanoma	108 (29.3)	0.28 (0.17–0.46)	<0.001	0.77 (0.16–3.25)	0.730
Renal and urothelial	27 (7.5)	1.61 (0.64–4.94)	0.347	2.10 (0.29–14.73)	0.457
Head and neck	48 (13.3)	1.22 (0.62–2.63)	0.574	0.54 (0.10–2.40)	0.429
Cancer duration	362 (100)	0.99 (0.99–1.00)	0.045	0.99 (0.99–1.00)	0.055
ECOG performance status					
0–1	288 (79.6)	Reference		Reference	
2–4	74 (20.4)	3.57 (1.73–8.35)	0.001	2.71 (1.17–6.93)	0.026
Metastatic cancer					
No	95 (26.2)	Reference		Reference	
Yes	267 (73.8)	0.87 (0.50–1.47)	0.600	1.23 (0.59–2.56)	0.580
Brain metastasis					
No	335 (92.5)	Reference		Reference	
Yes	27 (7.5)	1.27 (0.52–3.54)	0.622	1.86 (0.55–6.98)	0.334
Prior conventional chemotherapy					
No	151 (41.7)	Reference		Reference	
Yes	211 (58.3)	2.60 (1.62–4.22)	<0.001	1.82 (0.76–4.35)	0.175

(Continued)

Table 4. (Continued)

	N (%)*	Crude model		Adjusted model	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Prior targeted chemotherapy					
No	296 (81.8)	Reference		Reference	
Yes	66 (18.2)	1.03 (0.57–1.94)	0.921	0.95 (0.39–2.40)	0.917
ICIs					
Nivolumab	209 (57.7)	Reference		Reference	
Pembrolizumab	128 (35.4)	0.48 (0.29–0.80)	0.004	0.73 (0.34–1.56)	0.408
Ipilimumab	15 (4.1)	0.49 (0.16–1.64)	0.212	1.23 (0.28–5.69)	0.780
Nivolumab + ipilimumab	10 (2.8)	0.16 (0.04–0.60)	0.007	0.24 (0.04–1.31)	0.107
ATB use					
No	253 (69.9)	Reference		Reference	
Yes	109 (30.1)	5.72 (2.90–12.67)	<0.001	6.06 (2.80–14.53)	<0.001
PPI use					
No	217 (59.4)	Reference		Reference	
Yes	145 (40.6)	1.87 (1.14–3.12)	0.015	1.57 (0.85–2.91)	0.150
Opioid use					
No	195 (53.9)	Reference		Reference	
Yes	167 (46.1)	2.60 (1.59–4.34)	<0.001	1.63 (0.88–3.06)	0.123
Metformin use					
No	345 (95.3)	Reference		Reference	
Yes	17 (4.7)	0.38 (0.14–1.04)	0.053	0.51 (0.14–1.76)	0.283
Levothyroxine use					
No	323 (89.2)	Reference		Reference	
Yes	39 (10.8)	0.89 (0.44–1.95)	0.768	1.44 (0.58–3.71)	0.434
Oral corticosteroid use for an irAE					
No	341 (94.2)	Reference		Reference	
Yes	21 (5.8)	0.88 (0.35–2.54)	0.803	1.57 (0.48–6.05)	0.480
Oral corticosteroid use for another indication					
No	311 (85.9)	Reference		Reference	
Yes	51 (14.1)	2.48 (1.14–6.21)	0.033	1.90 (1.03–5.45)	0.048
Use of food supplements					
No	304 (84.0)	Reference		Reference	
Yes	58 (16.0)	5.77 (2.28–19.45)	0.001	3.40 (1.14–13.09)	0.045

*10 patients were excluded from the analysis because of missing data for the best overall response.

ATB, antibiotic; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; OR, odds ratio; PPI, proton pump inhibitor.

crude HR (95% CI): 1.48 (0.95–2.30), log-rank $p=0.081$, Supplementary Figure S5(c)], or (3) patients with a severe infection and those with a mild infection [median (95% CI) OS time: 26.9 (23.7–59.9) *versus* 45.6 (33.3–64.1) weeks, respectively; crude HR (95% CI): 1.31 (0.83–2.05), $p=0.240$ in a log-rank test, Supplementary Figure S5(d)].

OS did not differ in patients treated with amoxicillin or amoxicillin/clavulanic acid ($n=70$) *versus* patients treated with other ATBs [$n=42$; median (95% CI) OS time: 40.1 (27.3–56.9) *versus* 37.6 (26.6–64.1) weeks, respectively; crude HR (95% CI): 0.91 (0.58–1.42), $p=0.700$ in a log-rank test]. Furthermore, OS was significantly lower in patients treated with amoxicillin or amoxicillin/clavulanic acid than in patients in the ATB– group [median (95% CI) OS time: 40.1 (27.3–56.9) *versus* 96.9 (64.1–152.4) weeks, respectively; crude HR (95% CI): 1.69 (1.22–2.34), $p=0.001$ in a log-rank test]. Lastly, OS did not differ in patients treated with amoxicillin ($n=9$) *versus* those treated with amoxicillin/clavulanic acid [$n=61$; median (95% CI) OS time: 31.0 (21.0–NA) *versus* 42.7 (27.3–NA) weeks, respectively; crude HR (95% CI): 0.68 (0.32–1.46), $p=0.330$ in a log-rank test, Supplementary Figure S6].

Patients with melanoma. Overall, 16 of the 110 patients in the melanoma subgroup (14.5%) received ATBs. The baseline characteristics were similar in the ATB– and ATB+ groups, except that the proportion of PPI users was lower in the ATB+ group than in the ATB– group (12.5% *versus* 39.4%, respectively; $p=0.048$, Supplementary, Table S7). OS was shorter in the melanoma ATB+ group than in the melanoma ATB– group [median (95% CI) OS time: 68.9 (21.3–NA) *versus* 291.0 (128.9–NA) weeks, respectively; crude HR (95% CI): 2.27 (1.09–4.71), log-rank $p=0.024$, Supplementary Figure S7]. The Cox proportional hazards model confirmed this result [adjusted HR (95% CI): 2.60 (1.06–6.39), $p=0.037$]. Furthermore, the use or oral corticosteroids for an indication other than an irAE was associated with significantly poorer OS [adjusted HR (95% CI): 4.84 (1.86–12.64), $p<0.001$], whereas the use of corticosteroids for an irAE was not [adjusted HR (95% CI): 3.33 (0.61–18.30), $p=0.167$, Supplementary, Table S8].

The proportion of responders was higher in the melanoma ATB– group than in the melanoma

ATB+ group (46.8% *versus* 25.0%) but this difference was not significant ($p=0.116$, Supplementary Figure S8). After adjustment for confounding variables, the logistic regression analysis showed a significant association between ATB use and a worse tumor response [adjusted OR (95% CI): 4.41 (1.04–22.80), $p=0.045$]. Furthermore, the use of corticosteroids for an indication other than an irAE was associated with a worse tumor response [adjusted OR (95% CI): 4.97 (1.05–65.83), $p=0.039$] whereas the use of corticosteroids for an irAE was not [adjusted HR (95% CI): 1.96 (0.15–31.10), $p=0.609$, Supplementary Table S9].

Other drugs. OS did not differ significantly when comparing patients having received NSAIDs, PPIs, statins, AVK anticoagulants, levothyroxine, cholecalciferol, phloroglucinol, metformin or antiarrhythmics with patients not having received these drugs (Supplementary Figure S9). The same was true for the tumor response, except for patients treated with PPIs (response rate: 18.8% *versus* 30.1% in the other patients; $p=0.036$) or metformin (response rate: 47.1% *versus* 24.5% in the other patients; $p=0.020$; Supplementary Figure S10). Since only one patient received psychotropic medication (escitalopram), we did not analyze that drug class.

In patients treated with opioids (the Opioids+ group), the median (95% CI) OS time was significantly shorter than in patient who were not treated with opioids [the Opioids– group; 36.6 (26.6–48.1) *versus* 126.4 (77.7–168.4) weeks, respectively; crude HR (95% CI): 1.82 (1.40–2.37), $p<0.001$, Supplementary Figure S9(d)]. Moreover, the response rate in the Opioids+ group was lower than in the Opioids– group [16.2 *versus* 33.7, respectively; $p<0.001$, Supplementary Figure S10(d)]. In bivariate analyses, patients in the Opioids+ group had a worse prognosis than patients in the Opioids– group: the mean \pm SD BMI was lower (23.5 ± 5.0 *versus* 25.9 ± 5.6 , respectively; $p<0.001$), the prevalence of smoking was higher (82.1% *versus* 63.3%, respectively; $p<0.001$), the prevalence of alcohol consumption was higher (39.3% *versus* 28.6%, respectively; $p=0.039$) and the proportion of patients with a poor ECOG performance status was higher (31.2% *versus* 11.4%, $p<0.001$, respectively; Supplementary, Table S10). This trend was no longer significant after adjustment for confounding factors [adjusted HR (95% CI): 1.33 (0.99–1.79), $p=0.057$, Table 3].

The characteristics of patients taking NSAIDs, PPIs, statin, AVK, levothyroxine, cholecalciferol, antiarrhythmic, metformin, phloroglucinol or corticosteroids are summarized in Supplementary Tables S10–S20.

Discussion

Our present results showed that in a population of patients receiving ICIs (regardless of the indication), treatment with ATBs was associated with poorer OS [adjusted HR (95% CI): 1.38 (1.00–1.90); $p=0.048$] and a worse tumor response [adjusted OR (95% CI): 6.06 (2.80–14.53), $p<0.001$]. These findings are in line with some of the literature data,^{10,16,17,19,22} with a similar effect size (the adjusted HR) for OS. However, other studies have not found a negative association between ATB use and OS or the tumor response.^{15,20,21} There are several possible explanations for this disparity in the literature data. Firstly, it is difficult to set an optimal time cut-off when considering whether or not ATB use influences the effectiveness of ICIs. For example, the findings of Derosa *et al.*²² varied as a function of the cut-off: ATBs were associated with poorer OS when the treatment was initiated 30 days before ICI initiation but not when the cut-off considered was 60 days. This prompted us to take account of the time needed for the gut microbiota to recover after ATB discontinuation (according to the literature) for each molecule.¹³ However, the results of our sensitivity analyses showed poorer OS and a worse tumor response regardless of the cut-off (ATB exposure in the 30 or 60 days preceding or following ICI initiation). Secondly, the nature of the dysbiosis differs from one class of ATBs to another.¹³ For instance, vancomycin might boost the antitumor effects of CTLA-4 blockade, presumably by inducing an increase in the proportion of Bacteroidales.¹⁴ Again, we took this parameter in account by consulting the literature data.¹³ Thirdly, the previously published studies did not consider indication bias (i.e. with death being linked to the infection that prompted ATB use). In the present study, we minimized this bias by excluding patients who died or were lost to follow-up within 4 weeks of ATB discontinuation (considering that censorship could be linked to death); after this adjustment, the OS time was still shorter in the ATB+ group than in the ATB– group [crude HR (95% CI): 1.59 (1.19–2.12); $p=0.001$]. Within the ATB+ group, there was no difference in OS between patients with severe infections [i.e. those requiring hospitalization

(crude HR (95% CI): 1.48 (0.95–2.30), $p=0.081$)] or who met the international criteria for sepsis³⁹ [crude HR (95% CI): 1.31 (0.83–2.05), $p=0.240$] and the other patients, or between patients who discontinued ICIs as a result of the infection and the other patients [crude HR (95% CI): 1.06 (0.62–1.81), $p=0.840$]. Hence, these factors did not explain why OS was worse in the ATB+ group. Furthermore, recent *post hoc* analyses of randomized trials showed a negative impact of ATB use in patients treated with the anti-PD-L1 atezolizumab, relative to those in the control arm (conventional chemotherapy), reinforcing the validity of our results.^{23,24}

The vast majority of the previously cited studies focused on NSCLC, renal cell carcinoma or UC. Very few published studies have examined the impact of ATB use on OS and the tumor response in melanoma patients treated with ICIs. There were 10 patients with melanoma in Iglesias-Santamaría's study²¹ and 179 in the study of Tinsley *et al.*¹⁹ but neither of the studies specifically studied the association between ATB use and OS. In the present study, OS was lower in the ATB+ group than in the ATB– group when considering the 110 patients with melanoma [adjusted HR (95% CI): 2.60 (1.06–6.39), $p=0.037$], and ATB use was associated with a worse tumor response in this population [adjusted OR (95% CI): 4.41 (1.04–22.80), $p=0.045$], despite the fact that few ($n=16$, 14.5%) had received ATBs. This finding emphasizes the significance of our results.

We also focused on patients receiving the β -lactamase inhibitor amoxicillin or amoxicillin/clavulanic acid, since (1) these drugs might increase the abundance of the Bacteroidales and *Bifidobacterium* species in the gut microbiota,¹³ which appear to boost the effectiveness of ICIs,^{10,14,37,38} and (2) this class of ATB is widely prescribed. However, in our population, the OS (95% CI) time was significantly shorter in the amoxicillin or amoxicillin/clavulanic acid group than in the ATB– group [40.1 (27.3–56.9) *versus* 96.9 (64.1–152.4) weeks, respectively; crude HR (95% CI): 1.69 (1.22–2.34), $p=0.001$ in a log-rank test], showing that the use of these drugs is also associated with poorer clinical outcomes.

In the present study, exposure to other known dysbiosis-inducing drugs (except for opioids) was not associated with a difference in OS, perhaps

because of a low impact on the gut microbiota. However, it has been demonstrated that these drug classes induce dysbiosis. The use of PPIs is associated with a greater abundance of *Bifidobacterium* species,⁴⁴ which might boost the effectiveness of ICIs, but also with a decrease in the alpha diversity of the gut microbiota. Alpha diversity appears to be associated with higher response rates in ICI-treated patients with melanoma.^{45,46} These changes in the gut microbiota result from a decrease in stomach acidity and the compounds' direct effects.^{28,45–46} Retrospective studies have given conflicting results; some have shown poorer clinical outcomes in ICI-treated patients exposed to PPIs,⁴⁷ while others did not show a significant association^{15,21} and yet others showed better clinical outcomes in this population.^{48,49} In the present study, we failed to show an association between PPI use and clinical outcomes (OS and the tumor response) in multivariate analyses. However, recent *post hoc* analyses of randomized trials, with larger cohorts and without the inherent biases of retrospective studies, showed a negative impact of PPI use on OS and progression-free survival in patients treated with ICIs compared with patients treated with conventional chemotherapy.^{24,50} There are several possible explanations for these conflicting results. Firstly, the small sample size of retrospective studies, including ours, leads to a low statistical power and might prevent the identification of associations. Secondly, the heterogeneity of the population in retrospective studies (in terms of the type of cancer, the number of previous lines of chemotherapy, the type of ICI (anti-PD-L1 and anti-CTLA-4 agents) and the baseline characteristics) might create issues that might not be addressed in the multivariate analyses and might increase residual confounding bias. Indeed, the randomized trials performed by Hopkins *et al.*⁵⁰ and by Chalabi *et al.*²⁴ focused on patients with UC and NSCLC, respectively, and all the patients in the ICI arm were treated with the anti-PD-L1 atezolizumab. Moreover, all these patients were treatment-naïve or had been treated with only one or two cytotoxic chemotherapy regimens before inclusion in the trials, and none had received targeted chemotherapy. In contrast, some of patients in our cohort had received many lines of treatment, including targeted chemotherapy. Indeed, the PPIs' dysbiosis effect on ICI may be more pronounced during early lines of treatment because late-stage tumor cells can evolve novel strategies to escape immunosurveillance.⁵¹

Opioid use might affect the composition of the gut microbiota by activating opioid receptors and thus reducing intestinal motility.³⁴ Moreover, tramadol shows bactericidal activity *in vitro*,⁵² and a clinical study has described opioid-induced dysbiosis.³⁵ In the present study, however, opioid use was associated with poorer OS in a univariate analysis but not in a multivariate analysis. In our population, patients treated with opioids had a worse prognosis (particularly with regard to ECOG performance status) than those who were not. However, the use of opioids in patients with a worse prognosis might explain these findings. In Iglesias-Santamaría's study,²¹ opioid use was associated with poorer OS in a multivariate analysis [adjusted HR (95% CI): 3.63 (1.92–6.85); $p < 0.001$]. However, this difference might be due to the fact that (in contrast to the present study) Iglesias-Santamaría did not include ECOG performance status in the Cox model.

The present study also considered statins, NSAIDs, AVK anticoagulants, cholecalciferol, phloroglucinol, and antiarrhythmics, all of which are known to induce dysbiosis.^{26,28,31–33,46} We did not observe an association between the use of any of these drugs and OS. One can hypothesize that these drugs have less of an effect on the composition of the gut microbiota than ATBs do. Moreover, the low number of patients taking NSAIDs, AVK anticoagulants, phloroglucinol, metformin, and antiarrhythmics might have prevented us from evidencing significant associations. With regard to metformin and statins (which appear to have a protective role on gut microbiota^{26,27}), we failed to show a positive association with OS or the tumor response (except for metformin for the tumor response in bivariate analysis), as was also the case in the study of Failing *et al.*⁴⁹ This absence of an association could be related to (1) the low number of patients treated with metformin in our cohort, as mentioned above, and (2) the indications of these drugs themselves (i.e. comorbidity factors).

We found that corticosteroid use for an indication other than an irAE was associated with poorer OS and a worse tumor response, whereas corticosteroid use for an irAE was not. The fact that patients who experience irAEs survive for longer than patients without irAEs might explain these results.^{53–55} This finding is in line with studies showing that (1) the early use of corticosteroids

(which is not related to irAEs) is harmful upon ICI initiation^{40–42} and (2) the use of corticosteroids to treat irAEs during immunotherapy does not affect OS.^{56–58} Therefore, the fact that corticosteroids are not associated with poorer OS or a worse tumor response in the setting of an irAE argues that it is the indication for steroids and not the steroids themselves that affect OS. Further studies with a comparative arm are needed to explore this point.

Our study had several limitations. Firstly, the single-center, retrospective design resulted in inherent bias, including the heterogeneity of the study population. Secondly, data on several confounding factors for comorbidity in the general population (such as congestive heart failure, dementia, chronic lung disease, chronic kidney failure, connective disease, peptic ulcer, hemiplegia, cirrhosis, and HIV infection, as described in the Charlson index)⁵⁹ are lacking. Furthermore, specific prognostic factors for cancer were missing, such as PD-L1 tumor proportion score, the tumor mutational burden, the Breslow thickness or the Clark index in melanoma population. Thirdly, in the absence of a comparator arm, it is difficult to affirm that the use of any drug class has an impact on treatment effectiveness, even though we sought to minimize indication bias much as possible by performing sensitivity analyses. Fourthly, the study probably lacked statistical power for some of the analyses, especially with regards to NSAIDs, metformin, AVK anti-coagulants, phloroglucinol, and antiarrhythmics. No power thresholds were predefined. Fifthly, we did not study the gut microbiota *per se* and so could not directly confirm the induction of dysbiosis in our patients. Lastly, a number of factors known to influence the gut microbiota (such as diet, country of origin, and breast feeding) were not documented.

Conclusion

The use of ATBs (depending on their specific effects on the gut microbiota and the time needed for recovery of the latter following discontinuation) is associated with poorer OS and a lower tumor response rate in patients treated with ICIs (especially in patients with melanoma), regardless of the severity of infection. ATBs should be used with caution in clinical practice, and the prescribing physician should always take account of the risk/benefit ratio.

Author contribution statement

Louis Gaucher contributed to the conception/design of the work, acquisition and interpretation of data for the work, and drafting the manuscript. He approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Leslie Adda contributed to acquisition and interpretation of data for the work. She approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Alice Séjourné contributed to acquisition and interpretation of data for the work, and drafting the manuscript. She approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Camille Joachim revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Chaby Guillaume revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Claire Poulet revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Sophie Liabeuf revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Valérie Gras-Champel revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Kamel Masmoudi revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Aline Houessinon revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Youssef Bennis contributed to the conception/design of the work and interpretation of data for the work, and drafting the manuscript. He approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Benjamin Batteux contributed to the conception/design of the work, acquisition, analysis, and interpretation of data for the work, and drafting the manuscript. He approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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Impact of the corticosteroid indication and administration route on overall survival and the tumor response after immune checkpoint inhibitor initiation

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Abstract

Background: Based on their indications, systemic corticosteroids appear to negatively affect clinical outcomes in immune checkpoint inhibitor (ICI)-treated patients. There are few data on the influence of topical and inhaled corticosteroids on the ICIs' effectiveness.

Methods: In a single-center study, we retrospectively investigated the impact of systemic corticosteroids according to their indication [an immune-related adverse event (irAE) or another indication] on overall survival (OS) and the tumor response in all consecutive patients after initiation of ipilimumab, nivolumab or pembrolizumab over a 9-year period. The impacts of topical and inhaled corticosteroids were also examined.

Results: Three hundred and seventy-two patients were included. The mean \pm standard deviation age was 64.0 ± 12.1 years. The most frequently prescribed ICI was nivolumab (in 58.3% of the patients) and the most frequent indications were lung cancer (44.6%) and melanoma (29.6%). Systemic corticosteroid use for an irAE did not have a negative impact on OS [adjusted hazard ratio (HR) [95% confidence interval (CI)] 1.04 (0.56–1.95), $p=0.902$] or the best overall tumor response [adjusted odds ratio (OR) (95% CI) 1.69 (0.52–6.56), $p=0.413$], while systemic corticosteroid use for another indication was associated with shorter OS [adjusted HR (95% CI) 1.34 (1.05–2.03), $p=0.046$] and a poor best overall tumor response [adjusted OR (95% CI) 2.04 (1.07–5.80), $p=0.039$] with a cumulative dose cut-off of 3215 mg prednisolone equivalent (specificity 71.4%; sensitivity 65.3%) and a time cut-off of 132 days (specificity 71.4%; sensitivity 89.8%). The use of topical corticosteroids was associated with a longer OS; this was probably due to dermatological irAEs. Inhaled corticosteroid use did not influence OS.

Conclusion: Systemic corticosteroid use for an irAE does not impact OS or the tumor response, whereas use for other indications (themselves often associated with a worse prognosis) does. Topical and inhaled steroids do not have a negative impact on OS.

Keywords: immune checkpoint inhibitor, inhaled corticosteroid, overall survival, systemic corticosteroid, topical corticosteroid

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Introduction

Immunotherapy (modulation of the immune response to tumor cells) has given new hope to cancer patients. After proving its effectiveness in an indication of metastatic melanoma, this

approach has given good results in the treatment of other types of cancer (e.g. lung and renal cancers).^{1–3} However, up to 60–80% of treated patients fail to respond to immunotherapy.⁴ Several escape mechanisms have been identified.

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These include the concomitant or recent use of drugs that interact with the immune system. For example, the immunosuppression produced by corticosteroids might reduce the efficacy of immune checkpoint inhibitors (ICIs) by inducing lymphopenia and impairing the T-cell response to tumor antigens.⁵ Based on these immunosuppressive mechanisms, patients receiving systemic corticosteroids at baseline have been excluded from randomized controlled studies of the efficacy of ICIs in several indications.^{6–8} However, several clinical studies have highlighted a negative association between systemic corticosteroid use and overall survival (OS) and tumor response.^{9–12} Most of these studies focused on early corticosteroid use before ICI initiation. Ricciuti *et al.*¹¹ suggested that worse clinical outcomes were related to the corticosteroids' indication (namely those associated with a poor prognosis, such as cachexia and brain metastasis) rather than to the corticosteroids themselves. Although some data on clinical outcomes in ICI-treated patients receiving corticosteroids for an immune-related adverse event (irAE) have been collected, no cumulative dose or duration thresholds have been determined.^{13–15} Furthermore, topical and inhaled corticosteroids are known to have systemic effects^{16,17} but no data on OS are available for topical corticosteroid use in ICI-treated patients. A study of ICI-related pneumonitis in patients receiving inhaled corticosteroids did not find an influence on OS.¹⁸

We hypothesized that: (a) the use of systemic corticosteroids in an indication of an irAE is not associated with worse OS and a worse tumor response (unlike systemic corticosteroid use for another indication); and (b) the use of topical and inhaled corticosteroids in ICI-treated patients is associated with poorer OS and a worse tumor response.

The objectives of the present study of ICI-treated patients were thus to: (a) evaluate the impact of systemic corticosteroids (as a function of the indication: an irAE or another indication), topical corticosteroids and inhaled corticosteroids on OS and tumor response; and (b) determine the cumulative dose and duration thresholds for systemic corticosteroids associated with a worse tumor response.

Methods

Study design

We performed a retrospective, observational study of all consecutive adult patients (aged 18 years

and over) treated with an anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) agent (ipilimumab) and/or an anti-programmed death-1 (PD-1) agent (nivolumab or pembrolizumab) in the departments of oncology, dermatology, pulmonology, hematology and gastroenterology from December 2010 to December 2019 at Amiens University Medical Center (Amiens, France). Patients enrolled in clinical trials or receiving concurrent chemotherapy/targeted therapy were not included. Data on the patients' baseline characteristics were extracted from the hospital's electronic medical records.

Evaluation of the tumor response and OS

On the basis of data gathered from multidisciplinary team meeting reports and imaging reports, the best overall tumor response was defined as a complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1).¹⁹ A good response was defined as CR or PR status. OS was calculated from the date of ICI initiation to the time of death from any cause or the date of the last follow-up examination.

Collection of data on drug use

The use of oral and topical corticosteroids in the 60 days following the initiation of ICI treatment was documented, together with the indication and dosage for oral corticosteroids. The use of inhaled corticosteroids on ICI initiation or in the 60 days thereafter was also documented.

The use of drugs inducing dysbiosis (which potentially decreases the effectiveness of ICIs) was also documented: antibiotics (ATBs), proton pump inhibitors (PPIs), drugs for gastrointestinal functional disorders (particularly phloroglucinol), anti-vitamin K (AVK) anticoagulants, antiarrhythmics, non-steroidal anti-inflammatory drugs (NSAIDs), cholecalciferol, metformin, opioids, statins, and levothyroxine.²⁰ With regard to ATBs and in particular: (a) the importance of the time needed for recovery of the gut microbiota after ATB discontinuation;²¹ and (b) the difficulty setting an optimal time cut-off for determining whether or not ATB use influences the effectiveness of ICIs,^{22,23} we included patients in the ATB group when the treatment was initiated during the 60 days preceding ICI initiation or the 60 days following ICI initiation. With regard to other

drug classes and given the lack of data about the time needed for the gut microbiota to recover after discontinuation, patients were assigned to the corresponding drug class group when the treatment was received on ICI initiation or in the 60 days thereafter.

Ethical approval and informed consent

In line with the French legislation on retrospective analyses of routine clinical practice, patients were not required to give their informed consent. On admission to hospital, however, patients could refuse the use of their medical data for research purposes. The present study protocol was approved by an institutional committee with competency for studies not requiring approval by an independent ethics committee (Clinical Research Directorate, Amiens University Medical Center, Amiens, France) and was registered with the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés, Paris, France; reference: PI2018_843_0062, dated 11 November 2018).

Statistical analyses

In our descriptive analysis, categorical variables were expressed as the number (percentage), and continuous variables were expressed as the mean \pm standard deviation (SD), or the median (interquartile range), depending on the data distribution.

In bivariate analyses of patients receiving corticosteroids (the CS+ group) *versus* patients not receiving corticosteroids (the CS- group), continuous variables were compared using Student's *t* test or a Wilcoxon's rank sum test (depending on the data distribution), and categorical variables were compared using a chi-square test or Fisher's exact test. The Kaplan–Meier method and a log-rank test were used to compare the OS in the various groups. The groups' tumor response rates (according to the RECIST 1.1 criteria) were also compared. These two analyses were stratified by the corticosteroid indication (an irAE or another indication). In multivariate analyses, a Cox proportional hazards model was used for OS and a multiple logistic regression model was built for the best overall tumor response. Variables with a *p*-value < 0.2 in the bivariate analysis and the predictors of death most frequently described in the literature (i.e. age, sex, body mass index, current or past smoking, alcohol consumption, a

history of cardiovascular disease, cancer duration, and Eastern Cooperative Oncology Group (ECOG) performance status) were included in the models. In multivariate analyses, corticosteroid use was stratified by the indication.

In order to take account of the study population's heterogeneity, all the analyses were performed in subgroups: (a) patients with metastatic cancer; and (b) patients with the most common types of cancer in our population (i.e. lung cancer and melanoma). In the melanoma subgroup, known prognostic factors (i.e. brain metastasis, the serum lactate dehydrogenase (LDH) level on ICI initiation, and the melanoma's histological characteristics: ulceration, Breslow thickness, and Clark index)²⁴ were included in the multivariate analyses (the Cox proportional hazards model and the logistic regression). Considering the high percentage of missing data for Breslow thickness and Clark index and in order to limit the loss of statistical power, several Cox proportional hazards models and logistic regressions were applied to this subgroup.

In patients treated with systemic corticosteroids, a receiver operating characteristic (ROC) curve analysis was used to determine the cumulative dose and duration thresholds associated with a poorer response (SD or PD). These ROC curve analyses were stratified by the corticosteroid indication.

For systemic and topical corticosteroid use, OS was analyzed according to the indication for treatment.

Results

Patient characteristics

Three hundred and seventy-four patients started treatment with ipilimumab, nivolumab or pembrolizumab (alone or in combination) between 1 December 2010 and 31 December 2019. Two patients were excluded because of missing data. Hence, a total of 372 patients were included in the analysis. The mean \pm SD age was 64.0 ± 12.1 years. The most frequently prescribed ICI [in 217 patients (58.3%)] was nivolumab. The most frequent cancers were lung cancers (44.6%) and melanoma (29.6%). The study population's demographic and clinicopathological characteristics are summarized in Table 1.

Table 1. Characteristics of the overall study population and the CS- and CS+ groups .

	Overall population <i>n</i> =372	CS- group <i>n</i> =295	CS+ group <i>n</i> =77	<i>p</i> -Value
Age (years), mean \pm SD	64.0 \pm 12.1	64.8 \pm 12.2	60.5 \pm 11.4	0.005
Sex				
Male, <i>n</i> (%)	244 (65.6)	203 (68.8)	41 (53.2)	0.015
Female, <i>n</i> (%)	128 (34.4)	92 (31.2)	36 (46.8)	
Body mass index (kg/m ²), mean \pm SD	24.8 \pm 5.4	24.6 \pm 5.6	25.4 \pm 4.9	0.245
Smoking (current or past), <i>n</i> (%)	268 (72.0)	209 (70.8)	59 (76.6)	0.388
Alcohol consumption, <i>n</i> (%)	125 (33.6)	106 (35.9)	19 (24.7)	0.084
Cardiovascular history, <i>n</i> (%)	103 (27.7)	79 (26.8)	24 (31.2)	0.533
Diabetes mellitus, <i>n</i> (%)	51 (13.7)	45 (15.3)	6 (7.8)	0.131
High blood pressure, <i>n</i> (%)	171 (46.0)	136 (46.1)	35 (45.5)	1.000
Dyslipidemia, <i>n</i> (%)	104 (28.0)	83 (28.1)	21 (27.3)	0.994
History of cancer, <i>n</i> (%)	67 (18.0)	50 (16.9)	17 (22.1)	0.381
Tumor type				
Lung, <i>n</i> (%)	166 (44.6)	122 (41.4)	44 (57.1)	0.019
Melanoma, <i>n</i> (%)	110 (29.6)	88 (29.8)	22 (28.6)	0.400
Renal and urothelial, <i>n</i> (%)	27 (7.3)	24 (8.1)	3 (3.9)	0.322
Head and neck, <i>n</i> (%)	48 (12.9)	45 (15.3)	3 (3.9)	0.007
Hodgkin lymphoma, <i>n</i> (%)	5 (1.3)	5 (1.7)	0	0.588
Digestive, <i>n</i> (%)	4 (1.1)	3 (1.0)	1 (1.3)	1.000
Cutaneous squamous cell carcinoma, <i>n</i> (%)	1 (0.3)	0	1 (1.3)	0.207
Adenocarcinoma of unknown primary, <i>n</i> (%)	5 (1.3)	3 (1.0)	2 (2.6)	0.277
Squamous cell carcinoma of unknown primary, <i>n</i> (%)	5 (1.3)	4 (1.4)	1 (1.3)	1.000
Porocarcinoma, <i>n</i> (%)	1 (0.3)	1 (0.3)	0	1.000
Metastatic cancer, <i>n</i> (%)	276 (74.2)	204 (69.2)	72 (93.5)	<0.001
Number of metastatic sites, median (IQR)	1 (0–2)	1 (0–2)	2 (1–2)	<0.001
Brain metastasis, <i>n</i> (%)	29 (7.8)	12 (4.1)	17 (22.1)	<0.001
Cancer duration (months), median (IQR)	13.7 (6.9–33.3)	13.5 (7.1–35.0)	14.9 (6.7–27.5)	0.584
ECOG performance status				
0–1, <i>n</i> (%)	295 (79.3)	236 (80.0)	59 (76.6)	0.529
2–4, <i>n</i> (%)	77 (20.7)	59 (20.0)	18 (23.4)	
Prior conventional chemotherapy, <i>n</i> (%)	219 (58.9)	170 (57.6)	49 (63.6)	0.410
Number of lines, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.913

(Continued)

Table 1. (Continued)

	Overall population <i>n</i> = 372	CS- group <i>n</i> = 295	CS+ group <i>n</i> = 77	<i>p</i> -Value
Prior targeted chemotherapy, <i>n</i> (%)	66 (17.7)	51 (17.3)	15 (19.5)	0.779
Number of lines, median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	0.649
ICIs				
First-line treatment	372 (100)	295 (100)	77 (100)	1.000
Nivolumab, <i>n</i> (%)	217 (58.3)	175 (59.3)	42 (45.5)	0.531
Pembrolizumab, <i>n</i> (%)	130 (34.9)	104 (35.3)	26 (33.8)	0.913
Ipilimumab, <i>n</i> (%)	15 (4.0)	11 (3.7)	4 (5.2)	0.524
Nivolumab + ipilimumab, <i>n</i> (%)	10 (2.7)	5 (1.7)	5 (6.5)	0.036
Second-line treatment, <i>n</i> (%)	27 (7.3)	16 (5.4)	11 (14.3)	0.013
Nivolumab, <i>n</i> (%) / <i>n</i> ' = 27	11 (40.8)	5 (31.2)	6 (54.5)	0.013
Pembrolizumab, <i>n</i> (%) / <i>n</i> ' = 27	7 (25.9)	5 (31.2)	2 (18.2)	0.638
Ipilimumab, <i>n</i> (%) / <i>n</i> ' = 27	9 (33.3)	6 (37.5)	3 (27.3)	0.400
Third-line treatment, <i>n</i> (%)	2 (0.5)	1 (0.3)	1 (1.3)	0.372
Nivolumab, <i>n</i> (%) / <i>n</i> ' = 2	0	0	0	-
Pembrolizumab, <i>n</i> (%) / <i>n</i> ' = 2	1 (50.0)	0	1 (50.0)	-
Ipilimumab, <i>n</i> (%) / <i>n</i> ' = 2	1 (50.0)	1 (50.0)	0	-
Factors modifying gut microbiota				
Concomitant medications				
NSAIDs, <i>n</i> (%)	23 (6.2)	19 (6.4)	4 (5.2)	0.890
PPIs, <i>n</i> (%)	149 (40.1)	112 (38.0)	37 (48.1)	0.140
Statins, <i>n</i> (%)	83 (22.3)	69 (23.4)	14 (18.2)	0.410
Opioids, <i>n</i> (%)	173 (46.5)	131 (44.4)	42 (54.5)	0.144
Metformin, <i>n</i> (%)	17 (4.6)	16 (5.4)	1 (1.3)	0.216
AVKs, <i>n</i> (%)	16 (4.3)	14 (4.7)	2 (2.6)	0.541
Levothyroxine, <i>n</i> (%)	40 (10.8)	34 (11.5)	6 (7.8)	0.462
Cholecalciferol, <i>n</i> (%)	59 (15.9)	44 (14.9)	15 (1.5)	0.423
Phloroglucinol, <i>n</i> (%)	19 (5.1)	16 (5.4)	3 (3.9)	0.802
Antiarrhythmic drug, <i>n</i> (%)	20 (5.4)	18 (6.1)	2 (2.6)	0.352
ATB, <i>n</i> (%)	112 (30.1)	92 (31.2)	20 (26.0)	0.454
Use of food supplements	58 (15.6)	50 (16.9)	8 (10.4)	0.216
ATB, antibiotic; AVK, anti-vitamin K; CS, corticosteroid; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.				

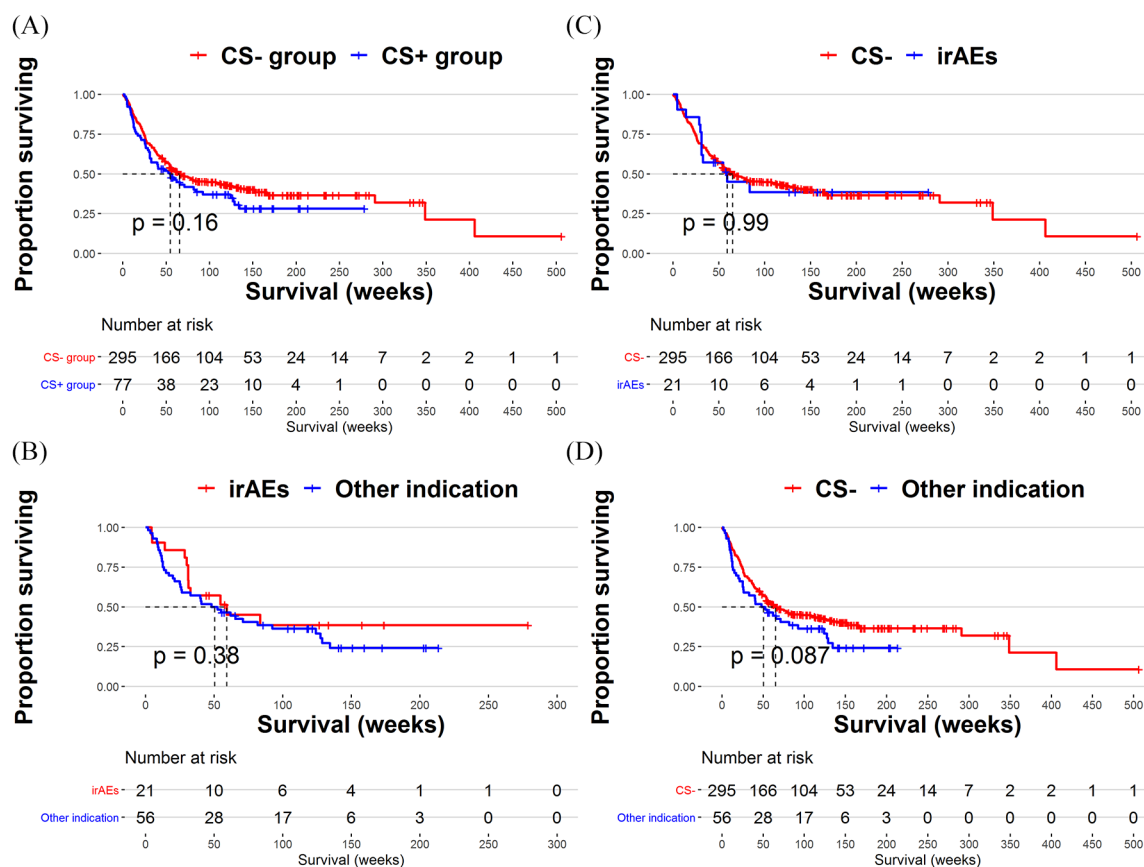


Figure 1. Overall survival in (A) patients treated with corticosteroids (the CS+ group, regardless of indication) and in patients not treated with corticosteroids (CS- group), (B) patients treated with corticosteroids for an irAE and in patients treated with corticosteroids for another indication, (C) patients treated with corticosteroids for an irAE and in patients not treated with corticosteroids and (D) patients treated with corticosteroids for an indication other than an irAE and in patients not treated with corticosteroids. CS, corticosteroid; irAE, immune-related adverse event.

Overall survival and the tumor response
Systemic corticosteroids

Overall population. Seventy-seven (20.7%) patients received oral corticosteroids for a median (interquartile range) duration of 61 (25–114) days. The median (interquartile range) cumulative prednisolone equivalent dose was 1520 (365–4080) mg per patient. The indications for oral corticosteroids were variously irAEs in 21 patients (27.3%), brain metastasis in 21 (27.3%), arthralgia (no irAEs) in seven (9.1%), an ear, nose and throat infection in five (6.5%), an allergic reaction in one (1.3%), and a compressive mediastinal mass in two (2.6%). The indication for corticosteroids was unknown in 20 patients (25.9%); all 20 had lung cancer.

In bivariate analyses, patients in the CS+ group had a worse prognosis than those in the CS- group; this was associated with the presence of metastatic cancer (in 93.5% versus 69.2% of the

patients, respectively; $p < 0.001$), the presence of brain metastasis (22.1% versus 4.1% respectively, $p < 0.001$), and the number of metastatic sites [median (interquartile range) 2 (1–2) versus 1 (0–2), respectively, $p < 0.001$, Table 1].

Overall survival was lower in the CS+ group than in the CS- group [median (95% confidence interval) OS time 54.7 (31.3–124) versus 65.3 (54.1–113) weeks, respectively; crude hazard ratio (HR) (95% CI) 1.25 (0.91–1.71), $p = 0.160$, Figure 1A]. When stratified by indication, OS was: (a) similar in patients receiving oral corticosteroids for an irAE (the irAE subgroup) and in the CS- group [median (95% CI) OS time 59.3 (31.1–NA) versus 65.3 (54.1–113) weeks, respectively; crude HR (95% CI) 1.01 (0.56–1.80), $p = 0.990$, Figure 1C]; and (b) lower in patients receiving oral corticosteroids for another indication (the ‘other indication’ subgroup) than in the

CS- group [median (95% CI) OS time 50.4 (26.1–124) *versus* 65.3 (54.1–113) weeks, respectively; crude HR (95% CI) 1.35 (0.96–1.91), $p=0.087$, Figure 1D]. The Cox proportional hazards model showed: (a) significantly shorter OS in patients in the ‘other indication’ subgroup than in the CS- group or the irAE subgroup [adjusted HR (95% CI) 1.34 (1.05–2.03), $p=0.046$]; and (b) similar OS value in the irAE subgroup, the CS- group and the ‘other indication’ subgroup [adjusted HR (95% CI) 1.04 (0.56–1.95), $p=0.902$, Table 2]. Finally, worse ECOG status [adjusted HR (95% CI) 2.67 (1.89–3.78), $p<0.001$] and ATB use [adjusted HR (95% CI) 1.43 (1.04–1.97), $p=0.040$] were also associated with worse OS (Table 2).

Moreover, the proportion of responders was lower in the CS+ group than in the CS- group (11.8% *versus* 29.6%, respectively; $p=0.024$, Figure 2). In bivariate analyses, patients in the CS+ group had a worse prognosis than those in the CS- group; this was associated with the presence of metastatic cancer (in 91.2% *versus* 75.0% of the patients, respectively; $p=0.008$) and the number of metastatic sites [median (interquartile range) 2 (0–5) *versus* 1 (0–5), respectively, $p=0.006$, Supplemental Table 1]. The Cox proportional hazards model confirmed the trend seen on the Kaplan–Meier curves [adjusted HR (95% CI) 1.79 (1.23–2.59), $p=0.002$, Table 2].

In bivariate analyses, the proportion of responders was significantly lower in the CS+ group than in the CS- group (16.9% *versus* 27.8%, respectively; $p=0.025$). When stratified by indication, the proportion of responders did not differ significantly in the irAE subgroup and CS- group (28.6% *versus* 27.8%, respectively; $p=0.296$) but was significantly lower in the ‘other indication’ subgroup than in the CS- group (12.5% *versus* 27.8%, respectively; $p=0.008$, Figure 2). After adjusting for confounders, the logistic regression model confirmed these trends: the use of oral corticosteroids for an irAE was not significantly associated with a worse tumor response [adjusted odds ratio (OR) (95% CI) 1.69 (0.52–6.56), $p=0.413$], while the use of oral corticosteroids for an indication other than an irAE was associated with a worse tumor response [adjusted OR (95% CI) 2.04 (1.07–5.80), $p=0.039$]. Finally, a worse ECOG status [adjusted OR (95% CI) 2.61 (1.15–6.57), $p=0.029$], ATB use [adjusted OR (95% CI) 6.60 (3.08–15.70), $p<0.001$] and PPI use [adjusted OR (95% CI) 1.84 (1.03–3.34),

$p=0.043$] were associated with a worse tumor response (Table 3).

With regard to patients with PD, the ROC analysis showed: (a) a time-dependent harmful effect (area under the curve 69.8%) with a threshold value of 114 days of corticosteroid treatment (specificity 61.5%; sensitivity 82.8%; Figure 3A); and (b) a dose-dependent harmful effect (area under the curve 62.0%) with a cumulative dose threshold value of 3215 mg prednisolone equivalent (specificity 53.8%, sensitivity 67.2%, Figure 3B). These results were improved after stratification by indication. When considering oral corticosteroid use for an irAE, the ROC analysis evidenced a smaller time-dependent effect (area under the curve 63.3%) with a threshold value of 114 days of corticosteroid treatment (specificity 50.0%; sensitivity 73.3%; Figure 3C) and a smaller dose-dependent effect (area under the curve 58.9%) with a cumulative dose threshold value of 1138.75 mg prednisolone equivalent (specificity 83.3%, sensitivity 60.0%, Figure 3D). When considering oral corticosteroid use for an indication other than an irAE, the ROC analysis showed a greater time-dependent effect (area under the curve 77.6%) with a threshold value of 132 days of corticosteroid treatment (specificity 71.4%; sensitivity 89.8%; Figure 3C) and a greater dose-dependent effect (area under the curve 66.5%) with a cumulative dose threshold value of 3215 mg prednisolone equivalent (specificity 71.4%, sensitivity 65.3%, Figure 3D).

Patients with metastatic cancer. Of the 276 patients with metastatic cancer, 72 (26.1%) received oral corticosteroids, including 18 (6.6%) for an irAE and 54 (19.9%) for another indication. Relative to the metastatic CS- group, patients in the metastatic CS+ group were younger (63.8 ± 12.4 *versus* 60.5 ± 11.6 years, respectively, $p=0.044$) and were more likely to have lung cancer (40.5% *versus* 57.8% of the patients, respectively, $p=0.006$) or brain metastases (5.9% *versus* 23.6%, respectively, $p<0.001$) (Supplemental Table S1).

Overall survival was shorter in patients who received oral corticosteroids than in patients who did not [median (95% CI) OS time 52.6 (31.3–128) *versus* 85.3 (60.3–168) weeks, respectively; crude HR (95% CI) 1.38 (0.98–1.94), $p=0.067$, Supplemental Figure S1A]. When stratified by indication, OS (a) did not differ significantly in patients receiving oral corticosteroids for an irAE

Table 2. Univariate and multivariate analyses of overall survival (Cox regression model).

	n (%)	Crude model		Adjusted model	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	372 (100)	1.00 (0.99–1.01)	0.556	1.01 (0.99–1.02)	0.275
Body mass index	372 (100)	0.95 (0.93–0.98)	<0.001	0.98 (0.95–1.02)	0.296
Sex					
Male	244 (65.6)	Reference		Reference	
Female	128 (34.4)	0.80 (0.60–1.06)	0.100	0.79 (0.58–1.09)	0.155
Smoking					
Never	104 (28.0)	Reference		Reference	
Current or past	268 (72.0)	1.65 (1.22–2.26)	0.001	0.99 (0.66–1.50)	0.965
Alcohol consumption					
No	247 (66.4)	Reference		Reference	
Yes	125 (33.6)	1.57 (1.20–2.06)	<0.001	1.19 (0.84–1.68)	0.335
History of cardiovascular disease					
Absence of cardiovascular disease	269 (72.3)	Reference		Reference	
Presence of cardiovascular disease	103 (27.7)	1.10 (0.82–1.46)	0.500	0.83 (0.61–1.13)	0.245
Type of cancer					
Lung	166 (44.6)	Reference		Reference	
Melanoma	110 (29.6)	0.45 (0.32–0.63)	<0.001	1.14 (0.60–2.15)	0.684
Renal and urothelial	27 (7.3)	0.76 (0.45–1.28)	0.306	0.92 (0.39–2.17)	0.844
Head and neck	48 (12.9)	1.05 (0.70–1.57)	0.824	0.70 (0.43–1.13)	0.141
Hodgkin lymphoma	5 (1.3)	0.45 (0.11–1.81)	0.260	0.47 (0.11–2.05)	0.314
Digestive	4 (1.1)	6.08 (2.19–16.85)	<0.001	3.75 (1.13–12.39)	0.030
Cutaneous squamous cell carcinoma	1 (0.3)	3.27 (0.45–23.58)	0.240	5.52 (0.68–45.06)	0.111
Adenocarcinoma of unknown primary	5 (1.3)	0.46 (0.11–1.86)	0.275	0.66 (0.16–2.79)	0.575
Squamous cell carcinoma of unknown primary	5 (1.3)	0.86 (0.27–2.70)	0.794	0.34 (0.10–1.15)	0.084
Porocarcinoma	1 (0.3)	2.11 (0.29–15.15)	0.459	2.74 (0.33–23.09)	0.353
Cancer duration	372 (100)	1.00 (0.99–1.00)	0.081	1.00 (0.99–1.00)	0.313
ECOG performance status					
0–1	295 (79.3)	Reference		Reference	
2–4	77 (20.7)	2.90 (2.15–3.90)	<0.001	2.67 (1.89–3.78)	<0.001
Metastatic cancer					
No	96 (25.8)	Reference		Reference	
Yes	276 (74.2)	0.74 (0.55–0.98)	0.040	0.89 (0.62–1.27)	0.510

(Continued)

Table 2. (Continued)

	n (%)	Crude model		Adjusted model	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Brain metastasis					
No	343 (92.2)	Reference		Reference	
Yes	29 (7.8)	1.13 (0.70–1.83)	0.600	1.21 (0.94–2.44)	0.509
Prior conventional chemotherapy					
No	153 (41.1)	Reference		Reference	
Yes	219 (58.9)	1.72 (1.30–2.28)	<0.001	1.52 (0.94–2.44)	0.087
Prior targeted chemotherapy					
No	306 (82.3)	Reference		Reference	
Yes	66 (17.7)	1.17 (0.83–1.63)	0.400	1.27 (0.78–2.08)	0.330
ICIs					
Nivolumab	217 (58.3)	Reference		Reference	
Pembrolizumab	130 (34.9)	0.58 (0.43–0.77)	<0.001	0.65 (0.45–0.95)	0.028
Ipilimumab	15 (4.0)	0.36 (0.17–0.78)	0.009	0.46 (0.19–1.15)	0.097
Nivolumab + Ipilimumab	10 (2.7)	0.56 (0.21–1.50)	0.247	1.07 (0.36–3.23)	0.901
ATB use					
No	260 (69.9)	Reference		Reference	
Yes	112 (30.1)	1.75 (1.33–2.30)	<0.001	1.43 (1.04–1.97)	0.040
PPI use					
No	223 (59.9)	Reference		Reference	
Yes	149 (40.1)	0.84 (0.54–1.29)	0.150	0.81 (0.61–1.09)	0.162
Opioid use					
No	199 (53.5)	Reference		Reference	
Yes	173 (46.5)	1.82 (1.40–2.37)	<0.001	1.32 (0.56–1.95)	0.064
Oral corticosteroid use for an irAE					
No	351 (94.4)	Reference		Reference	
Yes	21 (5.6)	1.25 (0.53–1.71)	0.900	1.04 (0.56–1.95)	0.902
Oral corticosteroid use for another indication					
No	316 (84.9)	Reference		Reference	
Yes	56 (15.1)	1.35 (0.96–1.90)	0.087	1.34 (1.05–2.03)	0.046
ATB, antibiotic; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PPI, proton pump inhibitor					

and patients who did not [median (95% CI) OS time 59.3 (31.1–NA) *versus* 85.3 (60.3–168) weeks, respectively; crude HR (95% CI) 1.10

(0.58–2.11), $p=0.770$, Supplemental Figure S1C] and (b) was significantly lower in patients receiving oral corticosteroids for another

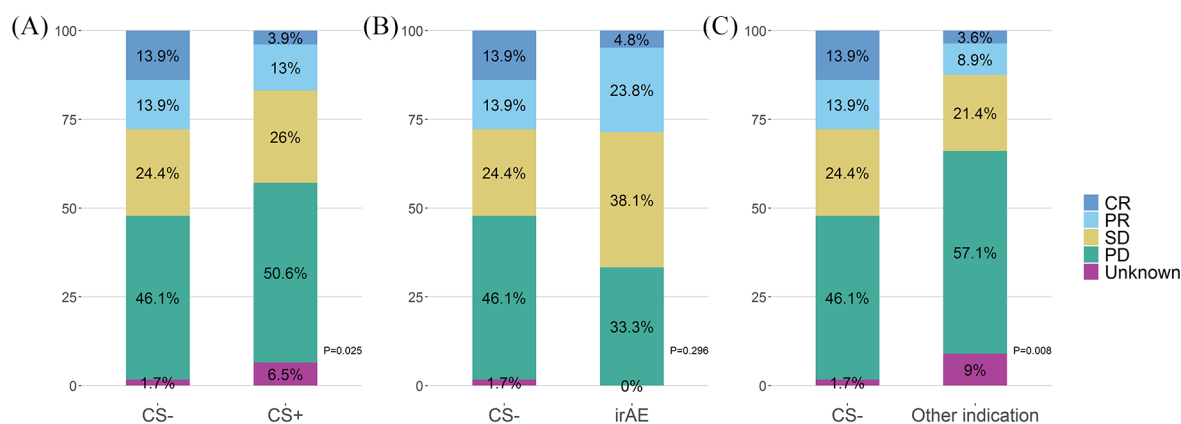


Figure 2. The best overall tumor response, according to systemic corticosteroid use: (A) the CS- group *versus* the CS+ group (regardless of the indication), (B) the CS- group *versus* the irAE subgroup and (C) the CS- group *versus* the 'other indication' subgroup. CR, complete response; CS, corticosteroid; irAE, immune-related adverse event; PD, progressive disease; PR, partial response; SD, stable disease.

indication than in patients who did not [median (95% CI) OS time 50.4 (26.1–128) *versus* 85.3 (60.3–168) weeks, respectively; crude HR (95% CI) 1.47 (1.01–2.13), $p=0.041$, Supplemental Figure S1D]. The Cox proportional hazards model showed: (a) significantly shorter OS in patients receiving oral corticosteroids for another indication than in patients who did not receive oral corticosteroids or who received oral corticosteroids for an irAE [adjusted HR (95% CI) 1.35 (1.02–1.81), $p=0.043$]; and (b) no difference in OS among patients receiving oral corticosteroids for an irAE, those who did not receive oral corticosteroids, and those who received oral corticosteroids for an indication other than an irAE [adjusted HR (95% CI) 1.04 (0.51–2.12), $p=0.916$]. Finally, a worse ECOG status [adjusted HR (95% CI) 3.47 (2.23–5.41), $p<0.001$] and ATB use [adjusted HR (95% CI) 1.39 (1.05–2.04), $p=0.039$] were associated with shorter OS (Supplemental Table S2).

The proportion of responders was significantly lower in the metastatic CS+ group than in the metastatic CS- group (18.1% *versus* 28.9%, respectively; $p=0.030$). When stratified by indication, the proportion of responders did not differ significantly in the metastatic irAE subgroup and the metastatic CS- group (33.4% *versus* 28.9%, respectively; $p=0.339$), and the proportion of responders was significantly lower in the metastatic 'other indication' subgroup than in the metastatic CS- group (13.0% *versus* 28.9%, respectively; $p=0.012$, Supplemental Figure S2). After adjusting for confounders, the logistic regression model confirmed these trends: the use

of oral corticosteroids for an irAE was not significantly associated with a worse tumor response [adjusted OR (95% CI) 1.64 (0.43–7.62), $p=0.491$], while the use of oral corticosteroids for an indication other than an irAE was associated with a worse tumor response [adjusted OR (95% CI) 1.68 (1.07–5.10), $p=0.042$]. Finally, worse ECOG status [adjusted OR (95% CI) 4.91 (1.51–22.63), $p=0.017$], ATB use [adjusted OR (95% CI) 10.83 (3.58–44.69), $p<0.001$], and PPI use [adjusted OR (95% CI) 2.32 (1.13–4.92)] were associated with a worse tumor response (Supplemental Table S3).

Patients with melanoma. Of the 110 patients with melanoma, 22 (20.0%) received oral corticosteroids, including seven (6.4%) for an irAE and 15 (13.6%) for another indication. Compared with the melanoma CS- group, the patients in the melanoma CS+ group were younger (66.9 ± 14.8 *versus* 56.4 ± 14.9 , respectively, $p=0.003$) and the proportion of patients receiving the nivolumab + ipilimumab combination (4.5% *versus* 22.7% respectively, $p=0.015$) was lower. The Breslow thickness was missing for 28 (25.5%) patients, the Clark index was missing for 43 (39.1%), and the LDH level was missing for two (1.8%) (Supplemental Table S4).

Overall survival was shorter in patients who received oral corticosteroids than in patients who did not [median (95% CI) OS time 81.7 (32.9–NA) *versus* 291.0 (152.9–NA) weeks, respectively; crude HR (95% CI) 2.52 (1.37–4.63), $p=0.002$, Supplemental Figure S3A]. When stratified by indication, OS (a) did

Table 3. Univariate and multivariate analysis (logistic regression) of the tumor response (comparison of non-responders with responders, according to the RECIST 1.1 criteria).

	n (%)*	Crude model		Adjusted model	
		OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age	362 (100)	1.00 (0.99–1.02)	0.640	1.02 (0.99–1.04)	0.183
Body mass index	362 (100)	0.94 (0.90–0.98)	0.003	0.98 (0.93–1.04)	0.514
Sex					
Male	237 (65.5)	Reference		Reference	
Female	125 (34.5)	0.73 (0.45–1.18)	0.193	0.73 (0.39–1.37)	0.332
Smoking					
Never	101 (27.9)	Reference		Reference	
Current or past	261 (72.1)	1.78 (1.07–2.93)	0.025	0.79 (0.37–1.68)	0.547
Alcohol consumption					
No	239 (66.0)	Reference		Reference	
Yes	123 (34.0)	1.51 (0.91–2.57)	0.115	0.94 (0.46–1.92)	0.867
History of cardiovascular disease					
Absence of cardiovascular disease	263 (72.7)	Reference		Reference	
Presence of cardiovascular disease	99 (27.3)	1.45 (0.85–2.57)	0.183	0.94 (0.49–1.82)	0.854
Type of cancer					
Lung	158 (43.6)	2.27 (1.39–3.80)	0.001	0.88 (0.22–2.97)	0.849
Melanoma	108 (29.3)	0.28 (0.17–0.46)	<0.001	0.82 (0.17–3.36)	0.790
Renal and urothelial	27 (7.5)	1.61 (0.64–4.94)	0.347	2.57 (0.38–16.91)	0.326
Head and neck	48 (13.3)	1.22 (0.62–2.63)	0.574	0.73 (0.15–3.18)	0.681
Cancer duration	362 (100)	0.99 (0.99–1.00)	0.045	0.99 (0.99–1.00)	0.061
ECOG performance status					
0–1	288 (79.6)	Reference		Reference	
2–4	74 (20.4)	3.57 (1.73–8.35)	0.001	2.61 (1.15–6.57)	0.029
Metastatic cancer					
No	95 (26.2)	Reference		Reference	
Yes	267 (73.8)	0.87 (0.50–1.47)	0.600	1.27 (0.61–2.66)	0.520
Brain metastasis					
No	335 (92.5)	Reference		Reference	
Yes	27 (7.5)	1.26 (0.52–3.54)	0.622	1.61 (0.48–5.97)	0.452

(Continued)

Table 3. (Continued)

	n (%)*	Crude model		Adjusted model	
		OR (95% CI)	p-Value	OR (95% CI)	p-Value
Prior conventional chemotherapy					
No	151 (41.7)	Reference		Reference	
Yes	211 (58.3)	2.60 (1.62–4.22)	<0.001	1.66 (0.71–3.89)	0.238
Prior targeted chemotherapy					
No	296 (81.8)	Reference		Reference	
Yes	66 (18.2)	1.03 (0.57–1.94)	0.921	0.91 (0.38–2.24)	0.832
ICI					
Nivolumab	209 (57.7)	Reference		Reference	
Pembrolizumab	128 (35.4)	0.48 (0.29–0.80)	0.004	0.73 (0.34–1.55)	0.405
Ipilimumab	15 (4.1)	0.49 (0.16–1.64)	0.212	1.11 (0.27–4.95)	0.883
Nivolumab + Ipilimumab	10 (2.8)	0.16 (0.04–0.60)	0.007	0.20 (0.03–1.16)	0.078
ATB use					
No	253 (69.9)	Reference		Reference	
Yes	109 (30.1)	5.72 (2.90–12.67)	<0.001	6.60 (3.08–15.70)	<0.001
PPI use					
No	217 (59.9)	Reference		Reference	
Yes	145 (40.1)	0.89 (0.44–1.95)	0.768	1.84 (1.03–3.34)	0.043
Opioid use					
No	195 (53.9)	Reference		Reference	
Yes	167 (46.1)	2.60 (1.59–4.34)	<0.001	1.72 (0.93–3.18)	0.082
Oral corticosteroid use for an irAE					
No	341 (94.2)	Reference		Reference	
Yes	21 (5.8)	0.88 (0.35–2.54)	0.803	1.69 (0.52–6.56)	0.413
Oral corticosteroid use for another indication					
No	311 (85.9)	Reference		Reference	
Yes	51 (14.1)	2.48 (1.14–6.21)	0.033	2.04 (1.07–5.80)	0.039

*Ten patients were excluded from this analysis because of missing data for the tumor response.

ATB, antibiotic; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PPI, proton pump inhibitor; RECIST, response evaluation criteria in solid tumors

not differ significantly in patients receiving oral corticosteroids for an irAE *versus* patients who did not [median (95% CI) OS time NA (28.7–NA) *versus* 291.0 (152.9–NA) weeks, respectively;

crude HR (95% CI) 2.06 (0.63–6.79), $p=0.220$, Supplemental Figure S3C] and (b) was significantly lower in patients receiving oral corticosteroids for another indication than in patients who

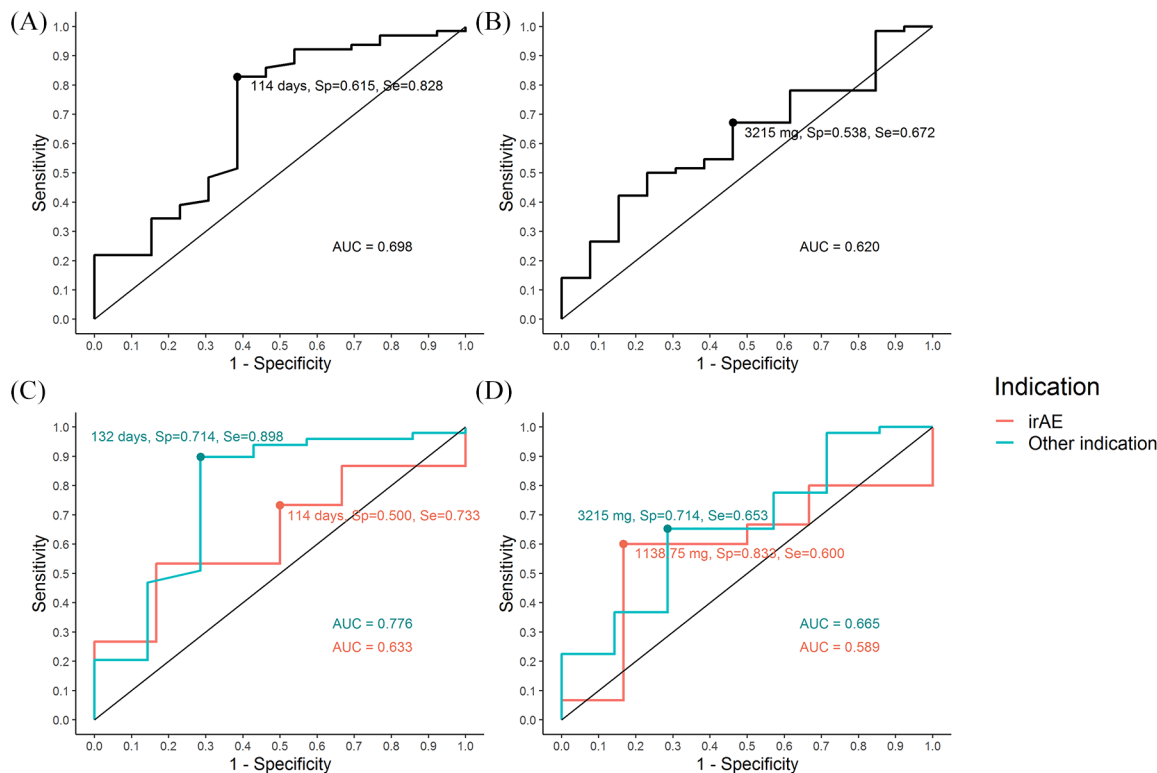


Figure 3. Relationships (ROC curve analysis) between stable disease or progressive disease and (A) the duration of systemic corticosteroid use (regardless of the indication), (B) the cumulative dose of systemic corticosteroids (regardless of the indication), (C) the duration of systemic corticoid use for an irAE and for another indication and (D) the cumulative dose of systemic corticoids for an irAE and for another indication. AUC, area under the curve; irAE, immune-related adverse event; ROC, receiver operating characteristic; Se, sensitivity; Sp, specificity.

did not [median (95% CI) OS time 81.7 (25.4–NA) *versus* 291.0 (152.9–NA) weeks, respectively; crude HR (95% CI) 2.69 (1.39–5.20), $p=0.002$, Supplemental Figure S3D]. The Cox proportional hazards models showed: (a) significantly shorter OS in patients receiving oral corticosteroids for an indication other than an irAE than in patients who did not receive oral corticosteroids or those who received oral corticosteroids for an irAE [adjusted HR (95% CI) 5.76 (2.10–15.79), $p<0.001$]; and (b) no difference in OS in patients receiving oral corticosteroids for an irAE *versus* patients who did not receive oral corticosteroids or who received oral corticosteroids for an indication other than an irAE [adjusted HR (95% CI) 3.60 (0.66–19.81), $p=0.141$, Supplemental Table S5A]. The use of corticosteroids for an indication other than an irAE was still associated with shorter OS after adjusting for Breslow thickness [adjusted OR (95% CI) 16.28 (3.74–70.95), $p<0.001$, Supplemental Table S5B] and for Clark index [adjusted OR (95% CI) 38.98 (5.28–287.74), $p<0.001$, Supplemental Table S5C].

The proportion of responders was significantly lower in the melanoma CS+ group than in the melanoma CS– group (22.7% *versus* 48.9% respectively; $p=0.040$). When stratified by indication, the proportion of responders did not differ significantly in the melanoma irAE subgroup *versus* the melanoma CS– group (42.9% *versus* 48.9% respectively; $p=0.101$), and the proportion of responders was significantly lower in the melanoma ‘other indication’ subgroup than in the melanoma CS– group (13.4% *versus* 48.9% respectively; $p=0.005$, Supplemental Figure S4). After adjusting for confounders, the logistic regression model confirmed these trends: the use of oral corticosteroids for an irAE was not significantly associated with a worse tumor response [adjusted OR (95% CI) 1.82 (0.15–28.69), $p=0.643$], while the use of oral corticosteroids for an indication other than an irAE was associated with a worse tumor response [adjusted OR (95% CI) 4.83 (1.05–62.71), $p=0.039$, Supplemental Table S6A]. The use of corticosteroids for an indication other than an irAE was still associated

with a poorer tumor response after adjusting for Breslow thickness [adjusted OR (95% CI) 12.65 (2.09–400.23), $p=0.036$, Supplemental Table S6B].

Patients with lung cancer. Of the 166 patients with lung cancer, 44 (26.5%) received oral corticosteroids, including 11 (6.6%) for an irAE and 33 (19.9%) for another indication (including 20 for an unknown indication). Overall survival did not differ significantly in patients who received oral corticosteroids than in patients who did not [median (95% CI) OS time 50.4 (31.1–92.4) *versus* 47.9 (37.6–64.1) weeks, respectively; crude HR (95% CI) 1.00 (0.66–1.52), $p=0.990$, Supplemental Figure S5A]. Even after stratification by indication, OS did not differ significantly between the groups (Supplemental Figure S5B, S5C and S5D). The proportion of responders did not differ significantly in the lung cancer CS+ group *versus* the lung cancer CS– group (15.9% *versus* 17.2%, respectively; $p=0.947$) – even after stratification by indication (Supplemental Figure S6).

Topical corticosteroids. Twenty-three (6.2%) patients received topical corticosteroids for a median (interquartile range) duration of 34 (26.9–49.1) weeks. The indications for topical steroids were dermatological irAEs in 17 patients (73.9%), psoriasis in four patients (17.4%), prurigo in one patient (4.3%) and maculopapular exanthema in one patient (4.3%). Overall survival was longer in patients who received topical corticosteroids than in those who did not [median (95% CI) OS time NA (124.1–NA) *versus* 55 (48.1–75.3) weeks, respectively; crude HR 0.42 (0.22–0.83), $p=0.010$ in a log-rank test; Supplemental Figure S7A]. After stratification by indication, the OS in patients receiving topical corticosteroids for a dermatological irAE was higher than in those who were not [median (95% CI) OS time 141.4 (71.9–NA) *versus* 55.7 (48.3–77.7) weeks, respectively; crude HR (95% CI) 0.54 (0.26–0.98), $p=0.029$ in a log-rank test; Supplemental Figure S7B].

Inhaled corticosteroids. Twenty-two (5.9%) patients received long-term treatment with inhaled corticosteroids (the inhaled CS+ group); the indication was chronic obstructive pulmonary disease in 21 patients and asthma for one patient. Sixteen of the 22 patients had lung cancer, three patients had head and neck cancer, two patients had melanoma, and one patient had urothelial cancer. Overall survival was similar in the inhaled CS+

group and inhaled CS– groups [median (95% CI) OS time 53.7 (28.1–NA) *versus* 63.6 (53.9–85.3) weeks, respectively; crude HR (95% CI) 1.16 (0.69–1.98), $p=0.560$ in a log-rank test; Supplemental Figure S8].

Discussion

Our results showed that corticosteroid use for an indication other than an irAE had a negative impact on OS [median (95% CI) OS time 50.4 (26.1–124) *versus* 65.3 (54.1–113) weeks in the ‘other indication’ subgroup and CS– group, respectively; adjusted HR (95% CI) 1.34 (1.05–2.03), $p=0.046$] and on the proportion of patients with a good tumor response [12.5% *versus* 27.8%, respectively; $p=0.008$, adjusted OR (95% CI) 2.04 (1.07–5.80), $p=0.039$]. However, patients receiving corticosteroids for an irAE and those not treated with corticosteroids did not differ significantly with regard to OS – suggesting that irAEs have a positive effect on OS. Indeed, patients who experience irAEs survive for longer than patients who do not.^{25–27} Our findings are in line with studies showing that: (a) the early use of corticosteroids in an indication other than an irAE is harmful on ICI initiation;^{9,10,12} and (b) the use of corticosteroids to treat irAEs during immunotherapy does not affect OS.^{13–15} Therefore, the fact that corticosteroids do not impact OS in the setting of irAE suggests survival is affected by the indication for corticosteroids, rather than corticosteroid use *per se*.

Our analyses of subgroups of patients with metastatic cancer or melanoma were consistent with these findings. In contrast to the literature data, however, the use of oral corticosteroids did not appear to affect OS or tumor response in patients with lung cancer.^{9–11} There are several possible explanations for the discrepancy. Firstly, the clinical outcomes in the studies by Arbour *et al.*⁹ and Ricciuti *et al.*¹¹ concerned the early use of oral corticosteroids (i.e. before ICI initiation), whereas we focused on corticosteroid use after ICI initiation. Secondly, Ricciuti *et al.*¹¹ categorized the reasons for corticosteroid use as either cancer-related (for palliative indications) or cancer-unrelated (for non-palliative indications); hence, poorer outcomes might have been related to prognostic factors rather than corticosteroid use *per se*. In the present study, the indication for corticosteroid use was an irAE or another indication (including both those related to cancer, such as brain metastasis, and those not). Moreover, data

on the indication were missing for 20 of our 44 lung cancer patients receiving corticosteroids. Thirdly, the PD-L1 tumor proportion score and the tumor mutational burden – known predictive biomarkers for the effectiveness of ICIs in non-small-cell lung carcinoma (NSCLC)²⁸ – were not available in the present study.

In the present study, and considering the use of corticosteroids for an indication other than an irAE, ROC analyses showed that: (a) a threshold value at 132 days of corticosteroid treatment (specificity 71.4%; sensitivity 89.8%); and (b) a cumulative threshold dose of 3215 mg prednisolone equivalent (specificity 71.4%; sensitivity 65.3%) are associated with progression of disease. Therefore, caution should be taken when these thresholds are reached.

To the best of our knowledge, the present study is the first to have reported on the influence of topical steroids on OS in patients treated with ICIs. However, it is well established that topical corticosteroids can pass into the circulation.¹⁶ Our results showed that treatment with topical corticosteroids is associated with longer OS [crude HR (95% CI) 0.42 (0.22–0.83), $p=0.010$ in a log-rank test]. The most frequent indication for topical steroid use was a dermatological irAE; this might explain why OS was longer in these patients because dermatological irAEs are associated with better OS.^{25,26} Finally, our results showed that OS was similar in patients treated with inhaled corticosteroids and in those not treated with these drugs, as already described by Li *et al.*¹⁸ Thus, the use of this corticosteroid administration route does not appear to influence the effectiveness of ICIs.

Finally, our present results showed that ATB use is associated with shorter OS [adjusted HR (95% CI) 1.43 (1.04–1.97), $p=0.040$] and a worse tumor response [adjusted OR (95% CI) 6.60 (3.08–15.70), $p<0.001$] in the overall patient population, in patients with metastatic cancer [adjusted HR (95% CI) 1.39 (1.05–2.04), $p=0.039$ for OS; adjusted OR (95% CI) 10.83 (3.58–44.69), $p<0.001$ for tumor response], and in patients with melanoma [adjusted HR (95% CI) 2.58 (1.04–6.38), $p=0.040$ for OS; adjusted OR (95% CI) 4.48 (1.05–23.09), $p=0.049$ for tumor response]. These results are in line with previous studies.^{23,29–32} ATBs appear to have an indirect negative impact on the ICIs' effectiveness by modifying the composition of gut microbiota.^{29,33}

However, these results could also be explained by the indication bias – that is, the infection for which the ATB is used – and not the ATB itself.

The present study had some limitations, including the biases associated with its retrospective single-center design. In the absence of a comparator arm, it is also difficult to affirm that the use of oral corticosteroids for an indication other than an irAE (rather than the indications themselves, i.e. prognostic factors reported by Ricciuti *et al.*)¹¹ is associated with a worse outcome. However, a prospective, randomized, controlled trial with a comparator arm would be difficult to set up. Furthermore, our study's retrospective design prevented us from collecting certain data (e.g. the PD-L1 tumor proportion score, the tumor mutational burden in the NSCLC population, and some of the indications for corticosteroids) and thus our ability to draw a robust conclusion for patients with NSCLC. Finally, our analyses of topical and inhaled corticosteroid use lacked statistical power.

Conclusion

Our present results show that after ICI initiation, systemic corticosteroid use for an irAE does not appear to affect the patients' clinical outcomes, whereas systemic corticosteroid use for another indication does. This negative impact appears to be greater after 134 days of treatment or beyond a cumulative prednisolone equivalent dose of 3215 mg. Topical and inhaled corticosteroids did not appear to influence the effectiveness of ICIs. These results must be confirmed in larger studies.

Author contributions

Louis Gaucher contributed to the conception/design of the work, acquisition and interpretation of data for the work, and drafting the manuscript. He approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Leslie Adda contributed to the acquisition and interpretation of data for the work. She approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Alice Séjourné contributed to the acquisition and interpretation of data for the work, and drafting the manuscript. She approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Camille Joachim revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Guillaume Chaby revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Claire Poulet revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Aurélié Moreira revised the work critically for important intellectual content, approved the

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Youssef Bennis contributed to the conception/design of the work and interpretation of data for the work, and drafting the manuscript. He approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Benjamin Batteux contributed to the conception/design of the work, acquisition, analysis, and interpretation of data for the work, and drafting the manuscript. He approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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Influence des médicaments induisant une dysbiose intestinale et des corticostéroïdes sur la survie globale et la réponse tumorale des patients traités par inhibiteurs de points de contrôle immunitaire

Thèse pour le diplôme d'état de Docteur en Pharmacie

Université de Picardie Jules Verne 2021

Mots-clés : inhibiteurs de point de contrôle immunitaire, microbiote intestinal, dysbiose intestinale, antibiotiques, corticostéroïdes, survie globale, réponse tumorale

Introduction : L'efficacité des inhibiteurs de points de contrôle immunitaire (IPCI) dépend de plusieurs facteurs incluant les modifications du microbiote intestinal et l'immunomodulation. Plusieurs classes de médicaments sont connues pour induire une dysbiose, notamment les antibiotiques (ATB). L'influence de la corticothérapie sur l'efficacité des IPCI semble dépendre de son indication.

L'objectif principal de cette étude était d'évaluer l'association entre l'exposition aux médicaments pouvant influencer l'efficacité des IPCI (ceux modifiant le microbiote intestinal et la corticothérapie par voie systémique, inhalée ou dermocorticoïdes) et la survie globale et la réponse tumorale chez les patients traités par IPCI. L'objectif secondaire était d'établir un seuil de dose cumulée et un seuil de durée de corticothérapie systémique associés à une mauvaise réponse tumorale.

Patients et méthodes : Nous avons réalisé une étude rétrospective monocentrique sur une période de 9 ans évaluant l'association entre l'exposition aux médicaments connus pour modifier le microbiote intestinal (ATB, inhibiteurs de la pompe à protons, anti-inflammatoires non stéroïdiens, statines, opioïdes, anti-vitamine K, lévothyroxine, cholécalférol, antiarythmiques, metformine et phloroglucinol) et aux corticostéroïdes (systémiques, inhalés, dermocorticoïdes) et la survie globale (SG) et la réponse tumorale chez des patients traités par un IPCI (ipilimumab, nivolumab ou pembrolizumab) sur une période de 9 ans. Un modèle de Cox et une régression logistique ont été respectivement réalisés. Un seuil de dose cumulée et un seuil de durée de corticothérapie associée à une mauvaise réponse tumorale ont été déterminés par analyses de courbes ROC.

Résultats : Trois cent soixante-quatorze patients ont été inclus. L'âge moyen \pm écart type était de $64,0 \pm 12,1$. L'IPCI le plus fréquemment prescrit était le nivolumab (58% des patients) et les indications les plus fréquentes étaient le cancer pulmonaire (44,2%) et le mélanome (29,6%). Cent douze patients (30,1%) recevaient des ATB. L'utilisation d'ATB était associée à une SG plus courte (HR ajusté [IC 95%] : 1,38 [1,00 – 1,90], $p=0,048$) et à une mauvaise réponse tumorale (OR ajusté [IC 95%] : 6,06 [2,80 – 14,53], $p<0,001$). L'utilisation des autres médicaments induisant une dysbiose n'étaient pas associée à une différence de SG ou de réponse tumorale. L'utilisation de corticostéroïdes pour une indication autre qu'un effet indésirable immunologique (irAE) était associée à une SG plus faible (HR ajusté [IC 95%] : 1,34 [1,05 – 2,03], $p = 0,046$) et une mauvaise réponse tumorale (OR ajusté [IC 95%] : 2,04 [1,07 – 5,80], $p=0,039$) avec un seuil de dose cumulée de 3215 mg d'équivalent prednisolone et un seuil de durée de 132 jours. L'utilisation de dermocorticoïdes et de corticostéroïdes inhalés ne semblaient pas influencer la SG.

Conclusion : Contrairement aux autres médicaments induisant une dysbiose intestinale, l'utilisation d'ATB est associée à une SG plus courte et à une mauvaise réponse tumorale chez les patients traités par IPCI, ainsi que l'utilisation de corticostéroïdes systémiques pour une indication autre qu'un irAE.

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