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Charlotte Cabanie

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Charlotte Cabanie. Analyse de données de vie réelle sur l'utilisation du palbociclib combiné à l'hormonothérapie dans le cancer du sein métastatique RH+/HER2-. Médecine humaine et pathologie. 2021. dumas-03618188

HAL Id: dumas-03618188

<https://dumas.ccsd.cnrs.fr/dumas-03618188v1>

Submitted on 24 Mar 2022

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UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE
pour le
DIPLOME D'ÉTAT DE DOCTEUR EN MÉDECINE
par

CABANIE Charlotte

Présentée et soutenue publiquement le 3 décembre 2021

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REMERCIEMENTS

A Madame la Professeure PENAULT-LLORCA,

Vous me faites l'honneur de présider ce jury, recevez mes sincères remerciements et le témoignage de ma profonde considération.

A Monsieur le Professeur DURANDO,

Je vous remercie d'avoir apporté vos connaissances et votre aide dans ce travail. Je vous remercie également pour votre disponibilité durant ces 5 dernières années.

A Monsieur le Professeur POMEL,

Vous me faites l'honneur d'apporter votre expérience à la critique de ce travail en siégeant dans mon jury de thèse. Je vous prie de bien vouloir accepter ma respectueuse considération.

A Madame le Docteur MOURET-REYNIER,

Je te remercie d'avoir accepté de siéger dans ce jury de thèse. Merci pour ta gentillesse, ta bienveillance et tes précieux conseils au quotidien.

A Cédric, merci de me supporter depuis bientôt 10 ans. Nous avons réalisé toutes ces années d'études main dans la main et elles se terminent de la plus merveilleuse des façons.

A Basile, je ne peux pas vraiment te remercier pour ton aide dans la réalisation de ce travail, mais tu as été mon meilleur soutien. Je suis déjà très fière d'être ta maman.

A ma Maman, merci d'avoir toujours cru en moi et de m'avoir permis de réaliser ces longues études dans de bonnes conditions.

A mon Papa, tes exigences pour le travail ont fini par payer, me voilà presque docteur.

A Lisa, mon premier bébé, tu m'as rejoint à Clermont pour mon plus grand bonheur. Merci d'avoir été présente ces derniers temps dans cette période si spéciale.

A Yann, les années passent et nous rapprochent malgré la distance. Merci d'être un super grand frère.

A ma Mamie Clara, mon modèle. Merci pour tout ce que tu as fait pour moi depuis toujours. J'espère te garder encore de longues années.

A Mamie Claudine et Papi Jeannot, merci d'avoir été et d'être toujours présents pour moi.

A Gilles, merci pour ta gentillesse et ta générosité.

A Connie, merci pour tes jolies attentions.

A mes tantes, oncles, cousines, cousins... C'est toujours un plaisir de partager des moments ensemble.

A ma belle-famille.

Reine, merci pour tout. Je n'aurais pas pu rêver meilleure belle-mère.

Eric, merci pour votre disponibilité sans faille... et de me tenir informée des actualités.

Mémie, merci d'être toujours aux petits soins.

Emmanuelle, Florent, merci pour tous ces bons moments passés ensemble, et d'avoir fait de supers neveux, Arthur et Martin.

Anne, Yann et Louise, c'est toujours un immense plaisir de vous voir.

A mes amis de toujours.

Anaïs, c'est un peu grâce à toi si je suis venue à Clermont. Merci d'être là pour moi depuis si longtemps.

Anna, Julie, Laura, Morgan, les années passent mais rien ne change, je vous aime.

A Julia, ma meilleure amie, on en a fait du chemin depuis cette première année de médecine si chaotique. Merci pour tout.

A Audrey, Elina, Florianne, Luz, Marine, Mathilde, Savinka, nos chemins se sont séparés depuis le lycée mais c'est toujours un bonheur de vous retrouver.

Les Nazes (Betty, Caroll, Célia, Elo, Léa, Margaux x2, Sophie, Vanessa), que de souvenirs... Les années facs avec vous c'était le rêve ! J'espère ne jamais vous perdre.

Elo et Gui (et Charlie), la vie à Clermont n'est plus pareille sans vous, vous me manquez !

A mes (anciens et actuels) co-internes : Marie, Laura, Morgane, Florent, Laure, Cécile, Elodie, Mélissa, MAO, et tous les autres... j'ai adoré tous mes stages d'internat grâce à vous.

Tressie, merci pour ta relecture et tes précieux conseils. Reste comme tu es, tu es géniale !

Aux hématos (Amandine, Caro, Jojo, Rémi, Thomas, Xav) : vous avez rendu le semestre le plus difficile le plus merveilleux.

Les Michtos (Camille, Emeline, Kaïssa) : l'aventure parisienne (ou plutôt Villejuifoise) a été encore plus belle grâce à vous.

A Thomas, une belle rencontre parisienne.

A mes chefs et mes collègues rencontrés pendant l'internat, merci de m'avoir tant appris.

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ABREVIATIONS

ABC/MBC	Locally advanced or metastatic breast cancer
ACE	Antigène Carcinoembryonnaire
AE	Adverse event
AI	Aromatase inhibitor
BC	Breast cancer
CDK4/6	Cyclin-dependent Kinase 4/6
CI	Confidence interval
CT	Computed Tomography
ER	Estrogen Receptor
ET	Endocrine therapy
HER2	Human Epidermal Growth Factor Receptor-2
IQR	Interquartile range
NLR	Neutrophils to lymphocytes ratio
OS	Overall survival
PET	Positron Emission Tomography
PFS	Progression-free survival
PR	Progesterone Receptor
RECIST	Response Evaluation Criteria In Solid Tumors
RH	Récepteurs Hormonaux
SG	Survie Globale
SSP	Survie sans progression

I. PRE-REQUIS

1. CANCER DU SEIN

1.1 Épidémiologie

En France, avec 58 500 nouveaux cas par an, le cancer du sein se situe au 1^{er} rang des cancers chez la femme, devant le cancer colorectal et le cancer du poumon (1). Il représente près de 8 % de l'ensemble des décès par cancer, tous sexes confondus, soit 12 146 décès par an. Le cancer du sein chez l'homme ne représente qu'environ 1 % des cas mais il est souvent de mauvais pronostic. L'âge médian au diagnostic est de 63 ans. La survie nette standardisée sur l'âge à 5 ans est de 87 %, et à 10 ans de 76 %. Cela s'explique par l'amélioration des traitements et un dépistage de plus en plus adapté au niveau de risque permettant de diagnostiquer ces cancers à un stade plus précoce (1).

1.2 Sous-types tumoraux

Les cancers du sein peuvent être classés selon l'expression des récepteurs hormonaux (RH) et du statut HER2. Ces informations sont essentielles à des fins pronostiques et thérapeutiques. L'expression des récepteurs aux œstrogènes (RE) et des récepteurs à la progestérone (RP) est évaluée par immunohistochimie (IHC). Les tumeurs sont considérées comme RH positives (RH+) lorsqu'au moins 10 % des cellules tumorales sont marquées (le seuil est à 1% en Europe et aux USA) (2). L'intensité du marquage est également précisée (faible/modérée/forte). Le score Allred allant de 0 à 8 représente la combinaison du pourcentage de cellules marquées (de 0 à 5) et de l'intensité (de 0 à 3) (2) (**Figure 1**).

Les récepteurs hormonaux sont positifs dans environ 80% des cas de cancer du sein (3).

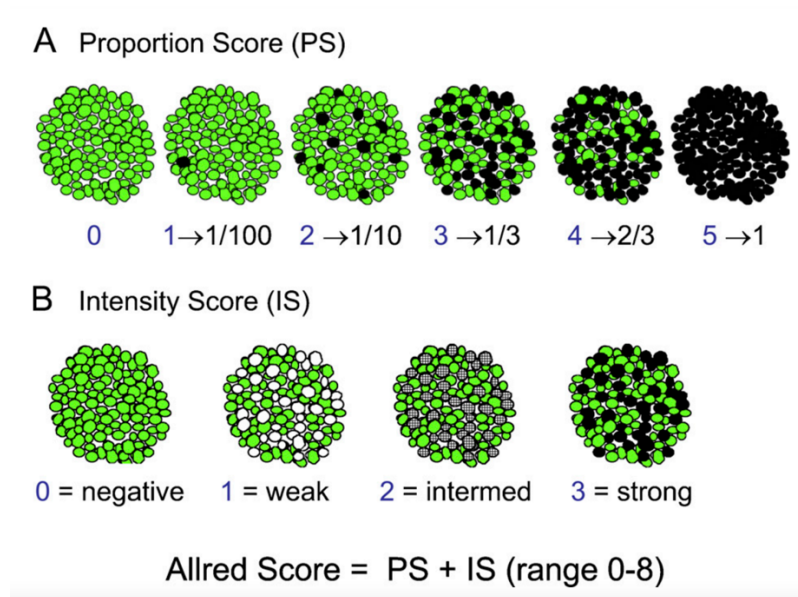


Figure 1. Méthode de calcul du score d'Allred (4).

La surexpression du récepteur HER2 concerne environ 20 % des patients et permet de prédire ceux qui bénéficieront d'un traitement ciblant HER2 (5). La surexpression de HER2 est détectée par une coloration membranaire intense et uniforme dans plus de 10% des cellules tumorales invasives (IHC 3+) ou la présence d'une amplification du gène *ErbB2* en hybridation in situ en fluorescence (FISH). L'amplification est définie par un nombre de copies d'*ErbB2* ≥ 6 ou par le rapport HER2/CEP17 ≥ 2 avec un nombre de copies du gène *ErbB2* ≥ 4 (6,7).

Environ 15% des cancers du sein sont triple négatifs (RH-, HER2-) (8).

Les cancers du sein peuvent être également classés selon leur sous-type moléculaire en fonction de leur profil d'expression génique (9):

- Luminal A ou B. Ils sont les sous-types les plus courants et constituent la majorité des

cancers du sein RE+. Dans le sous-type luminal A, les RE et RP sont positifs, le Ki67 est bas et HER2 est négatif. Dans le sous-type luminal B, les RE sont positifs, les RP sont négatifs et/ou le Ki67 est élevé et HER2 peut être négatif ou positif.

- Enrichi en HER2 : Le sous-type enrichi en HER2 se caractérise par une forte expression de HER2. Ces tumeurs sont souvent négatives pour les RE et RP.
- Basal : La plupart de ces tumeurs entrent dans la catégorie des cancers du sein triple-négatifs car elles sont négatives pour le RE, le RP et le HER2.

1.3 Le cancer du sein métastatique

Environ 30% des patients diagnostiqués pour un cancer du sein au stade précoce développeront des métastases au cours de leur maladie. Environ 5% des cancers du sein sont d'emblée métastatiques (10–12).

Récemment, les avancées thérapeutiques ont permis d'améliorer la survie chez les patients atteints d'un cancer du sein métastatique. La survie globale médiane avoisine les 3 ans, et peut varier de quelques mois à plusieurs années en fonction du sous-type moléculaire et des traitements reçus (13,14).

L'objectif des traitements du cancer du sein métastatique est le contrôle des symptômes et l'amélioration de la survie, et ce avec le moins d'effets secondaires possibles.

1.4 Facteurs pronostiques

Les facteurs pronostiques permettent, en l'absence de traitement, de prédire l'évolution de la maladie en termes de risque de rechute et de décès. Pour le cancer du sein métastatique, plusieurs paramètres ont été établis.

Cliniques

- La rechute à 2 ans et plus du cancer initial est un facteur favorable (par rapport à une rechute avant 2 ans) (15,16).
- Les patients avec une atteinte de la paroi thoracique, des ganglions ou des métastases osseuses ont en général une meilleure survie sans progression. Au contraire, les patients ayant des métastases pulmonaires ou hépatiques ont en général une moins bonne survie sans progression ou globale (16,17). Une crise viscérale est définie par un dysfonctionnement organique grave. Il peut s'agir par exemple d'une atteinte méningée, une atteinte hépatique entraînant une insuffisance hépatique ou une atteinte osseuse conduisant à des cytopénies. La crise viscérale est un facteur de mauvais pronostic (18).
- Les patients présentant des récepteurs hormonaux positifs ont généralement un pronostic plus favorable. Ceux dont les tumeurs sont positives à la fois pour les RE et les RP ont une survie significativement plus longue que ceux dont les tumeurs sont positives à un seul récepteur hormonal (RE-positif/RP-négatif ou RE-négatif/RP-positif) (19). Les patients présentant un cancer du sein triple négatif ont une survie médiane plus courte (20).
- D'autres facteurs comme la perte de poids, un Performans Status (PS) élevé, des LDH élevés sont de mauvais pronostic (17,21).

Les cellules tumorales circulantes

La présence de cellules tumorales circulantes dans le sang des femmes atteintes d'un cancer du sein semble être associé à un pronostic plus défavorable (22,23). Cependant, leur rôle dans

le suivi des patients reste controversé et ce prélèvement ne doit pas être réalisé en routine et ne devrait pas influencer les décisions thérapeutiques à l'heure actuelle (24).

L'ADN tumoral circulant

Un taux élevé d'ADN circulant dans le sang pourrait être également un facteur de mauvais pronostic mais les preuves de la validité clinique sont encore insuffisantes. Il n'est pas recommandé d'effectuer un dosage d'ADN circulant en pratique clinique (25,26).

Les tests d'expression géniques (ou tests génomiques)

Ils ont un rôle pronostique et prédictif établi dans le cancer du sein non métastatique et pourraient également être utiles dans la maladie métastatique. Cependant, des données supplémentaires sont nécessaires avant de recommander leur utilisation dans ce contexte (27,28).

1.5 Facteurs prédictifs

Les facteurs prédictifs permettent de prédire l'évolution de la maladie sous traitement et d'orienter une décision thérapeutique. Pour le cancer du sein métastatique, on retrouve plusieurs facteurs.

Tests effectués sur les tissus métastatiques

- Des biopsies devraient être réalisées chez toutes les patientes atteintes d'un cancer en rechute métastatique afin de réexaminer les RH et le statut HER2. Il peut y avoir des discordances entre le cancer initial et la récurrence (29,30). Comme évoqué précédemment, ces marqueurs sont importants pour la décision thérapeutique.

- Expression du PD-L1

L'expression de PD-L1 permettrait de prédire le bénéfice de l'ajout de l'anticorps anti-PD-L1 atezolizumab à un taxane dans les cancers du sein triple négatifs (31).

- Mutations de *PIK3CA*

Elles sont présentes dans 30 à 40% des cancers du sein et sont associées à un pronostic plus défavorable dans les cancers du sein avancés. Lorsque *PIK3CA* est muté (au niveau des exons 7,9 et 20), la survie sans progression pourrait être améliorée avec l'ajout d'un inhibiteur de PI3K, l'alpelisib, au fulvestrant dans les cancers du sein métastatiques RH+/HER2- (32). Cependant, ce traitement n'est actuellement plus recommandé.

Marqueurs tumoraux sériques

Les marqueurs tumoraux, notamment le CA 15-3 et l'ACE sont couramment utilisés en pratique clinique pour évaluer la charge tumorale dans le cadre d'une atteinte métastatique et peuvent être utiles pour le suivi de certains patients. Cependant, ces marqueurs tumoraux sériques ne sont pas prédictifs des résultats du traitement (24).

Mutation germinale de BRCA

Les patients porteurs d'une mutation germinale de *BRCA* peuvent potentiellement bénéficier des inhibiteurs de PARP par voie orale tels que l'olaparib ou le talazoparib (33,34).

Séquençage du génome (NGS) des cancers du sein

Bien que l'évaluation NGS dans le cancer du sein ne soit pas recommandée en routine clinique, il permet de déterminer si une anomalie génétique est retrouvée. En fonction des profils

d'altérations moléculaires, des essais cliniques ciblés et personnalisés pourraient être proposés aux patients.

Les mutations somatiques les plus fréquemment observées sont :

- Le gène *TP53* (environ 37% des cas), de façon prédominante dans les cancers du sein basal-like, et le sous-type enrichi en HER2 (35).
- La mutation du gène *PIK3CA* (environ 36%) notamment dans les cancers du sein luminaux (RE+) (32,35).
- D'autres mutations moins fréquentes sont également retrouvées : *MAP3K1*, *GATA3*, *MLL3*, *CDH1*, *MAP2K4*, *PTEN*, *AKT1*, *NTRK* (35).

2. TRAITEMENTS DES CANCERS DU SEIN METASTATIQUE

RH+/HER2-

2.1 Place de la chirurgie

À ce jour, l'ablation de la tumeur primaire chez les patientes atteintes d'un cancer du sein *de novo* de stade IV n'a pas été associée à une prolongation de la survie, à l'exception peut-être du sous-ensemble de patientes présentant uniquement une maladie osseuse (36). La chirurgie peut être envisagée chez certaines patientes dont la maladie systémique est contrôlée, notamment pour améliorer la qualité de vie (37,38).

2.2 Traitements systémiques en première ligne

L'hormonothérapie (seule ou en association avec des thérapies ciblées) est généralement moins toxique que la chimiothérapie pour des résultats comparables (39,40). Pour la plupart des patients atteints de cancer du sein RH+/HER2-, l'HT sera donc le traitement de première intention. La chimiothérapie est réservée aux patients dont le cancer semble réfractaire à l'HT, ou ceux présentant une crise viscérale (37).

Les inhibiteurs de l'aromatase (AIs) associés aux inhibiteurs de CDK4/6

Les trois inhibiteurs de CDK4/6 approuvés (palbociclib, ribociclib et abemaciclib) n'ont pas été comparés entre eux dans un essai clinique. Cependant, une méta-analyse n'a pas retrouvé de différence significative entre les trois inhibiteurs de CDK4/6 (37,41). Le choix de la molécule peut être réalisé en fonction du profil de toxicité. De plus, les essais randomisés évaluant les AIs en monothérapie démontrent qu'aucun AI n'est supérieur à un autre en terme d'efficacité (42,43).

A noter que l'abemaciclib a été évalué chez des patients présentant des métastases cérébrales et pourrait être préféré dans ce contexte (44).

Les patientes non-ménopausées doivent être traitées de la même façon que les patientes ménopausées mais en ajoutant une suppression ovarienne chirurgicale ou par agonistes de la LHRH (37).

Options thérapeutiques

- Le fulvestrant associé à un inhibiteur de CDK 4/6 constitue une alternative appropriée, en particulier pour les patients ayant déjà reçu un traitement par AI.
- Un traitement en monothérapie avec le fulvestrant ou un AI seul peut également

être proposé pour les patients les plus fragiles ou pour lesquels la maladie reste indolente.

2.3 Traitements systémiques après la première ligne

Après la 1^{ère} ligne d'hormonothérapie, la séquence optimale de traitement n'est pas connue actuellement (37). Aucune étude randomisée n'a pu définir le schéma thérapeutique mais plusieurs options thérapeutiques sont possibles. Elles sont dépendantes de la première ligne employée.

On retrouve notamment le fulvestrant seul (45), ou en association avec un inhibiteur de CDK4/6 (46–48). En association à une hormonothérapie (exemestane, fulvestrant ou tamoxifène), un inhibiteur de mTOR peut être utilisé en seconde ligne (49–51). La chimiothérapie peut être également un traitement de choix, mais sera réservée plutôt aux patients avec crise viscérale. Selon les données de profils moléculaires, d'autres thérapeutiques peuvent être envisagées, notamment *via* les essais cliniques avec des thérapies ciblées.

3. L'AVENEMENT DES INHIBITEURS DE CDK4/6 DANS LE CANCER

DU SEIN RH+

L'approbation récente des inhibiteurs de CDK4/6 dans le traitement des cancers du sein avancés RH+/HER2- constitue un tournant majeur dans la prise en charge des cancers du sein.

3.1 Mécanismes d'action

Le cycle cellulaire (Figure 2)

Le cycle cellulaire est un mécanisme composé de 4 phases (52):

- La phase G1 qui correspond à la croissance cellulaire.
- La phase S (S pour synthèse) qui correspond à la réplication de l'ADN.
- La phase G2.
- La phase M (M pour mitose) qui permet le partage égal des chromosomes entre

les deux cellules filles. Après la mitose, les cellules filles peuvent soit entrer en G1 pour effectuer un nouveau cycle de division, soit entrer en phase G0, correspondant à une phase de quiescence. L'ensemble de ces événements aboutit à la division cellulaire.

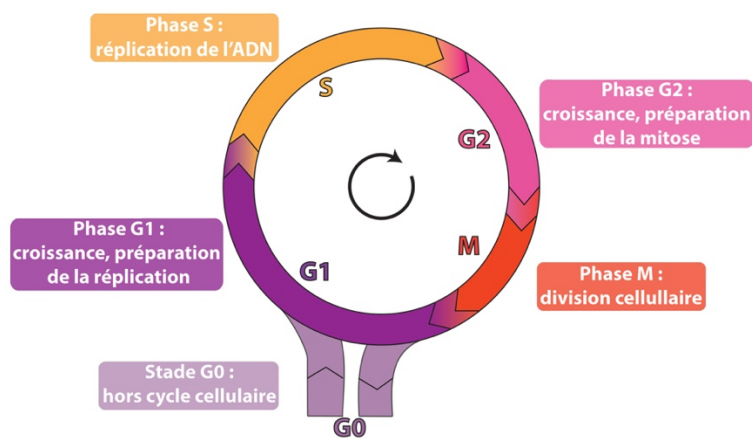


Figure 2. Les phases du cycle cellulaire (52).

La régulation du cycle cellulaire (Figure 3)

Durant un cycle, les quatre phases se succèdent dans un ordre immuable : G1, S, G2 et M. Pour cela et afin d'obtenir deux cellules filles rigoureusement identiques, la cellule dispose de systèmes de régulation, intervenant à différents niveaux (52).

Les kinases dépendantes des cyclines (CDK) sont une famille de protéines kinases qui jouent un rôle majeur dans la régulation du cycle cellulaire. Par définition, les CDK deviennent fonctionnelles lorsqu'elles sont associées à une cycline. Elles assurent la transition entre chaque phase du cycle (53).

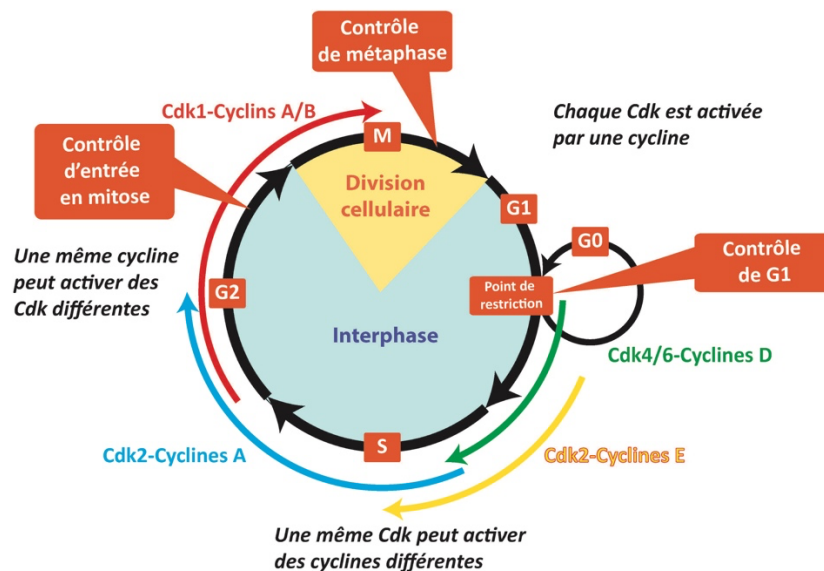


Figure 3. Les mécanismes de régulation du cycle cellulaire (52).

Les CDK4 et CDK6 se lient à la cycline D. Ce complexe permet la transition de la phase G1 à la phase S. Il permet la phosphorylation et donc l'inactivation de la protéine Rb (« Retinoblastoma protein »), ce qui a pour effet de libérer les facteurs de transcription E2F qui contrôlent l'expression de gènes nécessaires pour la transition G1/S et pour la progression de la phase S (54).

Dérégulation de la voie CDK4/6-Rb dans le cancer du sein

Les mécanismes de dérégulation de la voie CDK4/6-Rb sont différents selon le sous-type de cancer du sein. L'amplification du gène *CCND1* est observée dans environ 15% des cancers du sein, et la surexpression de la cycline D1 dans plus de 50% des cancers du sein (55,56). Bien

que les cancers du sein RH+ conservent généralement un Rb fonctionnel, la perte de l'expression de Rb est fréquemment observée dans le cancer du sein triple négatif. Elle est généralement associée à une moins bonne différenciation cellulaire et à un potentiel métastatique plus élevé (57,58).

Rationnel du ciblage des CDK4/6 dans le cancer du sein RH+

Les œstrogènes induisent l'expression de la cycline D1 et favorisent ainsi l'activité de CDK4/6 dans les cancers du sein RH+. Cela conduit à l'hyperphosphorylation du Rb et donc à la progression du cycle cellulaire (59–61). Il a été démontré que la diminution de la signalisation des œstrogènes réduisait la formation du complexe CDK-cycline, entraînant un arrêt du cycle cellulaire en G0 et G1 (59).

3.2 Les inhibiteurs de CDK4/6

Les études pré-cliniques

Yu *et al.* ont montré que la suppression de la cycline D1 et de CDK4 chez la souris prévenait les cancers du sein (62,63). Des années plus tard, de nombreuses études ont analysé la sensibilité *in vitro* du palbociclib, un inhibiteur réversible hautement sélectif de CDK4/6, dans de multiples lignées cellulaires de cancer du sein humain et ont rapporté que la sensibilité du palbociclib variait en fonction du sous-type moléculaire (64,65). Les lignées cellulaires RH+ avec des caractéristiques luminales, qui conservent un Rb fonctionnel, étaient plus sensibles. Au contraire, les lignées cellulaires triples négatives de type basales, présentant généralement une perte fonctionnelle de Rb, étaient généralement résistantes au palbociclib. A noter qu'une inhibition de la croissance a également été observée dans les lignées cellulaires avec une amplification d'HER2, principalement dans celles présentant des caractéristiques luminales

(65). Ces travaux ont conduit à un essai clinique évaluant le palbociclib associé à un anti-œstrogène dans le cancer du sein RH+. Cette étude a ensuite été étendue à l'essai pivot de phase 2 randomisé PALOMA-1 (66).

Les essais pivots

Il existe actuellement trois inhibiteurs hautement sélectifs de CDK4/6 approuvés pour le traitement du cancer du sein avancé RH+/HER2- : le palbociclib, l'abemaciclib et le ribociclib. Bien que ces trois molécules aient des mécanismes d'action similaires, il existe des différences en termes de pharmacocinétique et de toxicités.

Ces trois molécules sont approuvées en association avec des inhibiteurs de l'aromatase et avec le fulvestrant pour les cancers du sein avancés RH+/HER2-.

Ces différentes études sont synthétisées dans le **Tableau 1**.

Inhibiteur de CDK4/6	Ligne et population d'étude	n	Survie sans progression médiane (mois)	Survie globale médiane (mois)	
Essais en association avec inhibiteurs de l'aromatase					
PALOMA-2 (67)	Palbociclib	Femmes ménopausées en 1 ^{ère} ligne	666	24,8 vs 14,5 (HR 0,58; $p<0,001$)	-
MONALEESA-2 (68)	Ribociclib	Femmes ménopausées en 1 ^{ère} ligne	668	25,3 vs 16,0 (HR 0,57; $p<0,001$)	-
MONARCH-3 (69,70)	Abemaciclib	Femmes ménopausées en 1 ^{ère} ligne	493	28,2 vs 14,7 (HR 0,54, $p=0,000021$)	-
Essais en association avec fulvestrant					
PALOMA-3 (46,71)	Palbociclib	Femmes ménopausées ou non, \geq 1 ^{ère} ligne	521	9,5 vs 4,6 (HR 0,46; $p<0,001$)	34,9 vs 28,0 (HR 0,81; $p=0,09$)
MONALEESA-3 (48,72)	Ribociclib	Femmes ménopausées et hommes, 1 ^{ère} ou 2 ^{ème} ligne	726	20,5 vs 12,8 (HR 0,60; $p<0,001$)	Non atteinte vs 40,0 (HR 0,72; $p=0,005$)
MONARCH-2 (47,73)	Abemaciclib	Femmes ménopausées ou non, 1 ^{ère} ou 2 ^{ème} ligne	669	16,4 vs 9,3 (HR 0,55; $p<0,001$)	46,7 vs 37,3 (HR 0,76; $p=0,014$)
Essai en association avec tamoxifène ou avec inhibiteur de l'aromatase + goséréline					
MONALEESA-7 (74,75)	Ribociclib	Femmes non-ménopausées, 1 ^{ère} ligne	672	23,8 vs 13,0 (HR 0,55; $p<0,001$)	Non atteinte vs 40,9 (HR 0,71; $p=0,01$)

Tableau 1. Synthèse des essais pivots sur les inhibiteurs de CDK4/6 en association à l'hormonothérapie dans les cancers du sein avancés RH+/HER2-.

Palbociclib

À la suite des résultats des études PALOMA, l'agence européenne des médicaments (EMA) a approuvé le palbociclib dans le cadre du traitement du cancer du sein RH+ le 9 novembre 2016 (76).

Le palbociclib est indiqué dans le traitement du cancer du sein RH+/HER2-, localement avancé ou métastatique :

- en association avec un inhibiteur de l'aromatase ;
- en association avec le fulvestrant chez les femmes ayant été traitées antérieurement par hormonothérapie.

Chez les femmes non-ménopausées, l'hormonothérapie doit être associée à un agoniste de la LHRH (76).

La dose recommandée est de 125 mg par voie orale, une fois par jour pendant 21 jours consécutifs, suivis de 7 jours sans traitement (schéma 3/1), constituant un cycle complet de 28 jours (76).

La toxicité majeure du palbociclib est hématologique, principalement avec la neutropénie. Malgré tout, la neutropénie fébrile reste rare. Une analyse regroupant les effets indésirables des études PALOMA-1, PALOMA-2 et PALOMA-3 retrouve 65.4% de neutropénie de grade \geq 3. La fatigue et les nausées sont les toxicités non hématologiques les plus fréquentes, principalement de grade 1-2 (77).

Analyse de données de vie réelle sur l'utilisation du palbociclib combiné à l'hormonothérapie dans le cancer du sein métastatique RH+/HER2-

RESUME

Introduction : Les inhibiteurs de CDK4/6 sont indiqués en association avec l'hormonothérapie pour le traitement des cancers du sein localement avancés et/ou métastatiques RH+/HER2-. Le palbociclib est le premier inhibiteur de CDK4/6 à avoir été approuvé en Europe. Il est utilisé en association aux inhibiteurs de l'aromatase en première ligne ou à un anti-œstrogène, le fulvestrant, après progression sous hormonothérapie. L'objectif de cette étude était d'analyser les données de vie réelle concernant l'efficacité, les facteurs prédictifs et la tolérance du palbociclib chez des patientes suivies pour un cancer du sein avancé RH positifs, HER2 négatif.

Matériel et méthodes : Il s'agit d'une étude rétrospective menée de janvier 2016 à janvier 2019 au Centre Jean Perrin de Clermont-Ferrand. Les données cliniques, biologiques et radiologiques de patientes traitées par palbociclib pour un cancer du sein avancé RH+/HER2- ont été recueillies. Les données de survie ont été analysées afin d'identifier de potentiels facteurs prédictifs de réponse.

Résultats : 191 patientes ont été incluses dans l'étude. Le traitement par palbociclib était prescrit en 1^{ère} ligne chez 83 patientes (43,5%), en 2^{ème} ou 3^{ème} ligne chez 59 patientes (30,9%) et après 3 lignes chez 49 patientes (25,6%). Le suivi médian était de 36 mois. La survie sans progression (SSP) et la survie globale (SG) dans la population étudiée étaient de 12 mois (IC 95% = 9–17) et de 39 mois (IC 95% = 35–NA) respectivement. En analyse multivariée, les facteurs prédictifs suggérant une diminution de la SSP étaient : un ratio neutrophiles/lymphocytes élevé, un taux d'ACE ou de CA 15-3 élevés à l'initiation du palbociclib et un antécédent d'hormonothérapie en situation de cancer avancé. Une amélioration de la SSP était observée lorsque le score Allred était élevé pour les récepteurs aux œstrogènes et lorsqu'une diminution de dose du palbociclib était appliquée en cours de traitement. Le profil de toxicité était similaire aux données publiées.

Conclusion : Ces données de vie réelle sont concordantes avec les études pivots et les données de la littérature. La diminution de dose du palbociclib n'impacte pas le bénéfice du traitement par palbociclib et pourrait être un facteur prédictif de réponse.

Real-life data of palbociclib with endocrine therapy in HR positive HER2-negative advanced breast cancer

ABSTRACT

Introduction: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors are the treatment in hormone receptor positive (HR+) and HER2 positive (HER2+) locally advanced or metastatic breast cancer (ABC/MBC) in combination with endocrine therapy (ET). Palbociclib was the first CDK4/6 inhibitor approved in Europe for use in combination with aromatase inhibitors in the first line setting, or with an anti-estrogen, fulvestrant, after progression on ET.

The objective of this study was to analyze real-life data regarding the efficacy, predictive factors, and the safety of palbociclib.

Material and methods: A retrospective unicentric study was conducted from January 2016 to January 2019. Clinical, biological, and radiological data of patients treated with palbociclib for HR+/HER2- ABC/MBC were collected. Survival data and predictive factors of response were also analyzed.

Results: 191 patients were included in the study. Palbociclib therapy was prescribed in first line in 83 patients (43.5%), in 2nd or 3rd line in 59 patients (30.9%) and after 3 lines in 49 patients (25.6%). The median follow-up was 36 months. Progression-free survival (PFS) and overall survival (OS) in the global population were 12 months (95% CI [9-17]) and 39 months (95% CI [35-NA]) respectively. In multivariate analysis, several factors were identified as poor prognostic factors for PFS: a high neutrophil/lymphocyte ratio, elevated CEA or CA 15-3 levels at palbociclib initiation, and a history of ET in ABC/MBC setting. High Allred score for estrogen receptor and palbociclib dose reduction during treatment were predictive for better PFS. The toxicity profile was similar to published data.

Conclusion: These real-life data are consistent with previously published pivotal and real-life studies. Dose reduction of palbociclib does not impact the benefit of treatment and might be a good predictive factor of response.

II. ARTICLE

1. INTRODUCTION

Breast cancer (BC) is the most common cancer in women in France with an estimated incidence of 58,459 new cases in 2018 (78). In about 70% of cases, the cancer is hormone receptor positive and HER-2 negative (HR+/HER2-) (79).

Although mortality has decreased in recent years due to diagnostic and therapeutic advances, in cases of advanced or metastatic disease, the median overall survival (OS) is 3 years (11).

In recent years, CDK4/6 inhibitors (palbociclib, abemaciclib, ribociclib) have become the standard of care of HR+/HER2- advanced breast cancer (ABC) and/or metastatic breast cancer (MBC) in combination with endocrine therapy (ET) (37). CDK 4/6 inhibitors in combination with ET lead to cell cycle block. Indeed, to enter the cell cycle, a cell must go from the G1 phase to S phase. This transition is in part regulated by the retinoblastoma protein (Rb). Cyclin D (D1, D2, D3) are the main drivers of this transition. Cyclin D then binds and activates CDK 4/6. This complex phosphorylates retinoblastoma (Rb). When Rb is hyperphosphorylated, its inhibitory control of E2F transcription factors is reduced, and the cell cycle progresses (80). Cyclin D amplification has been described in many cancers, notably in breast cancer. In breast cancer, cyclin D1 binds to the transcriptional activity of the estrogen receptor (ER) (81). Thus, numerous studies (PALOMA, MONARCH, MONALEESA) have demonstrated an improvement in progression-free survival (PFS) and overall survival (OS) with a good toxicity profile of CDK4/6 inhibitors in combination with ET compared to ET alone (46–48,66,67,69,71,73,74,82).

Palbociclib was the first compound in this class to be approved in Europe, in combination with aromatase inhibitors (AI) or an antiestrogen, fulvestrant, following the results of the PALOMA-1, PALOMA-2 and PALOMA-3 pivotal studies (46,66,67).

The main adverse effects (AEs) of palbociclib are hematological, with mainly a risk of neutropenia. Nevertheless, febrile neutropenia remains rare (77).

However, the efficacy of CDK4/6 inhibitors combined with endocrine therapy remains limited due to acquired resistance. The mechanisms of which are still poorly understood (83). No predictive biomarkers have been identified in randomized trials (84).

To date, many real-life studies have found fairly similar results with clinical trials (85–88).

This trial will report here our experience at the Jean Perrin anticancer center in Clermont-Ferrand since 2016. The objectives of the study are to investigate the efficacy and safety of palbociclib combined to ET in patients with HR+/HER2- locally advanced or metastatic breast cancer in real life conditions. Predictive response factors to this treatment were evaluated.

2. METHODS

2.1 Study design and patients' selection

The study design was descriptive, observational, and retrospective, with no examination or drug interventions.

All patients treated from January 2016 to January 2019 with palbociclib in combination with ET for locally advanced or metastatic breast cancer were enrolled. The cohort included 216 patients.

Inclusion criteria were age 18 years or older, locally advanced, or metastatic breast cancer with documented HR+ (estrogen receptor-positive and/or progesterone receptor-positive) tumor based on local standards. Exclusion criteria were missing data regarding breast cancer molecular subtype, HER2+ tumor based on local standards, history of treatment with palbociclib. Men were also excluded to homogenize the population. In the end, 191 patients were selected for the study (**Figure 1**). We formed subgroups according to the number of prior lines to palbociclib: 0 (group A, n = 83), 1 or 2 lines (group B, n = 59) and ≥ 3 lines (group C, n = 49).

Allred score method was used to report expression of estrogen and progesterone receptors (scale range 0 to 8) (2). Assessment of HER2 positivity was via immunohistochemistry. Fluorescence in-situ hybridization tests were used to confirm HER2 status when immunohistochemistry results were equivocal (score 2+) (7).

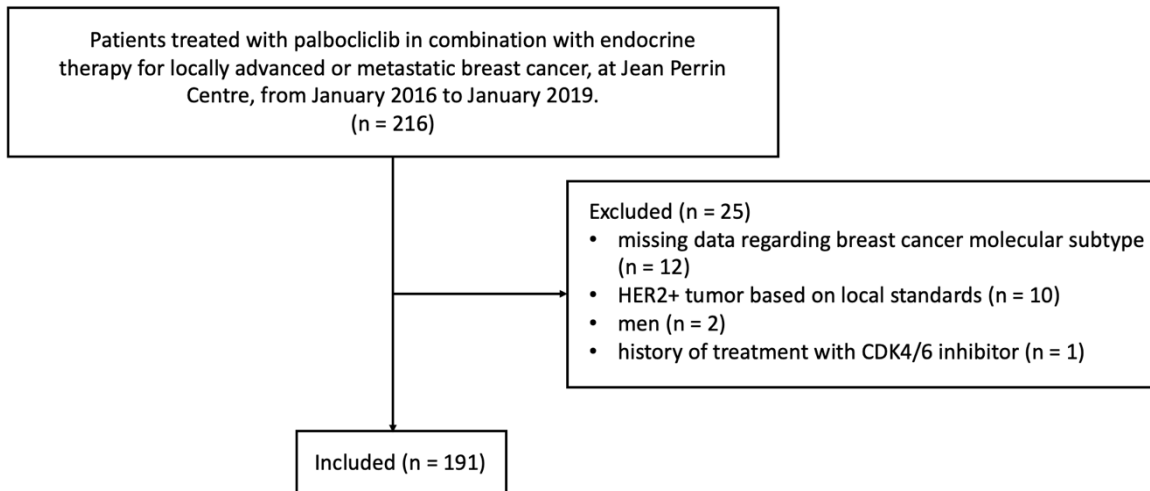


Figure 1. Flow-chart of the study.

2.2 Data collection

Clinical, laboratory, histological and radiological data of patients and outcomes data were retrospectively collected for all patients from electronic medical records. The data on therapeutic management were also recovered: number of prior lines, modalities of treatment, and major side effects.

Response to treatment as assessed by imaging [Computed Tomography (CT) scan and/or positron emission tomography (PET) scan] was also recorded. If available, molecular biology data were considered. Finally, when laboratory tests were available, we collected the values of CA 15-3, CEA, neutrophils and lymphocytes as well as the neutrophils to lymphocytes ratio (NLR) at the initiation of palbociclib.

Histological findings were collected from a sample (usually a biopsy) taken at the time of recurrence or metastatic tumors, if available, otherwise from the original tissue.

Follow-up included a clinical examination by oncologist before the beginning of each cycle (approximately every 28 days) and could differ according to the practices of the referring oncologist. CT scans and/or PET scans were performed at the discretion of the referring oncologist, usually every 2 to 3 months. Imaging responses were assessed according to RECIST v1.1.

2.3 Statistical analysis

Progression-free survival (PFS) was calculated as the time from the start of palbociclib to the date of failure or the patient's death which ever came first. Overall survival (OS) was defined as the time between the start of palbociclib and the patient's death.

Data were quoted as the median (range), the median [interquartile range (IQR)], or (for data on survival) the median [95% confidence interval (CI)]. Severity of adverse events of treatment

were assessed according to the National Cancer Institute common toxicity criteria for adverse events, version 5.0 (NCI–CTCAE).

Qualitative variables were reported as the frequency (percentage).

PFS and OS were calculated using the Kaplan–Meier method. Results were considered statistically significant at a value of $p < 0.05$. Predictors for PFS and OS were investigated using the Cox regression model for univariate and multivariate analyses. The variables with a log rank $p < 0.2$ in univariate analyses were included in the primary model for the multivariate analysis.

The statistical analyses were performed using R-Project, version 3.6.1 (R-Project, GNU GPL, <http://cran.r-project.org/>).

This work did not require any written patient consent. The local ethics committee of Jean-Perrin Centre approved this work.

3. RESULTS

3.1 Clinical characteristics

Overall, 191 patients were included in the study. The baseline detailed characteristics of patients treated by palbociclib combined with ET for locally advanced or metastatic breast cancer, at Jean Perrin Centre, from period January 2016 to January 2019 were summarized in

Table 1.

The median age of the patients was 64 years (range: 30-91) [64 years (35-91) in group A, 63 years (34-84) in group B, and 64 (30-79) in group C]. 163 patients (85.3%) were postmenopausal (80.7% in group A, 83.1% in group B, and 95.9% in group C).

1.1 Breast cancer characteristics

The baseline characteristics of breast cancer were summarized in **Table 1**.

Estrogen receptor (ER) was positive in 191 patients (100%) with a median Allred score of 8 (range: 4-8). Progesterone receptor (PR) was positive in 120 patients (63.2%) with a median Allred score of 5 (range: 0-8). The median Ki-67 was 15 (range: 0-95) and 57 patients (31.5%) had a Ki-67 > 20%. At diagnosis of ABC/MBC, 112 patients (58.6%) had a recurrence, and 79 patients (41.4%) had *de novo* disease. At the initiation of palbociclib, 129 patients (67.5%) had visceral metastases; 159 patients (83.2%) had bone metastases and 25 patients (15.7%) had only bone metastases (14.4% in group A, 13.6% in group B and 10.2% in group C). Patients receiving palbociclib in the first line had less visceral metastases (56.6%) than patients receiving palbociclib in the second or third line (72.9%), or after 3 lines (79.6%). Nine patients (4.7%) had locally advanced breast cancer with skin and/or lymph node involvement (8.4% in group A, 1.7% in group B and 2.0% in group C); 81 patients (42.4%) had 3 metastatic sites or more (36.1% in group A, 40.7% in group B and 55.1% in group C).

3.2 Treatment characteristics

The baseline characteristics for breast cancer treatments were summarized in **Table 1**.

One hundred forty-two patients (74.3%) had a history of breast surgery, included 28 (14.7%) in a metastatic situation. The surgical strategy was either mastectomy or breast-conserving surgery (58.2% and 41.8% respectively). One hundred fifty-three patients (80.5%) had a history of ET (65.1% in group A, 93.2% in group B and 91.7% in group C), including 102 (53.7%) in the adjuvant setting (61.4% in group A, 54.2% in group B and 38.8% in group C). Forty-one patients (40.2%) received an aromatase inhibitor, 40 patients (39.2%) received tamoxifen and 21 patients (20.6%) received both an aromatase inhibitor and tamoxifen sequentially in adjuvant setting. In the ABC/MBC setting and before palbociclib initiation, 83 patients (43.5%) had received no prior treatment and 49 patients (25.7%) had received more than 3 lines of treatment: the median number of previous lines was 1 (0-10). Seventy-one patients (37.2%) had received chemotherapy in ABC/MBC setting before palbociclib initiation. Eighty-nine patients (46.6%) had not received ET for ABC/MBC and 48 patients (25.1%) had received more than 2 lines of ET: the median number of previous lines was 1 (0-5). We noted that 42 patients (22.0%) received everolimus and 27 patients (14.1%) received fulvestrant prior to palbociclib initiation.

3.3 Laboratory tests

All patients had complete standard laboratory tests at the initiation of palbociclib, including a complete blood count with neutrophils and lymphocytes count. Some patients had tumor marker assays (CEA and CA 15-3) performed at the discretion of the physician. Their results are summarized in **Table 1**. At the initiation of palbociclib, the median neutrophil-to-lymphocyte ratio is 2.5 (0.4–21.6) [2.6 (0.4–7.9) in group A, 1.9 (0.7–21.6) in group B and 2.5

(1.0–7.5) in group C], and the median value of CEA and CA 15-3 is 5 µg/L (1-842) [3 µg/L (1 – 264) in group A, 6 µg/L (1–335) in group B and 8 µg/L (2–842) in group C] and 84 IU/mL (6-5863) [71 IU/mL (6–5863) in group A, 82 IU/mL (8–1552) in group B and 104 IU/mL (10–3581) in group C] respectively.

Some patients had molecular cancer screening. One or more molecular alterations were found in 37 patients: 8 patients had an *ESR1* mutation, 18 patients had a *PIK3CA* mutation, 6 patients had a *BRCA2* mutation. Anomalies of 8 other genes were found (*CCND1*, *MET*, *FGFR1*, *FGFR3*, *CDKN2A*, *TP53*, *MAP2K1*, *CTNNB1*).

Patients' demographics characteristics	Men	0	0.0
	Women	191	100.0
	Age, median in years (range)	64 (30–91)	
	Menopausal status		
	Premenopausal/Perimenopausal	28	14.7
Postmenopausal	163	85.3	
Cancer characteristics	Histology		
	Invasive ductal carcinoma	101	52.9
	Invasive lobular carcinoma	34	17.8
	Non-specific invasive carcinoma	47	24.6
	Others	9	4.7
	Grade (SBR)		
	I	24	13.3
	II	134	74.4
	III	22	12.2
	Hormonal receptors		
	Estrogen receptor (threshold: 10%)		
	Positive	100	100.0
	Negative	0	0.0
	Rate, median in % (range)	100 (10–100)	
	Allred score, median (range)	8(4–8)	
	Progesterone receptor (threshold: 10%)		
	Positive	120	63.2
	Negative	70	36.8
	Rate, median in % (range)	30 (0–100)	
	Allred score, median (range)	5 (0–8)	
	Ki67		
	Median in % (range)	15 (0–95)	
	Size of tumor at diagnosis (according to TNM)		
	T1 (≤ 2 cm)	47	27.0
	T2 (> 2 cm and ≤ 5 cm)	65	37.4
	T3 (> 5 cm)	24	13.8
	T4 (any size, with a direct extension to the chest wall or to the skin)	38	21.8
	Nodal status at diagnosis (according to TNM)		
	N0	54	38.8
	N1	44	31.7
	N2	29	20.9
	N3	12	8.6
	Breast cancer status		
Recurrence	112	58.6	
<i>De novo</i> metastatic	79	41.4	
Metastases			
Visceral	129	67.5	
Lung	48	25.1	
Liver	72	37.7	
Brain	6	3.1	
Other	58	30.3	
Bone	159	83.2	
Bone only	25	15.7	
Lymph node	98	51.3	
Skin	25	13.1	
Advanced breast cancer (with only skin and/or lymph node involvement)	9	4.7	
Number of metastatic sites			
<3	110	57.6	
≥ 3	81	42.4	
Laboratory values at palbociclib initiation	CA 15-3 in U/ml, median (range) [<i>normal values: < 31.3 U/ml</i>]	84 (6–5863)	
	CEA in μ g/L, median (range) [<i>normal values: < 3 μg/L</i>]	5 (1–842)	
	Neutrophils in G/L, median (range) [<i>normal values: 1.5-7.0 G/L</i>]	3.3 (1.0–10.8)	
	Lymphocytes in G/L, median (range) [<i>normal values: 1.5-4.0G/L</i>]	1.4 (0.4–3.8)	
	Neutrophil-to-lymphocyte ratio, median (range)	2.5 (0.4–21.6)	

Treatment of cancer characteristics	History of breast surgery		
	Yes	142	74.3
	No	49	25.7
	History of breast surgery in metastatic setting		
	Yes	28	14.7
	No	163	85.3
	Breast radiotherapy		
	Yes	137	71.7
	No	54	28.3
	History of endocrine therapy		
	Yes	153	80.5
	No	37	19.5
	History of adjuvant endocrine therapy		
	Yes	102	53.7
	No	88	46.3
	History of neoadjuvant or adjuvant chemotherapy		
	Neoadjuvant	42	22.1
	Adjuvant	41	21.6
	Neoadjuvant and adjuvant	2	1.1
	No	105	55.3
	Number of previous lines of endocrine therapy for ABC before palbociclib initiation		
0	89	46.6	
1	54	28.3	
≥2	48	25.1	
History of treatment by everolimus combined with ET			
Yes	42	22.0	
No	149	78.0	
History of treatment by fulvestrant			
Yes	27	14.1	
No	164	85.9	
Number of previous lines of cancer treatment for ABC before palbociclib initiation			
0	83	43.5	
1-2	59	30.9	
≥3	49	25.7	

Table 1 – Baseline demographic, clinical and laboratory characteristics

3.4 Management of palbociclib and outcomes

The initial dose of palbociclib was 125 mg daily in 178 patients (93.2%), or 100 mg daily in 13 patients (6.8%), 3 out of 4 weeks for all these patients. At the initiation of the treatment, palbociclib was combined with an aromatase inhibitor in 97 patients [(50.8%) (69.9% in group A, 32.2% in group B and 40.8% in group C)] and with an anti-estrogen (fulvestrant in 92 patients and tamoxifen in 2 patients) in 94 patients [(49.2%) (30.1% in group A, 67.8% in group B and 59.2% in group C)]. Twenty-nine patients (15.2%) received additional ovarian suppression: a luteinizing hormone-releasing hormone (LHRH) agonist was prescribed in 13 patients. Ten patients underwent oophorectomy before starting CDK4/6 inhibitors and 6 patients were treated with LHRH agonist before the oophorectomy. Fifteen patients (7.8%) had a switch in endocrine therapy during palbociclib treatment: 2 patients switched to an anti-aromatase, 11 patients received an anti-aromatase followed by an anti-estrogen and 2 patients received an anti-estrogen followed by an anti-aromatase (**Table 2**).

According to imaging criteria, at CT scan, the overall response rate was 25.9% for the total population (45.7% in group A, 16.3% in group B and 7.7% in group C) (**Table 2**). At the end of the follow-up, 158 patients (82.3%) discontinued treatment with palbociclib (68.7% in group A, 93.2% in group B and 93.9% in group C). The causes of palbociclib discontinuation were tumor progression in 127 patients (80.7%), toxicities in 17 patients (10.8%), death for 5 patients (3.2%), and other cause for 8 patients (5.1%). The median duration of treatment with palbociclib was 11 months (0-52): 21 months (0-44) in group A, 11 months (1-40) in group B and 7 months (0-52) in group C (**Table 2**).

	Total		Group A (1 st line)		Group B (line < 3)		Group C (line ≥ 3)	
	n = 191	%	n = 83	%	n = 59	%	n = 49	%
Endocrine therapy combined with palbociclib at starting palbociclib								
Aromatase inhibitor	97	50.8	58	69.9	19	32.2	20	40.8
Anti-estrogen	94	49.2	25	30.1	40	67.8	29	59.2
Palbociclib treatment at the end of study								
Ongoing	33	17.3	26	31.3	4	6.8	3	6.1
Discontinued	158	82.3	57	68.7	55	93.2	46	93.9
Causes of palbociclib permanent discontinuation								
Progression	127	80.9	44	78.6	47	85.5	36	78.3
Toxicity	17	10.8	6	10.7	6	10.9	5	10.9
Death	5	3.2	1	1.8	1	1.8	3	6.5
Other	8	5.1	5	8.9	1	1.8	2	4.3
Dose at initiation of palbociclib								
125 mg	178	93.2	77	92.8	56	94.9	45	91.8
100 mg	13	6.8	6	7.2	3	5.1	4	8.2
First dose reduction								
100 mg	70	37	33	40.2	21	36.2	16	32.7
75 mg	7	3.7	2	2.4	2	3.4	3	6.1
None	112	59.3	47	57.3	35	60.3	30	61.2
Second dose reduction								
75 mg	28	14.8	11	13.4	10	17.2	7	14.3
None	161	85.2	71	86.6	48	82.8	42	85.7
Best antitumor response at CT scan obtained with palbociclib								
Complete response	1	0.7	1	1.8	0	0	0	0
Partial response	35	25.2	25	43.9	7	16.3	3	7.7
Stable disease	69	49.6	24	42.1	24	55.8	21	53.8
Progressive disease	34	24.5	7	12.3	12	27.9	15	38.5
Best antitumor response at PET scan or bone scan obtained with palbociclib								
Complete response	17	19.5	14	25.5	3	13	0	0
Partial response	26	29.9	16	29.1	9	39.1	1	11.1
Stable disease	29	33.3	18	32.7	6	26.1	5	55.6
Progressive disease	15	17.2	7	12.7	5	21.7	3	33.3
Duration of treatment with palbociclib in months, median (range)	11 (0-52)		21 (0-44)		11 (1-40)		7 (0-52)	

Table 2 – Management of palbociclib and outcomes

3.5 Description of long treatment responders

In the study, 53 patients had a response to palbociclib > 24 months. Among them, 20.7% were pre- or perimenopausal (*versus* 14.7% in the overall population). The median Allred score for PR was 7 compared with 5 in the overall population. Grade ≥ 3 toxicity were observed in 71.7% (*versus* 66.7% in the overall population) including transaminase elevations and stomatitis. A dose reduction was applied in 55.8% of the cohort (*versus* 40.7% in the overall population). It was a locally advanced disease in 9.7% (*versus* 4.7% in the overall population). Patients had fewer visceral metastases (58.5% *versus* 67.5% in the overall population) in particular fewer liver metastases (13.2% *versus* 37.7% in the overall population). These patients had received less ET prior to palbociclib treatment (34% never received ET *versus* 19.5% in the overall population) and only 30.2% had received at least one line ET for ABC/MBC (*versus* 53.4% in the overall population). Palbociclib treatment was more often associated with an AI (56.6% *versus* 43.0% in the overall population). Most patients received palbociclib as first line (67.9% *versus* 43.5% in the overall population). At the initiation of palbociclib, the median CA 15-3 level was 42 UI/mL (6-1273) *versus* 84 UI/mL (6-5663) in the overall population; the median CEA level was 2 $\mu\text{g/L}$ (1-64) *versus* 5 $\mu\text{g/L}$ (1-842) in the overall population; the median NLR was lower: 2.2 (0.7-10.5) *versus* 2.5 (0.4-21.6) in the overall population.

3.6 Outcomes of patients

The median follow-up is 36 months [95% CI (34–38)]. At the end of the study, 87 patients were deceased.

Progression-free survival

For all patients, PFS at 12 months, 24 months and 36 months were 49.2% (95% CI = 42.6–56.8%), 28.3% (95% CI = 22.5–35.4%), and 16.8% (95% CI = 11.8–23.8%), respectively. The median PFS was 12 months (95% CI = 9–17) (**Figure 2**).

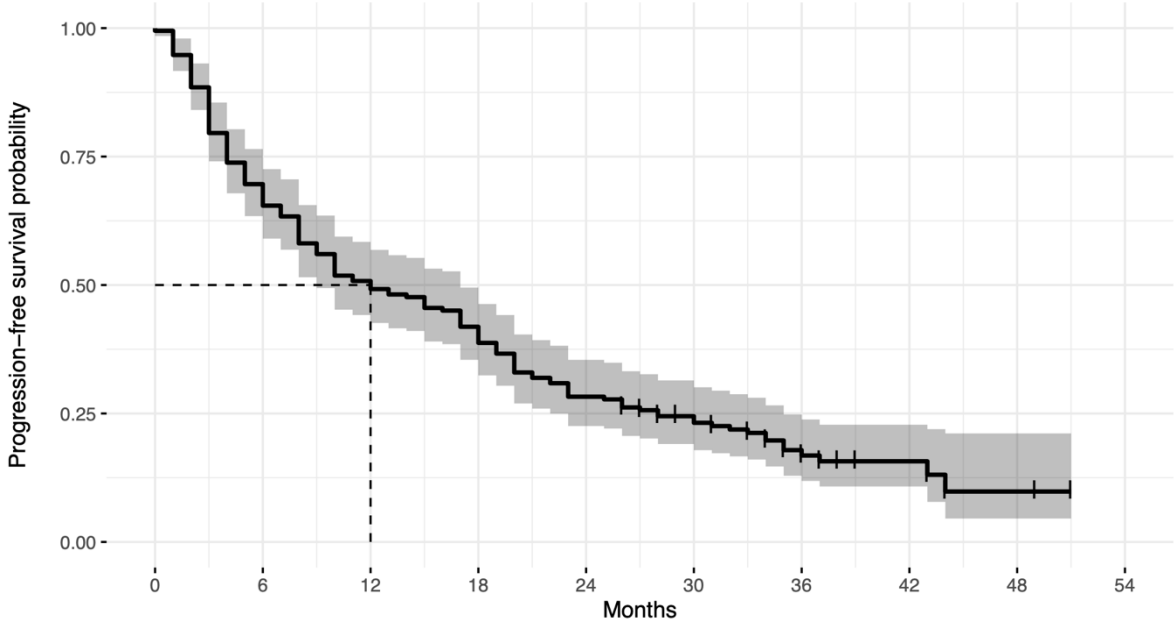


Figure 2. Progression-free-survival of the overall population.

For group A, PFS at 12 months, 24 months and 36 months were 66.3% (95% CI = 56.8–77.3%), 44.6% (95% CI = 35.0–56.7%), and 26.9% (95% CI = 17.7–40.8%), respectively. The median PFS was 20 months (95% CI = 17–32) (**Figure 3**).

For group B, PFS at 12 months, 24 months and 36 months were 44.1% (95% CI = 33.0–58.7%), 18.6% (95% CI = 10.9–31.8%), and 9.3% (95% CI = 4.0–21.4%), respectively. The median PFS was 10 months (95% CI = 8–18) (**Figure 3**).

For group C, PFS at 12 months, 24 months and 36 months were 26.5% (95% CI = 16.6–42.3%), 12.2% (95% CI = 5.7–25.9%), and 8.2% (95% CI = 3.1–20.9%), respectively. The median PFS was 6 months (95% CI = 4–8) (**Figure 3**). Patients receiving palbociclib in the first line had a better PFS than those receiving palbociclib from the second line ($p < 0.0001$).

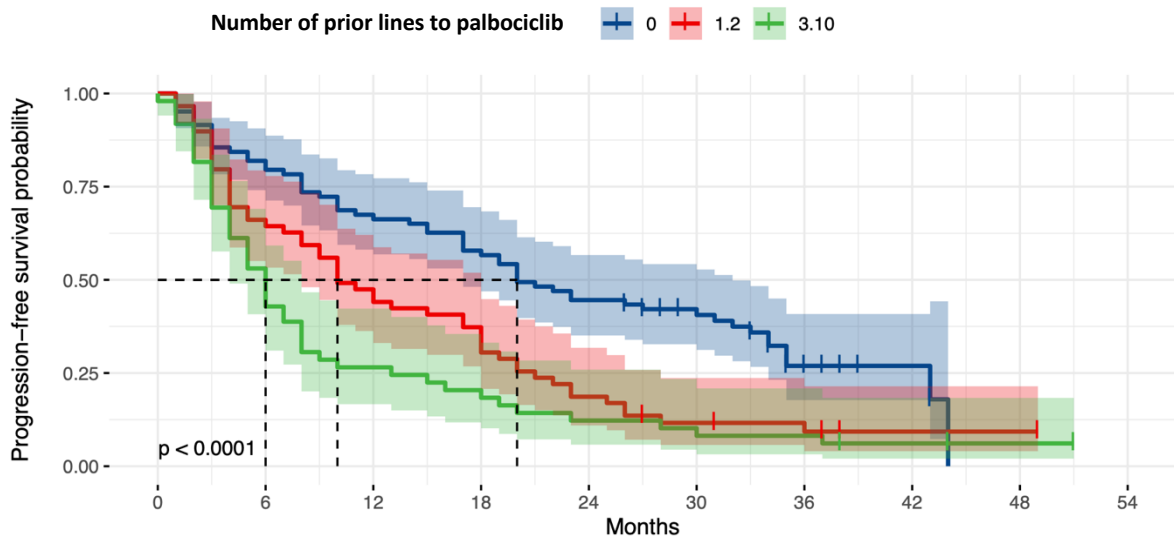


Figure 3. Progression-free-survival according to the number of lines prior to palbociclib.

Patients receiving palbociclib in combination with an anti-aromatase had a median PFS of 17 months (95% CI = 10–23); those receiving palbociclib in combination with an anti-estrogen had a median PFS of 8 months (95% CI = 6–12). Patients receiving palbociclib in combination with an anti-aromatase and an anti-estrogen sequentially had a median PFS of 23 months (95% CI = 17–NA). This difference was significant ($p = 0.016$) (**Figure 4**).

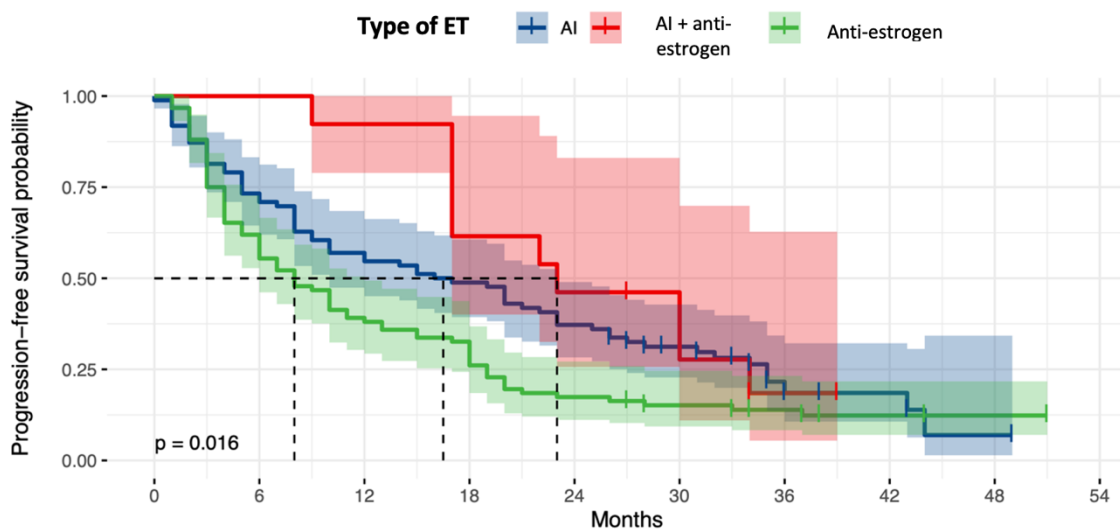


Figure 4. Progression-free-survival according to combined ET with palbociclib.

The age and the menopausal status were not statistically predictive for PFS ($p = 0.9$, and $p = 0.18$ respectively) (**Figure 5**).

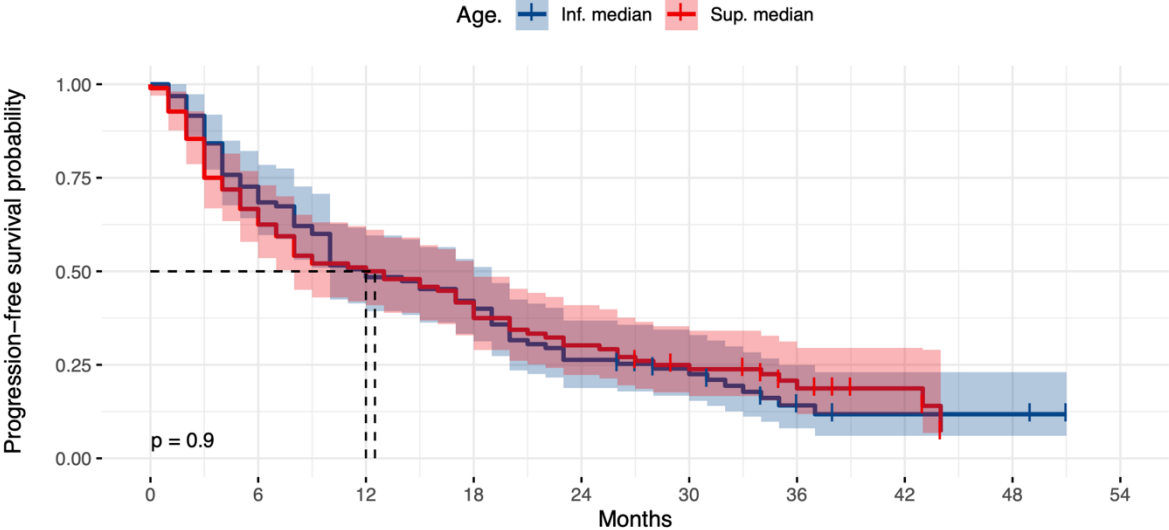


Figure 5. Progression-free-survival according to the age of patients

Overall survival

For all patients, OS at 12 months, 24 months and 36 months were 84.3% (95% CI = 79.2–89.6%), 70.1% (95% CI = 63.9–76.9%), and 54.0% (95% CI = 46.6–62.6%), respectively. The median OS was 39 months (95% CI = 35–NA) (**Figure 6**).

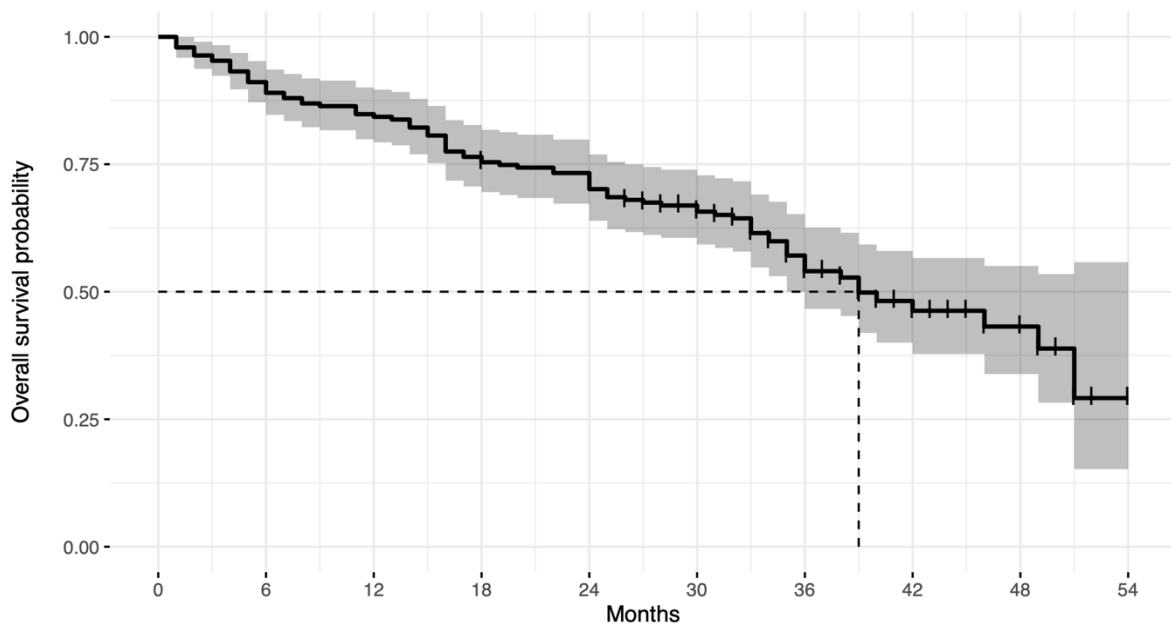


Figure 6. Overall survival of the overall population.

For group A, OS at 12 months, 24 months and 36 months were 89.2% (95% CI = 82.7–96.1%), 79.5% (95% CI = 71.2–88.7%), and 67.4% (95% CI = 56.7–80.1%), respectively. The median OS was not reached (**Figure 7**).

For group B, OS at 12 months, 24 months and 36 months were 84.7% (95% CI = 76.0–94.4%), 72.9% (95% CI = 62.3–85.2%), and 48.0% (95% CI = 35.2–65.5%), respectively. The median OS was 36 months (95% CI = 34.0–NA) (**Figure 7**).

For group C, OS at 12 months, 24 months and 36 months were 75.5% (95% CI = 64.3–88.6%), 51.0% (95% CI = 38.7–67.1%), and 38.9% (95% CI = 27.0–56.1%), respectively. The median OS was 25 months (95% CI = 22.0–40.0) (**Figure 7**). Patients receiving palbociclib in the first line had a better OS than patients receiving palbociclib later ($p = 0.00089$).

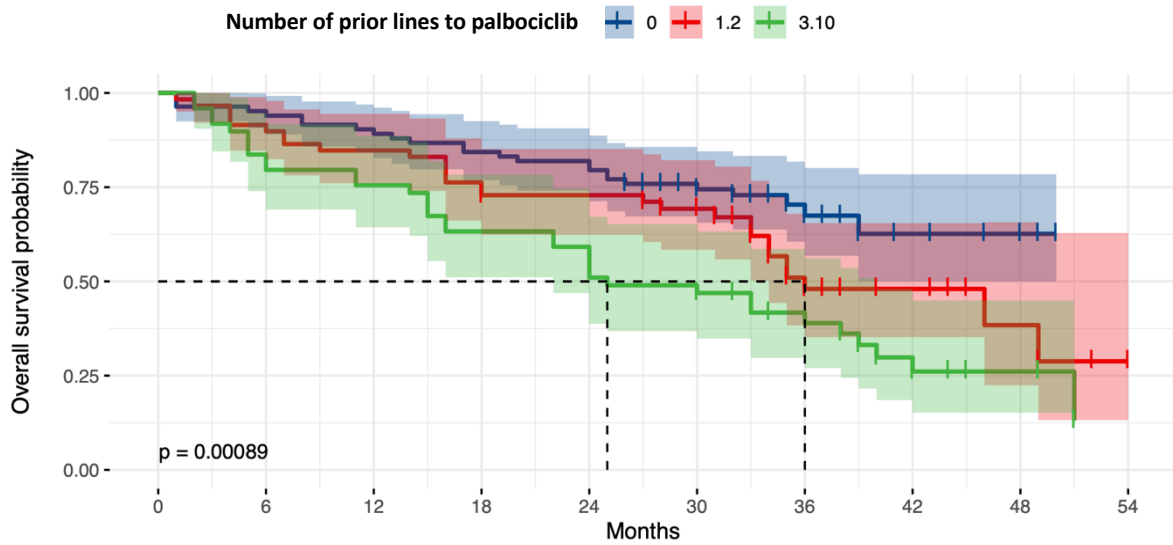


Figure 7. Overall survival according to the number of lines prior to palbociclib treatment

Patients receiving palbociclib in combination with an anti-aromatase had a median OS of 51 months (95% CI = 39–NA); those receiving palbociclib in combination with an anti-estrogen had a median OS of 35 months (95% CI = 31–49). Patients receiving palbociclib in combination with an anti-aromatase and an antiestrogen sequentially had a median OS of 40 months (95% CI = NA–NA). This difference was not significant ($p = 0.05$) (**Figure 8**).

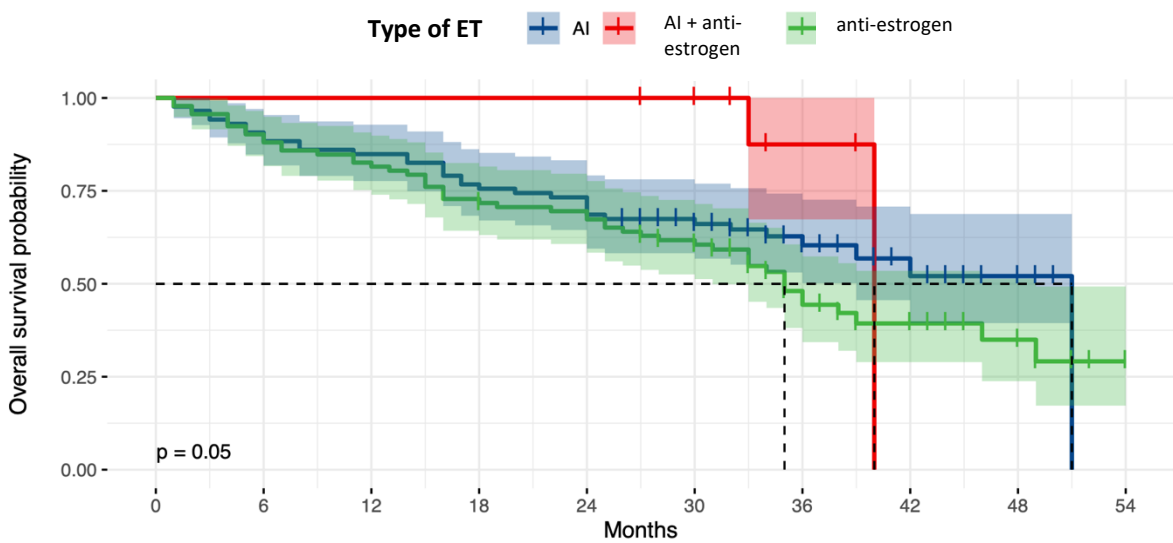


Figure 8. Overall survival according to combined ET with palbociclib

3.7 Predictive factors of survival

Predictive factors of progression-free survival

a) For global population

Results of the univariate and the multivariate analysis are shown in **Table 3**.

In univariate analysis, PFS was better if ER and PR rate according to the Allred score ($p=0.003$ and $p=0.005$) were high. ER and PR rates in percentage ($p=0.004$ and $p=0.002$) tended to increase PFS if they were high. Dose adjustment of palbociclib was also associated with improved PFS ($p<0.001$).

Number of metastatic sites ≥ 3 ($p<0.001$), presence of visceral metastases ($p=0.002$), and history of ET in adjuvant setting ($p=0.049$) and/or for ABC ($p<0.001$) were associated with poorer PFS. The higher the level of NLR at palbociclib initiation ($p=0.005$), the more the PFS was decreased. CEA and CA 15-3 markers at palbociclib initiation ($p=0.006$ and $p<0.001$) appeared to be associated with poorer PFS.

In multivariate analysis, the reduction of palbociclib dose during the treatment ($p=0.009$) and the ER rate according to the Allred score ($p=0.036$) were significant in improving PFS. The significant predictive factors of poorer PFS were a history of ET therapy for ABC ($p=0.003$) and a high NLR at palbociclib initiation ($p<0.001$). CEA and CA 15-3 markers at palbociclib initiation ($p<0.001$ and $p=0.001$) appeared to be associated with poorer PFS.

Predictive Factors	Univariate analysis		Multivariate analysis	
	HR (95 CI%)	p	HR (95 CI%)	p
Age	0.998 (0.986 – 1.010)	0.732	-	-
Size of tumor at diagnosis (according to TNM)		0.498		-
T2	1.260 (0.823 – 1.927)		-	
T3	1.305 (0.754 – 2.258)		-	
T4	1.420 (0.886 – 2.275)		-	
Nodal status at diagnosis (according to TNM) ≥ N1	1.376 (0.948 – 1.997)	0.086	-	-
<i>De novo</i> metastatic	0.877 (0.637 – 1.207)	0.418	-	-
History of breast surgery in metastatic situation	0.761 (0.476 – 1.217)	0.239	-	-
Histology		0.532		-
Invasive ductal carcinoma	1.026 (0.496 – 2.123)		-	
Non-specific invasive carcinoma	0.934 (0.436 – 1.998)		-	
Invasive lobular carcinoma	0.742 (0.336 – 1.640)		-	
Grade (SBR)		0.409		-
II	0.900 (0.558– 1.451)		-	
III	1.266 (0.675 – 2.374)		-	
Ki-67				
> 14%	1.170 (0.839 – 1.633)	0.352	-	-
> 20%	1.155 (0.818 – 1.632)	0.417	-	-
Estrogen receptor				
Rate	0.986 (0.978 – 0.995)	0.004	-	-
Allred score	0.736 (0.610 – 0.888)	0.003	0.700 (0.502 – 0.977)	0.036
Progesterone receptor				
Rate	0.993 (0.989 – 0.998)	0.002	0.997 (0.991 – 1.003)	0.327
Allred score	0.927 (0.881 – 0.977)	0.005	-	-
Toxicity ≥ grade 3	0.735 (0.532 – 1.015)	0.065	-	-
Reduction of palbociclib dose	0.514 (0.368 – 0.718)	< 0.001	0.510 (0.306 – 0.847)	0.009
Number of metastatic sites ≥ 3	1.768 (1.290 – 2.422)	< 0.001	1.413 (0.867 – 2.302)	0.165
Visceral metastases	1.723 (1.215 – 2.445)	0.002	-	-
Endocrine therapy in adjuvant treatment	1.503 (0.985 – 2.293)	0.049	1.552 (0.716 – 3.362)	0.265
Number of previous lines of endocrine therapy for ABC		< 0.001		-
1	1.959 (1.340 – 2.865)		2.710 (1.420 – 5.172)	0.003
≥ 2	2.461 (1.671 – 3.626)		2.471 (1.326 – 4.602)	0.004
NLR at palbociclib initiation	1.134 (1.048 – 1.228)	0.005	1.219 (1.104 – 1.346)	< 0.001
CA 15-3 at palbociclib initiation	1.001 (1.000 – 1.001)	<0.001	1.001 (1.000 – 1.001)	0.001
CEA at palbociclib initiation	1.003 (1.001 – 1.004)	0.006	1.005 (1.002– 1.008)	< 0.001

Table 3 – Results of univariate and multivariate analyses of progression-free survival for the overall population

b) For patients with palbociclib in first line (group A)

Results of the univariate and the multivariate analysis are shown in **Appendix 1**.

In univariate analysis, PFS was better when ER rate in percentage ($p=0.012$) and according to the Allred score ($p=0.009$) were high. Dose adjustment of palbociclib during treatment was also predictive of better PFS ($p=0.003$). PR rate in percentage tended to increase PFS if it was high ($p=0.013$).

Number of metastatic sites ≥ 3 ($p=0.013$) and high NLR at palbociclib initiation ($p=0.031$) were associated with poorer PFS. CA 15-3 marker at palbociclib initiation ($p<0.001$) appeared to be associated with poorer PFS.

In multivariate analysis, one parameter was associated with poorer PFS: a high NLR at palbociclib initiation ($p=0.011$). CEA and CA 15-3 markers at palbociclib initiation ($p=0.028$ and $p=0.006$) tended to be associated with poorer PFS.

c) For patients with palbociclib in second or third line (group B)

Results of the univariate and the multivariate analysis are shown in **Appendix 2**.

In univariate analysis, only a high level of CA 15-3 at palbociclib initiation ($p<0.001$) tended to be associated with poorer PFS.

In multivariate analysis, the significant predictive factor of better PFS was the reduction of palbociclib dose ($p=0.034$). On the contrary, the high level of CA 15-3 at palbociclib initiation ($p<0.001$) tended to be a factor decreasing the PFS.

d) For patients with palbociclib after three lines (group C)

Results of the univariate and the multivariate analysis are shown in **Appendix 3**.

In univariate analysis, the significant predictor of better PFS was the histological type of breast cancer ($p=0.037$).

There was no predictive factor for PFS in multivariate analysis.

Predictive factors of overall survival

a) For global population

Results of the univariate and the multivariate analysis are shown in **Table 4**.

In univariate analysis, PR rate according to the Allred score ($p=0.014$) was significant for improvement of OS. Dose adjustment during palbociclib treatment was also predictive of better OS ($p=0.019$). PR rate in percentage tended to increase OS if it was high ($p=0.026$).

Number of metastatic sites ≥ 3 ($p<0.001$), presence of visceral metastases ($p<0.001$), history of ET for ABC ($p=0.021$) and high NLR at palbociclib initiation ($p=0.003$) were associated with poorer PFS. CEA and CA 15-3 markers at palbociclib initiation ($p=0.002$ and $p<0.001$) tended to be associated with poorer OS.

In multivariate analysis, the significant predictive factor of poorer OS was a high NLR at palbociclib initiation ($p=0.001$). The high level of CEA at palbociclib initiation ($p<0.001$) tended to be a factor decreasing the OS.

Predictive Factors	Univariate analysis		Multivariate analysis	
	HR (95 CI%)	p	HR (95 CI%)	p
Age	1.013 (0.996 – 1.030)	0.124	-	-
Size of tumor at diagnosis (according to TNM)		0.941		-
T2	1.108 (0.634 – 1.937)		-	
T3	1.233 (0.592 – 2.566)		-	
T4	1.172 (0.616 – 2.230)		-	
Nodal status at diagnosis (according to TNM) ≥ N1	1.164 (0.716 – 1.893)	0.537	-	-
<i>De novo</i> metastatic	1.027 (0.667 – 1.580)	0.904	-	-
History of breast surgery in metastatic situation	0.956 (0.519 – 1.762)	0.886	-	-
Histology		0.709		-
Invasive ductal carcinoma	1.298 (0.466 – 3.611)		-	
Non-specific invasive carcinoma	0.961 (0.322 – 2.867)		-	
Invasive lobular carcinoma	1.270 (0.423 – 3.812)		-	
Grade (SBR)		0.681		-
II	0.757 (0.414 – 1.384)		-	
III	0.797 (0.340 – 1.872)		-	
Ki-67				
> 14%	1.471 (0.927 – 2.333)	0.095	-	-
> 20%	1.300 (0.828 – 2.039)	0.26	-	-
Estrogen receptor				
Rate	0.996 (0.985 – 1.008)	0.531	-	-
Allred score	0.937 (0.738 – 1.189)	0.60	-	-
Progesterone receptor				
Rate	0.994 (0.988 – 0.999)	0.026	-	-
Allred score	0.917 (0.856 – 0.982)	0.014	-	-
Toxicity ≥ grade 3	0.942 (0.611 – 1.451)	0.786	-	-
Reduction of palbociclib dose	0.590 (0.374 – 0.929)	0.019	-	-
Number of metastatic sites ≥ 3	2.166 (1.418 – 3.309)	< 0.001	-	-
Visceral metastases	2.424 (1.439 – 4.084)	< 0.001	-	-
Endocrine therapy in adjuvant treatment	1.487 (0.824 – 2.685)	0.168	-	-
Number of previous lines of endocrine therapy for ABC		0.021		-
1	1.727 (1.016 – 2.935)		-	
≥ 2	1.961 (1.175 – 3.275)		-	
NLR at palbociclib initiation	1.180 (1.078 – 1.291)	0.003	1.170 (1.063 – 1.287)	0.001
CA 15-3 at palbociclib initiation	1.001 (1.000 – 1.001)	<0.001	1.000 (1.000 – 1.001)	0.001
CEA at palbociclib initiation	1.004 (1.002 – 1.006)	0.002	1.006 (1.003 – 1.010)	<0.001

Table 4 – Results of univariate and multivariate analyses of overall survival for the overall population

b) For patients with palbociclib in first line (group A)

Results of the univariate and the multivariate analysis are shown in **Appendix 4**.

In univariate analysis, results were similar as the global population. Indeed, PR rate according to the Allred score ($p=0.039$), as well as dose adjustment during palbociclib treatment ($p=0.005$) were significant for better OS. PR rate in percentage tended to increase OS if it was high ($p=0.024$).

The higher the level of NLR at palbociclib initiation ($p=0.008$), the more the OS was decreased. CA 15-3 marker at palbociclib initiation ($p=0.003$) tended to be associated with poorer OS ($p=0.005$).

In multivariate analysis, the only significant predictive factor of better OS was the dose adjustment during palbociclib treatment ($p=0.023$).

c) For patients with palbociclib in second or third line (group B)

Results of the univariate and the multivariate analysis are shown in **Appendix 5**.

In univariate analysis, OS was significantly decreased in the presence of visceral metastases ($p=0.039$), history of ET for ABC ($p=0.015$) and a high NLR at the initiation of palbociclib ($p=0.031$). CA 15-3 marker at palbociclib initiation ($p=0.003$) tended to be associated with poorer OS ($p=0.005$).

There was no predictive factor for OS in multivariate analysis.

d) For patients with palbociclib after three lines (group C)

Results of the univariate and the multivariate analysis are shown in **Appendix 6**.

In univariate analysis, the presence of visceral metastases ($p=0.039$), history of ET for ABC ($p=0.015$) and a high NLR at the initiation of palbociclib ($p=0.031$) were associated with poorer OS. CA 15-3 marker at palbociclib initiation ($p=0.003$) tended to be associated with poorer OS ($p=0.005$).

In multivariate analysis, the significant predictive factor of poorer OS was a high NLR ($p=0.009$). The high level of CA 15-3 at palbociclib initiation ($p=0.007$) tended to be a factor decreasing the OS.

3.8 Toxicities

Adverse events (AEs) data are shown in **Table 5**.

In the study, 176 patients (93.1%) had at least one palbociclib-related AE of any grade, and 117 patients (63%) had grade 3 toxicity (53.7% in group A, 70.7% in group B and 65.3% in group C). The most common grade 3 toxicity was neutropenia with 54.5% of the cohort (47% in group A, 64.4% in group B and 55.1% in group C). In 18 cases, grade 4 toxicity was observed including 4.7% of neutropenia and 2.1% of febrile neutropenia. Anemia was found in 27 cases (14.1%) including 2 cases of grade 3 (1%). Thrombocytopenia was found in 35 cases (18.4%) including 3 cases of grade 3 (1.6%) and 3 cases of grade 4 (1.6%). All grades palbociclib-associated hematologic AEs were more frequent in group B (84.7% of neutropenia, 27.1% of thrombocytopenia, 18.6% of anemia) and group C (75.5% of neutropenia, 20.5% of thrombocytopenia, 16.3% of anemia) than group A (66.3% of neutropenia, 10.8% of thrombocytopenia, 9.6% of anemia).

Grade 3 non-hematologic side effects were detected for 19 patients (9.9%). The most frequent was asthenia (6.3%). We noted that 2 patients (1.0%) had elevated transaminases and 4 patients (2.1%) had stomatitis.

No patients had non-hematologic grade 4 toxicity.

Ten patients (5.3%) had a thromboembolic disease: 5 pulmonary embolism (2.6%), 3 deep veinous thrombosis (1.6%) and 2 strokes (1.1%).

Seventy-seven patients (40.7%) had at least one dose reduction due to an AE. Seventeen patients (10.8%) permanently discontinued palbociclib treatment due to an AE. There were no AE-related deaths.

	Grade 1-2	Grade 3	Grade 4
All toxicities	129 (68.3%)	117 (63.0%)	18 (9.5%)
Hematologic toxicities			
Anemia	25 (13.1%)	2 (1.0%)	0 (0.0%)
Neutropenia	29 (15.2%)	104 (54.5%)	9 (4.7%)
Febrile neutropenia	0 (0%)	3 (1.6%)	4 (2.1%)
Thrombopenia	29 (15.2%)	3 (1.6%)	3 (1.6%)
Non-hematologic toxicities			
Alopecia	15 (7.9%)	0 (0.0%)	0 (0.0%)
Anorexia	4 (2.1%)	0 (0.0%)	0 (0.0%)
Arthralgia	27 (14.1%)	1 (0.5%)	0 (0.0%)
Asthenia	43 (22.5%)	12 (6.3%)	0 (0.0%)
Hot flashes	11 (5.8%)	0 (0.0%)	0 (0.0%)
Headaches	3 (1.6%)	0 (0.0%)	0 (0.0%)
Conjunctivitis	1 (0.5%)	0 (0.0%)	0 (0.0%)
Constipation	2 (1.0%)	0 (0.0%)	0 (0.0%)
Elevation of transaminases	2 (1.0%)	2 (1.0%)	0 (0.0%)
Diarrhea	11 (5.8%)	0 (0.0%)	0 (0.0%)
Stomatitis	7 (3.7%)	4 (2.1%)	0 (0.0%)
Skin rash	1 (0.5%)	0 (0.0%)	0 (0.0%)
Epigastralgia	1 (0.5%)	0 (0.0%)	0 (0.0%)
Myalgia	2 (1.0%)	0 (0.0%)	0 (0.0%)
Nausea / vomiting	6 (3.1%)	0 (0.0%)	0 (0.0%)
Dizziness	1 (0.5%)	0 (0.0%)	0 (0.0%)
	Yes	No	
Thromboembolic Disease*	10 (5.3%)	179 (94.7%)	
Stroke	2 (1.1%)	187 (98.9%)	
Pulmonary embolism	5 (2.6%)	184 (97.4%)	
Deep venous thrombosis	3 (1.6%)	186 (98.4%)	

Table 5 – Palbociclib-related toxicities

4. DISCUSSION

This study reports real-life data from our center with palbociclib treatment combined with endocrine therapy in patients with HR+/HER2- ABC/MBC.

Here, we compared the patients' characteristics and outcomes with those of PALOMA-2 and PALOMA-3 and those of the real-life studies (**Tables 6-7**) (46,67,85,87–89). In our study, the population appeared to be older than in PALOMA-2 and PALOMA-3. These results remained consistent with the real-world studies. We included 85.3% of postmenopausal patients. Their proportion was higher in group C. This is probably due to menopause induced by previous treatments. These results were similar to the literature (46,90). Compared to the literature, there were more patients with visceral metastases (67.5%) and less patients with bone metastases only (15.7%) (**Tables 6-7**). Unlike the PALOMA-3 trial in which everolimus or fulvestrant were exclusion criteria, our trial had respectively 22% and 14.1% of patients treated with those molecules (46).

Our study confirms the efficacy of palbociclib combined with ET in a large population of unselected patients with HR+/HER2- ABC/MBC. The median PFS was 12 months for the overall population. The PFS of our study appeared to be longer than the PALOMA-3 median PFS (9.5 months) but patients in PALOMA-3 had received ≥ 2 prior lines of ET in 54.0%, whereas in our study 25.1% of patients had received ≥ 2 prior lines of ET. However, in our study, patients had received more prior lines of chemotherapy (only one prior line of chemotherapy was tolerated in PALOMA-3).

The PFS of our study seems like the PFS of the real-world study by Palumbo *et al.* (13 months) with similar characteristics. When analyzed according to line of treatment, median PFS values were significantly prolonged when palbociclib was administered in early treatment lines. These results are consistent with results of similar studies (88,91). We also observed a

significant difference for PFS according to the ET treatment associated with palbociclib. PFS was longer when palbociclib was combined with an anti-aromatase (17 months) or both types of endocrine therapy sequentially (23 months) than with an anti-estrogen (8 months). This can be explained by the fact that when palbociclib is administered in first line, it is more often combined with an AI therapy (69.9% in group A versus 32.2% and 40.8% in groups B and C respectively). Similarly, patients who received ET with AI and anti-estrogen sequentially, almost all received palbociclib as first line treatment. A phase 2 trial found no significant difference in PFS whether palbociclib was combined with fulvestrant or letrozole as first-line therapy (92). In the overall population, a high ER rate according to the Allred score was predictor of better PFS. On contrary, in the PALOMA-3 study, the efficacy of Palbociclib was not influenced by ER or PR expression levels. The threshold for hormone receptor positivity was probably 1% for the majority of cases, whereas it was 10% in our study. Palbociclib dose reduction during the treatment was also a predictive factor of better PFS. These results differ from other studies. Indeed, Wilkie *et al.* reported a similar AE profile and outcomes as PALOMA-2 and concluded that dose reductions do not affect the efficacy of palbociclib (93). Also, the detailed safety analysis of the PALOMA-3 study showed that dose modifications for grade 3-4 neutropenia did not affect PFS (94). While Moftakhar *et al.* found that a dose reduction of palbociclib in the first 12 weeks, when used in combination with an AI in the first-line setting, was associated with worse PFS (95). Dose reductions were mainly due to neutropenia. In our study, we did not collect variations of neutrophil values during treatment. A real-world study by Sun *et al.* reported that the occurrence of neutropenia during treatment with palbociclib is significantly associated with a lower risk of disease progression (96). The hypothesis is that neutropenia leads to the suppression of the pro-tumor effects of neutrophils (97). Another study reported improved PFS when neutropenia occurred during

the first two cycles of palbociclib (98). This may also be explained by variabilities in pharmacological parameters and genetic variabilities between individuals that may confer greater sensitivity to the drug or a link between AEs and efficacy (99).

Predictors of poorer PFS were elevated NLR at palbociclib initiation and prior treatment with endocrine therapy for ABC/MBC. Some studies identify elevated NLR as an independent predictor of mortality and is associated with worse outcomes in cancers including breast cancers (100,101), however Sun *et al.* do not find an association between NLR and the risk of disease progression (96). Elevated CEA or CA 15-3 markers at palbociclib initiation tended to be associated with poorer PFS. It is known that high levels of CA 15-3 and CEA markers may reflect tumor burden and are associated with advanced disease and poor outcomes in breast cancer (102).

We found that the median OS for global population was 39 months. These results are consistent with the OS reported in PALOMA-3 which was 34.9 months (46). In real-life studies, the OS results are quite variable (**Table 7**). Indeed, the populations of these trials are heterogeneous (88,103).

The follow-up of our study does not allow us to determine the median OS for patients treated with palbociclib in first line. There was no significant difference in OS according to the type of ET combined with palbociclib.

In the overall population, the predictor of poorer OS was a high NLR at palbociclib initiation. A high CEA at palbociclib initiation tended to be associated with a poorer OS. As discussed previously, both are known to be associated with poorer outcomes. For patients receiving palbociclib as first-line therapy, we found that palbociclib dose reduction was associated with better OS.

The presence of visceral metastases seemed to be a predictor of poorer survival (PFS or OS) in univariate analysis but not in multivariate analysis. In PALOMA-2 and PALOMA-3, patients benefited from the addition of palbociclib in terms of PFS regardless of the presence or absence of visceral metastases.

In 53 patients, a response to palbociclib > 24 months was observed. These patients had a lower disease burden at baseline. They tended to have fewer sites of disease, non-visceral disease as indicated by a lower incidence of liver metastases and were less heavily pre-treated. These results are consistent with the study evaluating the predictive factors for prolonged benefit of palbociclib plus fulvestrant in patients in the PALOMA-3 cohort (104). However, here, 7 patients (3.7% of the total population) receiving palbociclib from the fourth line onwards had a prolonged benefit from this treatment.

The AEs related to palbociclib are similar to the AEs reported in PALOMA-2 and PALOMA-3. We observed grade 3 and grade 4 AEs in 63% and 9.5% of patients, respectively, with neutropenia being the most frequent. Only 2.1% of patients had febrile neutropenia. At least one dose reduction of palbociclib was observed in 40.7% of patients due to an AE. A permanent discontinuation had to be done in 10% of the cases. These rates appear to be higher than in the pivotal or real-life studies (**Tables 6-7**). There were also 5.3% thromboembolic events (1.1% arterial and 4.2% venous) with palbociclib. It is difficult to affirm the causal relationship, however, other studies have also shown this association (105,106).

The strength of our study is the large and heterogeneous cohort, representative of the patient population eligible for palbociclib treatment in real life. The median follow-up of 36 months is long in comparison with other real-life studies.

This trial was retrospective and monocentric and, as a result, had some limitations. Indeed, data were missing in some cases. Other parameters could have been collected such as

neutrophil count during treatment or lines subsequently received. Also, palbociclib is now given in most cases as first or second line therapy. Our results are therefore no longer applicable to current and future practice. However, our results are interesting because they show that some patients, even heavily pre-treated, benefit from palbociclib, the question remains why.

	Study at Jean Perrin Centre in Clermont-Ferrand	PALOMA-2 (67)	PALOMA-3 (46)
Line of palbociclib combined with ET	1st line in 43.5% 2 nd or 3rd line in 30.9% > 3 lines in 25.6%	1 st line in 100%	2nd line in 46% 3 rd line in 40% > 3 lines in 14%
Combined ET	50.8% with AI 49.2% with AO	100% with AI	100% with fulvestrant
n	191	444	347
Age (mean with range)	64 (30–91)	62.0 (30.0–89.0)	57.0 (30–88)
Postmenopausal patients (%)	85.3%	100%	79%
Visceral disease (%) Overall population (group A-B-C)	67.5% (56.6% - 72.9% - 79.6%)	48.2%	59%
Bone metastases only (%) Overall population (group A-B-C)	15.7% (14.5% - 13.6% - 10.2%)	23.2%	22%
<i>De novo</i> disease (%) Overall population (group A-B-C)	41.4% (37.3% - 40.7% - 49%)	31.3%	0%
Prior adjuvant or neoadjuvant chemotherapy (%)	44.7%	48.0%	40%
Prior adjuvant endocrine therapy (%)	53.7%	56.1%	NA
Median follow-up (mean)	36 months [95% CI (34–38)]	37.6 (37.2–38.0)	8.9 months (IQR 8.7–9.2)
Median PFS (mean) Overall population (group A-B-C)	12 months (95% CI = 9–17) 20 months (95% CI = 17–32) 10 months (95% CI = 8–18) 6 months (95% CI = 4–8)	27.6 months (95% CI 22.4–30.3)	9.5 months (95% CI 9.2–11.0)
Median OS (mean) Overall population (group A-B-C)	39 months (95% CI = 35–NA) Not reached (95% CI, not estimable) 36 months (95% CI = 34–NA) 25 months (95% CI = 22–40)	NA	34.9 months (95% CI, 28.8 to 40.0)
Dose reduction of Palbociclib (%)	40.7%	36.0%	34.0%
AE grade 3 (%)	63.0%	62.2%	73% grade 3 or 4
AE grade 4 (%)	9.5%	13.5%	73% grade 3 or 4
Febrile neutropenia (%)	3.7%	2.0%	0.9%
Permanent discontinuation of Palbociclib because AE(s) (%)	10.8%	12.2%	4.0%

Table 6 – Comparison of characteristics patients and outcomes with pivotal studies

	Study at Jean Perrin Centre in Clermont-Ferrand	RENATA (multicentre, prospective study in Argentina) (85)	IRIS (multicentre, retrospective study in US) (89)	De Michele et al. (multicentre, retrospective study in US) (87)	Palumbo et al. (multicentre, prospective study in Italy)(88)
Line of palbociclib combined with ET	1st line in 43.5% 2 nd or 3rd line in 30.9% > 3 lines in 25.6%	1st line in 59.4% 2 nd line in 15.0% > 2 lines in 26.0%	1 st line in 71.5% 2 nd line in 24.8% > 2 lines in 3.7%	1 st line in 100%	1 st line in 35.5% 2 nd line in 31.1% 3 rd line in 21.1% > 3 lines in 12.3%
Combined ET	50.8% with AI 49.2% with AO	61.7% with letrozole 35.9% with fulvestrant	55.2% with letrozole 44.8% with fulvestrant	100% with letrozole	49.5% with letrozole 50.5% with fulvestrant
n	191	128	652	772	182
Age (mean with range)	64 (30-91)	57.0 (29.0–84.0)	65.0 (30.0-90.0)	67.0 (59.0–75.0)	62.0 (47.0-79.0)
Postmenopausal patients (%)	85.3%	79.7%	87.4%	NA	73%
Visceral disease (%) Overall population (group A-B-C)	67.5% (56.6% - 72.9% - 79.6%)	29%	46.4%	38.2%	53.8%
Bone metastases only (%) Overall population (group A-B-C)	15.7% (14.5% - 13.6% - 10.2%)	26.6%	46.4%	36.9%	24.7%
<i>De novo</i> disease (%) Overall population (group A-B-C)	41.4% (37.3% - 40.7% - 49%)	20.7%	43.7%	40.3%	24.2%
Prior adjuvant or neoadjuvant chemotherapy (%)	44.7%	52%	43.6%	-	53.0%
Prior adjuvant endocrine therapy (%)	53.7%	>90%	71.9%	-	75.7%
Median follow-up (mean)	36 months [95% CI (34–38)]	NA	Mean 9.9 months	24.2 months (IQR, 14.2–34.9)	24.0 months (6.0-32.0)
Median PFS (mean) Overall population (group A-B-C)	12 months (95% CI = 9–17) 20 months (95% CI = 17–32) 10 months (95% CI = 8–18) 6 months (95% CI = 4–8)	29.6 months (95%CI 19.5–38.8)	NA At 12 months, PFS was 84.1% in group with AI and 79.8% in group with fulvestrant	20.0 months (95% CI, 17.5–21.9)	13.0 months (range 3.2–25.0)
Median OS (mean) Overall population (group A-B-C)	39 months (95% CI = 35–NA) not reached (95% CI, not estimable) 36 months (95% CI = 34–NA) 25 months (95% CI = 22–40)	Not reached	NA	not reached (95% CI, not estimable)	25.0 months (range 12.5–32.4+)
Dose reduction of Palbociclib (%)	40.7%	15.2%	17.3%	NA	34.0%

AE grade 3 (%)	63.0%	55% (grade 3-4)	NA	NA	NA (50.5% of grade 3-4 neutropenia)
AE grade 4 (%)	9.5%	55% (grade 3-4)	NA	NA	NA (50.5% of grade 3-4 neutropenia)
Febrile neutropenia (%)	3.7%	7.6%	NA	NA	4.3%
Permanent discontinuation of Palbociclib because AE(s) (%)	10.8%	2.0%	NA	NA	NA

Table 7 – Comparison of characteristics patients and outcomes with real-world studies

5. CONCLUSION

In conclusion, our real-world cohort, which included heavily pre-treated patients, showed similar results in terms of efficacy and safety compared to the pivotal and real-life studies. Predictive factors for poorer outcomes are already known in breast cancer (elevated NLR, CA 15-3 and CEA). Dose reduction during treatment was associated with better PFS. This observation shows that despite side effects, palbociclib diminution is not a risk factor for patients. These results need to be confirmed by further prospective studies. Guidelines recommend treatment with CDK4/6 inhibitors in combination with endocrine therapy in the first or second line setting in patients with HR+/HER2– disease without visceral crisis. Of note, the three CDK4/6 inhibitors have not been compared head-to-head within a clinical trial. Nevertheless, the optimal sequence of treatments in this context remains a major debate and the identification of predictive biomarkers of response or resistance remains to be found to obtain the best benefit for each patient.

III. CONCLUSION THÈSE

En conclusion, les données de vie réelle concernant les patientes recevant un traitement par palbociclib combiné à l'hormonothérapie pour un cancer du sein RH+/HER2- avancé ou métastatique au Centre Jean Perrin, ont montré des résultats similaires à ceux des études pivots et de vraie vie en termes d'efficacité et de sécurité. Notre étude incluait des patientes lourdement prétraitées, souvent exclues des essais cliniques. Les facteurs prédictifs de moins bonne réponse au palbociclib sont déjà connus dans le cancer du sein (ratio neutrophiles/lymphocytes élevé, CA 15-3 et ACE élevés à l'initiation du palbociclib). Nous mettons ici en évidence un lien possible entre une réponse favorable et la réduction de dose du palbociclib. En effet, la réduction de la dose était associée à une meilleure survie sans progression. Cette observation montre que malgré les effets secondaires présentés, la diminution du palbociclib n'est pas un facteur de risque pour les patientes. Ces résultats méritent d'être confirmés par d'autres études prospectives.

Les recommandations actuelles préconisent un traitement par inhibiteurs de CDK4/6 en association avec l'hormonothérapie en première ou deuxième ligne chez les patientes présentant un cancer du sein avancé ou métastatique RH+/HER2- sans crise viscérale. Il convient de noter que les trois inhibiteurs de CDK4/6 n'ont pas été comparés entre eux dans le cadre d'un essai clinique.

Néanmoins, déterminer la séquence optimale des traitements dans ce contexte et identifier des biomarqueurs prédictifs de réponse ou de résistance restent un enjeu majeur afin d'obtenir le meilleur bénéfice pour chaque patient.

Clermont-Ferrand, le
Pierre CLAVELOU
Doyen - Directeur



Clermont-Ferrand, le 10/11/21
Le Président du Jury

A handwritten signature in black ink, appearing to be "Fou", written below the text of the President of the Jury.

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ANNEXES

Appendix 1 – Results of univariate and multivariate analyses of progression-free survival for patients with palbociclib in first line (group A)

Predictive Factors	Univariate analysis		Multivariate analysis	
	HR (95 CI%)	p	HR (95 CI%)	p
Age	0.988 (0.969 – 1.007)	0.208	-	-
Size of tumor at diagnosis (according to TNM)		0.521		-
T2	1.568 (0.772 – 3.188)		-	
T3	1.153 (0.459 – 2.895)		-	
T4	1.619 (0.749 – 3.498)		-	
Nodal status at diagnosis (according to TNM) ≥ N1	1.747 (0.931 – 3.280)	0.07	-	-
<i>De novo</i> metastatic	0.724 (0.420 – 1.250)	0.24	-	-
History of breast surgery in metastatic situation	0.566 (0.204 – 1.565)	0.234	-	-
Histology		0.762		-
Invasive ductal carcinoma	1.999 (0.459 – 8.712)		-	
Non-specific invasive carcinoma	1.743 (0.400 – 7.584)		-	
Invasive lobular carcinoma	1.983 (0.449 – 8.762)		-	
Grade (SBR)		0.933		-
II	1.038 (0.441 – 2.445)		-	
III	1.212 (0.391 – 3.765)		-	
Ki-67				
> 14%	0.861 (0.505 – 1.469)	0.585	-	-
> 20%	0.925 (0.511 – 1.675)	0.796	-	-
Estrogen receptor				
Rate	0.982 (0.970 – 0.994)	0.012	-	-
Allred score	0.645 (0.477 – 0.871)	0.009	0.680 (0.390 – 1.188)	0.175
Progesterone receptor				
Rate	0.991 (0.984 – 0.998)	0.013	0.998 (0.988 – 1.008)	0.327
Allred score	0.919 (0.839 – 1.006)	0.073	-	-
Toxicity ≥ grade 3	0.645 (0.381 – 1.090)	0.103	-	-
Reduction of palbociclib dose	0.447 (0.256 – 0.780)	0.003	0.704 (0.319 – 1.553)	0.384
Number of metastatic sites ≥ 3	1.983 (1.170 – 3.361)	0.013	1.294 (0.595 – 2.815)	0.516
Visceral metastases	1.675 (0.974 – 2.882)	0.058	-	-
Endocrine therapy in adjuvant treatment	1.019 (0.587 – 1.768)	0.948	1.552 (0.716 – 3.362)	0.265
NLR at palbociclib initiation	1.207 (1.023 – 1.424)	0.031	1.478 (1.095 – 1.996)	0.011
CA 15-3 at palbociclib initiation	1.001 (1.000 – 1.001)	< 0.001	1.001 (1.000 – 1.001)	0.006
CEA at palbociclib initiation	1.005 (1.001 – 1.010)	0.062	1.007 (1.001 – 1.014)	0.028

Appendix 2 – Results of univariate and multivariate analyses of progression-free survival for patients with palbociclib in second or third line (group B)

Predictive Factors	Univariate analysis		Multivariate analysis	
	HR (95 CI%)	p	HR (95 CI%)	p
Age	1.002 (0.981 – 1.024)	0.827	-	-
Size of tumor at diagnosis (according to TNM)		0.726		-
T2	1.136 (0.504 – 2.559)		-	
T3	1.790 (0.642 – 4.986)		-	
T4	1.145 (0.468 – 2.804)		-	
Nodal status at diagnosis (according to TNM) ≥ N1	1.195 (0.625 – 2.284)	0.586	-	-
<i>De novo</i> metastatic	1.068 (0.617 – 1.849)	0.813	-	-
History of breast surgery in metastatic situation	0.484 (0.174 – 1.347)	0.124	-	-
Histology		0.158		-
Invasive ductal carcinoma	0.530 (0.182 – 1.543) (0.607 (0.199 – 1.854)	0.381
Non-specific invasive carcinoma	1.094 (0.362 – 3.304)		0.985 (0.310 – 3.127)	0.979
Invasive lobular carcinoma	0.648 (0.191 – 2.195)		0.617 (0.167 – 2.277)	0.469
Grade (SBR)		0.752		-
II	1.291 (0.541– 3.080)		-	
III	1.562 (0.471 – 5.176)		-	
Ki-67				
> 14%	1.387 (0.777 – 2.475)	0.263	-	-
> 20%	1.450 (0.813 – 2.584)	0.216	-	-
Estrogen receptor				
Rate	0.988 (0.971 – 1.006)	0.232	-	-
Allred score	0.745 (0.554 – 1.000)	0.069	-	-
Progesterone receptor				
Rate	0.996 (0.988 – 1.003)	0.226	-	-
Allred score	0.931 (0.854 – 1.015)	0.11	-	-
Toxicity ≥ grade 3	0.557 (0.309 – 1.004)	0.06	-	-
Reduction of palbociclib dose	0.605 (0.341 – 1.072)	0.08	0.453 (0.217 – 0.944)	0.034
Number of metastatic sites ≥ 3	1.364 (0.791 – 2.350)	0.268	-	-
Visceral metastases	1.377 (0.746 – 2.543)	0.295	-	-
Endocrine therapy in adjuvant treatment	1.024 (0.369 – 2.848)	0.963	1.552 (0.716 – 3.362)	0.265
Number of previous lines of endocrine therapy for ABC		0.472		-
1	1.691 (0.659 – 4.343)		-	
≥ 2	1.374 (0.474 – 3.988)		-	
NLR at palbociclib initiation	1.107 (1.003 – 1.221)	0.067	-	-
CA 15-3 at palbociclib initiation	1.002 (1.001 – 1.003)	<0.001	1.003 (1.002 – 1.004)	< 0.001
CEA at palbociclib initiation	1.001 (0.997 – 1.006)	0.585	-	-

Appendix 3 – Results of univariate and multivariate analyses of progression-free survival for patients with palbociclib after three lines (group C)

Predictive Factors	Univariate analysis		Multivariate analysis	
	HR (95 CI%)	p	HR (95 CI%)	p
Age	1.013 (0.990 – 1.038)	0.265	-	-
Size of tumor at diagnosis (according to TNM)		0.727		-
T2	1.086 (0.500 – 2.358)		-	
T3	1.474 (0.562 – 3.863)		-	
T4	1.537 (0.652 – 3.621)		-	
Nodal status at diagnosis (according to TNM) ≥ N1	1.072 (0.545 – 2.107)	0.84	-	-
<i>De novo</i> metastatic	0.712 (0.395 – 1.282)	0.256	-	-
History of breast surgery in metastatic situation	0.780 (0.402 – 1.512)	0.453	-	-
Histology		0.037		-
Invasive ductal carcinoma	0.203 (0.045 – 0.921)		0.607 (0.199 – 1.854)	0.381
Non-specific invasive carcinoma	0.275 (0.047 – 1.616)		0.985 (0.310 – 3.127)	0.979
Invasive lobular carcinoma	0.063 (0.009 – 0.424)		0.617 (0.167 – 2.277)	0.469
Grade (SBR)		0.254		-
II	0.625 (0.278 – 1.404)		-	
III	1.170 (0.437 – 3.130)		-	
Ki-67				
> 14%	1.508 (0.772 – 2.948)	0.219	-	-
> 20%	1.204 (0.620 – 2.338)	0.588	-	-
Estrogen receptor				
Rate	0.985 (0.966 – 1.004)	0.143	-	-
Allred score	0.743 (0.476 – 1.160)	0.215	-	-
Progesterone receptor				
Rate	0.994 (0.987 – 1.001)	0.103	-	-
Allred score	0.959 (0.876 – 1.049)	0.366	-	-
Toxicity ≥ grade 3	0.755 (0.413 – 1.380)	0.367	-	-
Reduction of palbociclib dose	0.602 (0.327 – 1.109)	0.097	-	-
Number of metastatic sites ≥ 3	1.425 (0.789 – 2.575)	0.236	-	-
Visceral metastases	1.271 (0.612 – 2.640)	0.509	-	-
Endocrine therapy in adjuvant treatment	2.436 (0.749 – 7.919)	0.093	-	-
Number of previous lines of endocrine therapy for ABC		0.342		-
1	0.854 (0.108 – 6.761)		-	
≥ 2	1.411 (0.191 – 10.411)		-	
NLR at palbociclib initiation	1.143 (0.872 – 1.498)	0.345	-	-
CA 15-3 at palbociclib initiation	1.000 (1.000 – 1.001)	0.135	-	-
CEA at palbociclib initiation	1.002 (1.000 – 1.004)	0.07	-	-

Appendix 4 – Results of univariate and multivariate analyses of overall survival for patients with palbociclib in first line (group A)

Predictive Factors	Univariate analysis		Multivariate analysis	
	HR (95 CI%)	p	HR (95 CI%)	p
Age	0.988 (0.969 – 1.007)	0.208	-	-
Size of tumor at diagnosis (according to TNM)		0.521		-
T2	1.568 (0.772 – 3.188)		-	
T3	1.153 (0.459 – 2.895)		-	
T4	1.619 (0.749 – 3.498)		-	
Nodal status at diagnosis (according to TNM) ≥ N1	1.747 (0.931 – 3.280)	0.07	-	-
<i>De novo</i> metastatic	0.724 (0.420 – 1.250)	0.24	-	-
History of breast surgery in metastatic situation	0.566 (0.204 – 1.565)	0.234	-	-
Histology		0.762		-
Invasive ductal carcinoma	1.999 (0.459 – 8.712)		-	
Non-specific invasive carcinoma	1.743 (0.400 – 7.584)		-	
Invasive lobular carcinoma	1.983 (0.449 – 8.762)		-	
Grade (SBR)		0.933		-
II	1.038 (0.441 – 2.445)		-	
III	1.212 (0.391 – 3.765)		-	
Ki-67				
> 14%	0.861 (0.505 – 1.469)	0.585	-	-
> 20%	0.925 (0.511 – 1.675)	0.796	-	-
Estrogen receptor				
Rate	0.982 (0.970 – 0.994)	0.012	-	-
Allred score	0.645 (0.477 – 0.871)	0.009	0.680 (0.390 – 1.188)	0.175
Progesterone receptor				
Rate	0.991 (0.984 – 0.998)	0.013	0.998 (0.988 – 1.008)	0.327
Allred score	0.919 (0.839 – 1.006)	0.073	-	-
Toxicity ≥ grade 3	0.645 (0.381 – 1.090)	0.103	-	-
Reduction of palbociclib dose	0.447 (0.256 – 0.780)	0.003	0.704 (0.319 – 1.553)	0.384
Number of metastatic sites ≥ 3	1.983 (1.170 – 3.361)	0.013	1.294 (0.595 – 2.815)	0.516
Visceral metastases	1.675 (0.974 – 2.882)	0.058	-	-
Endocrine therapy in adjuvant treatment	1.019 (0.587 – 1.768)	0.948	1.552 (0.716 – 3.362)	0.265
NLR at palbociclib initiation	1.207 (1.023 – 1.424)	0.031	1.478 (1.095 – 1.996)	0.011
CA 15-3 at palbociclib initiation	1.001 (1.000 – 1.001)	< 0.001	1.001 (1.000 – 1.001)	0.006
CEA at palbociclib initiation	1.005 (1.001 – 1.010)	0.062	1.007 (1.001 – 1.014)	0.028

Appendix 5 – Results of univariate and multivariate analyses of overall survival for patient with palbociclib in second or third line (group B)

Predictive Factors	Univariate analysis		Multivariate analysis	
	HR (95 CI%)	p	HR (95 CI%)	p
Age	1.015 (0.983 – 1.048)	0.358	-	-
Size of tumor at diagnosis (according to TNM)		0.975		-
T2	0.863 (0.299 – 2.492)		-	
T3	1.104 (0.259 – 4.703)		-	
T4	1.028 (0.307 – 3.437)		-	
Nodal status at diagnosis (according to TNM) ≥ N1	1.041 (0.434 – 2.498)	0.929	-	-
<i>De novo</i> metastatic	1.084 (0.497 – 2.363)	0.84	-	-
History of breast surgery in metastatic situation	0.530 (0.125 – 2.252)	0.347	-	-
Histology		0.08		-
Invasive ductal carcinoma	0.358 (0.097 – 1.326)		-	
Non-specific invasive carcinoma	1.067 (0.286 – 3.977)		-	
Invasive lobular carcinoma	0.939 (0.222 – 3.974)		-	
Grade (SBR)		0.164		-
II	4.537 (0.608 – 33.828)		-	
III	3.124 (0.279 – 34.924)		-	
Ki-67				
> 14%	1.440 (0.644 – 3.218)	0.366	-	-
> 20%	1.696 (0.791 – 3.637)	0.181	-	-
Estrogen receptor				
Rate	0.999 (0.976 – 1.022)	0.941	-	-
Allred score	0.956 (0.648 – 1.412)	0.825	-	-
Progesterone receptor				
Rate	0.996 (0.986 – 1.007)	0.481	-	-
Allred score	0.889 (0.784 – 1.009)	0.069	-	-
Toxicity ≥ grade 3	0.903 (0.407 – 2.001)	0.802	-	-
Reduction of palbociclib dose	0.719 (0.325 – 1.593)	0.408	-	-
Number of metastatic sites ≥ 3	1.972 (0.937 – 4.152)	0.074	-	-
Visceral metastases	2.725 (0.942 – 7.886)	0.039	-	-
Endocrine therapy in adjuvant treatment	1.444 (0.338 – 6.172)	0.602	-	-
Number of previous lines of endocrine therapy for ABC		0.015		-
1	1.436 (0.423 – 4.875)		-	
≥ 2	0.251 (0.042 – 1.505) ???		-	
NLR at palbociclib initiation	1.163 (1.033 – 1.309)	0.031	-	-
CA 15-3 at palbociclib initiation	1.002 (1.001 – 1.003)	0.005	-	-
CEA at palbociclib initiation	1.004 (0.999 – 1.010)	0.162	-	-

Appendix 6 – Results of univariate and multivariate analyses of overall survival for patients with palbociclib after three lines (group C)

Predictive Factors	Univariate analysis		Multivariate analysis	
	HR (95 CI%)	p	HR (95 CI%)	p
Age	1.015 (0.983 – 1.048)	0.358	-	-
Size of tumor at diagnosis (according to TNM)		0.975		-
T2	0.863 (0.299 – 2.492)		-	
T3	1.104 (0.259 – 4.703)		-	
T4	1.028 (0.307 – 3.437)		-	
Nodal status at diagnosis (according to TNM) ≥ N1	1.041 (0.434 – 2.498)	0.929	-	-
<i>De novo</i> metastatic	1.084 (0.497 – 2.363)	0.84	-	-
History of breast surgery in metastatic situation	0.530 (0.125 – 2.252)	0.347	-	-
Histology		0.08		-
Invasive ductal carcinoma	0.358 (0.097 – 1.326)		-	
Non-specific invasive carcinoma	1.067 (0.286 – 3.977)		-	
Invasive lobular carcinoma	0.939 (0.222 – 3.974)		-	
Grade (SBR)		0.164		-
II	4.537 (0.608– 33.828)		-	
III	3.124 (0.279 – 34.924)		-	
Ki-67				
> 14%	1.440 (0.644 – 3.218)	0.366	-	-
> 20%	1.696 (0.791 – 3.637)	0.181	3.727 (0.891 – 15.587)	0.072
Estrogen receptor				
Rate	0.999 (0.976 – 1.022)	0.941	-	-
Allred score	0.956 (0.648 – 1.412)	0.825	-	-
Progesterone receptor				
Rate	0.996 (0.986 – 1.007)	0.481	-	-
Allred score	0.889 (0.784 – 1.009)	0.069	-	-
Toxicity ≥ grade 3	0.903 (0.407 – 2.001)	0.802	-	-
Reduction of palbociclib dose	0.719 (0.325 – 1.593)	0.408	-	-
Number of metastatic sites ≥ 3	1.972 (0.937 – 4.152)	0.074	-	-
Visceral metastases	2.725 (0.942 – 7.886)	0.039	-	-
Endocrine therapy in adjuvant treatment	1.444 (0.338 – 6.172)	0.602	-	-
Number of previous lines of endocrine therapy for ABC		0.015		-
1	1.436 (0.423 – 4.875)		-	
≥ 2	0.251 (0.042 – 1.505) ???		-	
NLR at palbociclib initiation	1.163 (1.033 – 1.309)	0.031	2.920 (1.307 – 6.521)	0.009
CA 15-3 at palbociclib initiation	1.002 (1.001 – 1.003)	0.005	1.010 (1.003 – 1.017)	0.007
CEA at palbociclib initiation	1.004 (0.999 – 1.010)	0.162	0.993 (0.972 – 1.015)	0.516

(Conseil national de l'ordre des médecins)

SERMENT D'HIPPOCRATE

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

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

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

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

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

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

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

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

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

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admise dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

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

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