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Présentée et publiquement soutenue devant

LA FACULTÉ DES SCIENCES MÉDICALES ET PARAMÉDICALES

DE MARSEILLE

Le 1er Avril 2022

Par Monsieur Alexandre BERTUCCI

Né le 28 juin 1994 à Marseille 06ème (13)

Pour obtenir le grade de Docteur en Médecine

D.E.S. d'ONCOLOGIE

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GRANDVAL Philippe (PU-PH)
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GENTILE Stéphanie (PU-PH)

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OLIVE Daniel (PU-PH)
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SARI/MINODIER Irène (MCU-PH)

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CASANOVA Ludovic (MCF Méd. Gén. Temps plein)

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FIERLING Thomas (MCF associé Méd. Gén. À mi-temps)
FORTE Jenny (MCF associé Méd. Gén. À mi-temps)
JANCZEWSKI Aurélie (MCF associé Méd. Gén. À mi-temps)
NUSSLI Nicolas (MCF associé Méd. Gén. À mi-temps)
ROUSSEAU-DURAND Raphaëlle
(MCF associé Méd. Gén. À mi-temps)
THERY Didier (MCF associé Méd. Gén. À mi-temps)
(nomination au 1/10/2019)

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VALERO René (PU-PH)

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CHABANNON Christian (PR) (66ème section)
SOBOL Hagay (PR) (65ème section)

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DENIS Danièle (PU-PH)

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FAKHRY Nicolas (PU-PH)
GIOVANNI Antoine (PU-PH)
LAVIEILLE Jean-Pierre (PU-PH)
MICHEL Justin (PU-PH)
NICOLLAS Richard (PU-PH)
TRIGLIA Jean-Michel (PU-PH) Surnombre

RADULESCO Thomas (MCU-PH)

REVIS Joana (PAST) (Orthophonie) (7ème Section)

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DUSSOL Bertrand (PU-PH)
JOURDE CHICHE Noémie (PU PH)
MOAL Valérie (PU-PH)

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REGIS Jean (PU-PH)
ROCHE Pierre-Hugues (PU-PH)
SCAVARDA Didier (PU-PH)

CARRON Romain (MCU PH)
GRAILLON Thomas (MCU PH)
TROUDE Lucas (MCU-PH)

NEUROLOGIE *4901*

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AUDOIN Bertrand (PU-PH)
AZULAY Jean-Philippe (PU-PH)
CECCALDI Mathieu (PU-PH)
EUSEBIO Alexandre (PU-PH)
FELICIAN Olivier (PU-PH)
PELLETIER Jean (PU-PH)
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POINSO François (PU-PH)

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A. Thèse article : Inhibiteurs de phosphoinositide 3-kinase (PI3K) et cancer du sein, une revue systématique de la littérature

I/ Introduction

1. Le cancer du sein

Dans le monde, en 2020, le cancer du sein (CS) représente le premier cancer le plus fréquent pour les deux sexes confondus avec environ 2,3 millions de cas et la quatrième cause de décès avec environ 685 000 décès (1). En France, entre 1900 et 2018, il a été démontré que le taux d'incidence augmente d'environ 1,1 % par an (2). Le CS est une maladie hétérogène comprenant de petites tumeurs localisées curables ou des tumeurs métastatiques avec un très mauvais pronostic (3). En pratique, les caractéristiques cliniques et pathologiques sont utilisées pour définir le stade et l'agressivité de la tumeur. Le profil d'expression intrinsèque des gènes de ces tumeurs est corrélé à l'expression ou non de trois récepteurs cellulaires (récepteur aux œstrogènes (RE), récepteur à la progestérone (RP) et récepteur au facteur de croissance épidermique humain-2 (HER2)). Il existe différents sous-types moléculaires de CS, mais dans la pratique clinique, les sous-types sont définis par l'expression des récepteurs cellulaires et l'état de prolifération qui peut être approché par la mesure du Ki67 (4,5). Au diagnostic, un grade histologique plus élevé est associé à une taille tumorale plus importante, une plus grande fréquence de l'atteinte ganglionnaire et à un risque plus élevé de métastases à distance. Le développement des puces à acide désoxyribonucléique complémentaire (ADNc) a introduit un nouveau concept de classification moléculaire, cependant, il n'entre toujours pas dans la pratique clinique en raison de sa bonne concordance avec la classification actuelle, de sa faisabilité plus complexe et d'un prix plus élevé (6).

Les différents sous-types sont les suivants : Luminal, avec des tumeurs positives aux RE et/ou RP et HER2 non surexprimé (luminal A si la prolifération est faible, luminal B si celle-ci est élevée), représentent les CS les plus fréquents, HER2+, en cas de surexpression de HER2, qui est retrouvée dans environ 15 à 20 % des tumeurs, triple négatif (TNBC) si aucun de ces récepteurs n'est exprimé, dans environ 10% des cas. Les TNBC se caractérisent par une agressivité, un âge plus jeune au diagnostic et une évolution moins favorable (7,8). Le cancer du sein inflammatoire (CSI) représente une entité distincte, et a une définition clinique pure avec un début rapide (<6 mois) par l'apparition d'un érythème mammaire, d'œdème et/ou de peau d'orange et/ou de sein chaud, avec ou sans une masse sous-jacente palpable et certaines caractéristiques pathologiques telles que les emboles dermiques. Le CSI est peu fréquent, représentant moins de 5 % des cas, et néanmoins il est associé à une survie plus faible (9,10).

Concernant le CS localisé, qui représente environ 90 % des cas, le traitement repose sur la chirurgie, la radiothérapie et, selon les sous-types, sur l'hormonothérapie (HT), la chimiothérapie et la thérapie ciblée anti-HER2. Le risque de rechute varie entre 10 et 41 % et dépend des sous-types et d'autres caractéristiques clinico-pathologiques (11).

Concernant le CS localement avancé et métastatique, la prise en charge est basée sur le traitement systémique. Concernant le CS surexprimant HER2, le traitement initial repose sur une association d'une chimiothérapie et d'une double thérapies anti-HER2 (trastuzumab et pertuzumab) (12). Initialement, la surexpression de HER2 était associée à un mauvais pronostic mais après l'introduction du trastuzumab puis des autres agents anti-HER2, une étude récente a montré que les CS avec surexpression de HER2 étaient désormais associés avec la plus longue survie (13). Pour le TNBC, le traitement standard est la chimiothérapie et plus récemment l'immunothérapie avec les anticorps anti-PD-1 (pembrolizumab) en association avec la chimiothérapie qui a reçu une autorisation de la Food and Drug

Administration (FDA) et de l'Agence européenne des médicaments (EMA) pour les cancers TNBC avec PD-L1-positif (c'est-à-dire avec un score positif combiné (CPS) égal ou supérieur à 10 en IHC) (14). Dans les formes avec mutation germinale des gènes BRCA1 ou BRCA2, les inhibiteurs de PARP sont également une option (15-18).

Pour le CS localement avancé ou métastatique avec RE et/ou RP et HER2 non surexprimé, le traitement de première intention est l'association d'une HT et d'un inhibiteur de CDK4/6, sauf si le patient présente une crise viscérale où l'on privilégiera une chimiothérapie (19-21). L'histoire naturelle de ces patientes est caractérisée par de multiples lignes d'HT et de thérapie ciblée jusqu'à l'apparition de l'hormono-résistance et la nécessité de recourir à une chimiothérapie palliative. Une méta-analyse a confirmé que toutes les patientes bénéficiaient du traitement par les inhibiteurs de CDK4/6 en première ligne par rapport à une HT en monothérapie (22). Pour les patientes pré ménopausées, la suppression ovarienne (SO) est systématique et les résultats récents d'études randomisées ont montré que les femmes pré ménopausées traitées par HT et SO avec des inhibiteurs de CDK4/6 avaient une survie sans progression (SSP) similaire à celle des femmes ménopausées (23-25). Quelques données de faible niveau de preuve suggèrent une activité clinique de l'utilisation de l'abemaciclib (inhibiteur de CDK4/6) après l'utilisation du palbociclib (inhibiteur de CDK4/6) (26). Pour les patientes porteuses d'une mutation germinale de BRCA, l'olaparib et le talazoparib (inhibiteur de PARP) ont montré un bénéfice significatif pour la SSP, mais la séquence optimale entre les inhibiteurs de CDK4/6 et les inhibiteurs de PARP n'est pas clairement établi (16,27)). L'évérolimus (inhibiteur de la cible de la rapamycine chez les mammifères (mTOR)) avec l'exémestane ont significativement amélioré la SSP par rapport à l'exémestane en monothérapie, 11 mois contre 4,1 mois respectivement dans l'essai de phase III BOLERO-2 pour les patientes progressant sous ou après un traitement par inhibiteurs

de l'aromatase (IA) (28). L'avènement des inhibiteurs de CDK4/6 a repoussé l'évérolimus dans les lignes ultérieures. Peu de données ont exploré le bénéfice de l'évérolimus avec l'exémestane après d'inhibiteur de CDK4/6, cependant dans la pratique clinique, l'évérolimus est couramment utilisé en deuxième ligne après l'échec des inhibiteurs de CDK4/6. Les chimiothérapies par anthracyclines, taxanes, capécitabine, éribuline, vinorelbine, gemcitabine, alkylants sont classiquement utilisées en phase d'hormono-résistance ou de crise viscérale. Pour le CS exprimant les RE et/ou RP, la prochaine étape pourrait inclure l'utilisation d'anticorps conjugués (ADC) tels que le trastuzumab deruxtecan (DS-8201a) pour les HER2 faiblement exprimé (c'est-à-dire HER2 1+ ou 2+ et hybridation in situ), le patritumab deruxtecan (HER3-DXd, U3-1402), le sacituzumab govitecan ou le datopotamab deruxtecan.

2. La voie PI3K

Chez l'homme, la voie de phosphatidylinositol 3-kinase (PI3K) est l'une des voies les plus fréquemment altérées dans les tumeurs. Ce réseau de signalisation se compose principalement de PI3K, d'AKT et de mTOR (29). PI3K appartient à la famille des kinases lipidiques intracellulaires et peut être divisée en trois groupes selon la structure et la fonction. La classe I est activée par l'insuline ou d'autres facteurs de croissance et peut être subdivisée en classe IA et classe IB. La classe IA de PI3K est associée aux récepteurs tyrosine kinase (RTK) et la classe IB de PI3K est associée aux récepteurs couplés aux protéines G (RCPG). Les deux classes sont composées d'une sous-unité catalytique et d'une sous-unité régulatrice. Nous poursuivrons notre sujet uniquement sur la classe IA qui est la plus directement impliquée dans la cancérogenèse humaine (30-33). Pour la classe IA de PI3K, les isoformes de la sous-unité catalytique sont p110α, p110β, p110γ ou p110δ. Le gène PIK3CA est situé sur le chromosome 3q26.3 et code pour la sous-unité catalytique p110α. La sous-unité catalytique

peut être associée à l'une des cinq sous-unités régulatrices (p85α, p55α, p50α codée par PIK3R1 ou p85β codée par PIK3R2 ou p55γ codée par PIK3R3) (34,35). La sous-unité catalytique est composée d'un domaine hélical et d'un domaine kinase. La sous-unité régulatrice est composée de 3 domaines « homologies Src-2 » (SH2), 2 sont présents dans la partie C-terminale et 1 est présent dans la partie N-terminale, on retrouve également le domaine « homologie Breakpoint Cluster Region » (domaine BH) et une partie inter-SH2 (35–37). Les différentes sous-unités ont plusieurs fonctions et une distribution inégale. Ainsi, p110α intervient dans l'activation des processus anaboliques, l'angiogenèse, l'embryogenèse et la prolifération, p110γ et p110β interviennent dans les cellules de l'inflammation, et p110δ se retrouve notamment l'immunité adaptative (29,38). Les sous-unités régulatrices ont trois actions particulières : l'inhibition de l'activité kinase de p110, la stabilisation de p110 et la promotion d'un rétrocontrôle négatif (34). Les domaines SH2 se trouvant sur les sous-unités régulatrices jouent deux rôles clés. Tout d'abord, SH2 permet de lier PI3K au complexe du récepteur de l'insuline-IRS qui se situe au niveau de la membrane cellulaire et donc de rapprocher PI3K du phosphatidylinositol 3,4-bisphosphate (PIP2). Deuxièmement, SH2 se lie au « SH2 domain-containing inositil 5'-phosphatase » (SHIP), ce qui permet l'inhibition de p110 (36).

La particularité de la classe I PI3K est la production de phosphatidylinositol-3,4,5-trisphosphate (PIP3). Lorsque le RTK est activé par des facteurs de croissance, PI3K est alors recruté par les récepteurs ancrés à la membrane cytoplasmique et est ainsi activé ; p110 est verrouillé au niveau de la membrane par RAS. PI3K activé peut ainsi phosphoryler PIP2 pour générer PIP3. PIP3 est l'un des seconds messagers les plus importants dans les cellules humaines, notamment en recrutant et se liant à AKT ou à d'autres protéines avec un domaine d'homologie à la pleckstrine (PH) telles que la protéine kinase 1 dépendante de la 3-

phosphoinositide (PDK1). Ensuite, AKT est phosphorylé et activé par PDK1 et par mTORC2 (39). Une fois AKT activé, ce dernier permet la transmission du signal de croissance et déclenche plusieurs cascades de signalisation. En générant PIP3, qui met en contact AKT et PDK1 (40), PI3K joue un rôle central dans plusieurs processus cellulaires dont la synthèse de l'ADN, le métabolisme et l'action sur le cytosquelette d'actine (41,42). Le « Phosphatase and TENsin homolog » (PTEN) régule négativement l'action de PIP3, par l'activité 3'-phosphatase, transformant PIP3 en PIP2 (43), ce qui arrête la cascade de phosphorylation. PIP3 peut aussi être régulé négativement par un autre acteur, SHIP qui est capté par le domaine SH2 de la sous-unité régulatrice. Il convient de noter que l'activité phosphatase de SHIP permet éliminer le phosphate de la position 5' et non 3', ce qui implique que SHIP est incapable de supprimer seul l'activité d'AKT, car l'activité 5´ phosphatase de SHIP n'interfère pas avec l'interaction AKT-PDK1 et par conséquent AKT reste actif (44,45).

3. Altérations de la voie PI3K dans le cancer

Chez l'homme, l'altération de la voie PI3K est l'une des altérations les plus courantes dans le cancer, estimée à 14 % pour toutes tumeurs solides (46). La relation entre l'altération de PI3K et l'oncogenèse a commencé avec la découverte de l'association entre l'activité kinase et l'expression d'une oncoprotéine virale (47-49). Chaque acteur de la voie PI3K peut être concerné par différentes altérations (mutations, délétions ou amplifications), avec en tête de liste PIK3CA et PTEN qui sont respectivement les deuxièmes et troisièmes gènes les plus mutés dans les cancers humains (29,50,51).

Le gène suppresseur de tumeur PTEN, identifié à la fin des années 90 (52,53), est couramment inactivé dans les cancers sporadiques. La perte de PTEN induit une augmentation

de PIP3. Des niveaux élevés de PIP3 entraînent une activation constitutive de la voie PI3K et favorisent la prolifération cellulaire et la progression du cycle cellulaire (51,54).

AKT, une kinase plus en aval dans la voie, peut également être concernée par l'amplification et la mutation. L'amplification d'AKT est rapportée dans certains cancers sans implication solide dans la carcinogenèse. La mutation E17K d'AKT1 est identifiée dans les CS dans environ 4 % des cas. La mutation E17K provoque une altération entre AKT et la membrane cellulaire entraînant une fixation constitutive à la membrane et par conséquent augmente l'activation de la voie (55-57).

L'inositol poly phosphate 4-phosphatase de type II (INPP4B) est connu pour être un suppresseur de tumeur dans le TNBC et d'autres cancers en déphosphorylant PIP2 en PIP, puis en supprimant la signalisation d'AKT. D'autres études ont rapporté INPP4B comme oncogène. INPP4B est fortement associé à la présence des récepteurs hormonaux et au grade de la tumeur. Dans des lignées cellulaires de CS exprimant les récepteurs hormonaux, une étude récente confirme qu'une expression accrue d'ARNm et de protéines d'INPP4B induisent une croissance tumorale via l'activation de Wnt/β-caténine (57-58).

Dans des conditions physiologiques, le complexe tubéroscléreux (TSC) 1/2 inhibe l'activation de mTOR1. Des mutations ou une haplo-insuffisance de TSC1/2 peuvent être observées dans la lymphangioléiomyomatose et dans la sclérose tubéreuse, respectivement. La perte de la fonction TSC1/2 conduit à l'activation constitutive de mTORC1 et favorise la prolifération et le métabolisme cellulaire. Récemment, des mutations TSC1/2 ont été découvertes dans le carcinome hépatocellulaire (CHC) et de plus, ces CHC ont réagi au sirolimus (un inhibiteur de mTOR) (57,59).

Les mutations de PIK3CA ou de PIK3R1 favorisent le cancer par de multiples mécanismes, les mutations de PIK3CA peuvent être trouvées dans environ 30% des tumeurs

solides (60). A l'origine, les mutations de PIK3CA, à potentiel oncogène, ont été identifiées dans le cancer colorectal et notamment dans les domaines kinase et hélical. Samuels et al. ont déterminé 8 gènes de PI3K et 8 gènes de « PI3K-like » dans des cellules humaines de cancer colorectales et ils ont analysé la séquence de ces exons. PIK3CA était le seul gène de ce panel à porter des mutations somatiques, dans le cancer colorectal, 32% de mutations au sein de PIK3CA ont été retrouvé. Par la suite, ils ont exploré dans d'autres cancers et ils ont retrouvé des mutations de PIK3CA dans 27% des glioblastomes, 25% des cancers gastriques et 8% des CS (61). Le catalogue des mutations somatiques dans le cancer (COSMIC) a découvert que 80 % des mutations de PIK3CA ne concernent seulement que trois « hotspot » et qu'elles sont toutes localisées sur les domaines kinase et hélical des sous-unités catalytiques. Ces « hotspot » sont H1047R, E542K et E545K et ils peuvent être trouvés dans un large panel de tumeurs, par exemple du sein, colorectal, glioblastome, endométrial, cervical, etc. (62).

Ces mutations « hotspot » ont plusieurs actions sur les sous-unités catalytiques. Dans le domaine kinase, la mutation H1047R sur l'exon 20 permet un ancrage de p110 à la membrane cellulaire sans la présence de RAS. Dans le domaine hélical, les mutations E542K et E545K sur l'exon 9 perturbent l'interaction avec SH2 et bloquent par conséquent l'action de la sous-unité régulatrice (57,63).

Les mutations de PIK3CA ont potentiellement un impact sur un très large spectre d'actions au niveau cellulaire, favorisant ainsi la résistance à l'apoptose, conduisant à augmenter la capacité invasive via la transition épithélio-mésenchymateuse, induisant une instabilité chromosomique et favorisant un environnement immunosuppresseur (64–67).

Les mutations de la voie de PI3K peuvent également provoquer des maladies non malignes et non solides : par exemple les mutations de PIK3CD et de PIK3R1, qui codent respectivement pour la sous-unité catalytique p110δ et la sous-unité régulatrice p85,

induisent des syndromes d'immunodéficience primaire, nommés syndrome activateur PI3Kdelta (APDS 1 et 2) (68,69). La sous-unité p110δ est impliquée dans toutes les étapes du développement des lymphocytes et notamment dans la croissance des lymphocytes B. Selon la localisation de la mutation, p110δ peut favoriser des hémopathies malignes (70).

Dans cette logique, le développement d'inhibiteurs de PI3K ciblant p110δ a été lancé. Des études ont permis d'obtenir les approbations de la FDA et de l'EMA pour l'idelalisib en tant qu'inhibiteur de PI3Kδ (dans la leucémie lymphoïde chronique en rechute, le lymphome folliculaire non hodgkinien en rechute, le petit lymphome lymphocytaire en rechute) (71,72), le copanlisib en tant qu'inhibiteur pan-PI3K (dans le lymphome folliculaire récidivant) (73), le duvelisib comme double inhibiteur PI3Kδ-PI3Kγ (dans la leucémie lymphoïde chronique réfractaire, le lymphome lymphocytique, le lymphome folliculaire récidivant ou réfractaire) (74,75) et l'umbralisib comme double inhibiteur PI3Kδ-CK1ε (dans la leucémie lymphocytaire, lymphome folliculaire réfractaire et lymphome des zones marginales) (76,77).

4. Inhibiteurs de PI3K dans le cancer du sein : rationnel

Dans le CS, la voie PI3K peut être dérégulée par de multiples altérations, par exemple des mutations de PIK3CA, des dysfonctionnements de PTEN, des mutations d'AKT ou des amplifications d'HER2 (78). Souvent, les mutations sur la même voie sont mutuellement exclusives, comme on peut le voir dans le cancer du poumon (79). Pourtant, dans le CS, les mutations de PI3KCA peuvent être observées de manière concomitante avec une amplification d'HER2, une perte de PTEN ou des mutations d'AKT, suggérant qu'une mutation isolée n'a pas un potentiel oncogène suffisant pour induire une tumeur. Des observations similaires ont été faites dans les cancers colorectaux avec les mutations concomitantes de KRAS et de BRAF (80).

Dans tous les sous-types de CS, la prévalence des mutations de PIK3CA varie entre 25 et 40 %. La prévalence atteint 40 %, chez les CS RE-positif/HER2-négatif (81). Une méta-analyse a trouvé une association positive entre la mutation de PIK3CA et l'expression du RE, tandis que pour la surexpression d'HER2, les résultats ne sont pas clairs et nécessitent plus d'exploration. Les mutations de PIK3CA ont également été associées à la présence du récepteur aux androgènes (RA) dans le TNBC (82).

Concernant l'impact pronostique de la mutation de PIK3CA, les résultats sont encore controversés. Les mutations de PIK3CA sont associées à une amélioration de la survie sans récidive locale chez les patientes atteintes de CS localisé, mais n'ont aucun impact sur la survie sans récidive à distance ou la survie globale (SG) (83). Dans le CS localisé RE-positif/HER2-négatif, les mutations de PIK3CA n'ont pas prédit la réponse à l'HT et les résultats ne sont pas clairs en situation métastatique. Une méta-analyse, incluant tous les sous-types de CS (n = 1929) en situation localisés ou métastatiques, a trouvé que la mutation de PIK3CA est un facteur de mauvais pronostic indépendant. Dans cette étude, les différentes mutations de PIK3CA ont été regroupées (84). Mosele et al. ont constaté que les résultats peuvent varier selon les sous-types de CS. Le CS métastatique RE-positif/HER2-négatif avec mutation de PIK3CA semblait être moins sensible à la chimiothérapie et avait une faible survie comparativement au PIK3CA sauvage (19,6 mois contre 23,5 mois, respectivement). Pour le TNBC, les patients porteurs de la mutation PIK3CA avaient une meilleure survie que les patients sauvage (24 mois contre 14 mois, respectivement). Cela peut être en rapport avec le fait que certaines des patientes avec des TNBC étaient initialement RE-positifs et qu'elles ont perdu l'expression des RE lorsque les tumeurs ont acquis la mutation PIK3CA, cela peut également être dû aux sous types de TNBC avec RA-positifs, qui sont enrichis en mutations PIK3CA et dont on suppose une évolution plus indolente comparativement à d'autres sous-

types de TNBC (82). Plusieurs études ont montré un impact pronostique différent entre les 2 mutations « hotspot » sur les exons 9 et 20, les résultats sont flous et contradictoires. Une étude retrouve que les mutations de l'exon 20 sur le domaine kinase sont associées à un pronostic plus favorable que les mutations de l'exon 9 sur le domaine hélical. Les CS avec mutation du domaine Kinase seraient associés à une meilleure SSP et SG par rapport à PIK3CA non muté et les PIK3CA non muté seraient associés à une meilleure SSP et SG par rapport à la mutation du domaine hélical (85–87). Mangone et al. ont exploré l'impact pronostique de la mutation de l'exon 9 ou de l'exon 20 de PIK3CA pour les patientes atteintes de CS, environ 75 % d'entre elles ayant un CS métastatiques. Ils ont trouvé un mauvais pronostic pour les patients porteurs de la mutation de l'exon 20 de PIK3CA. Les patientes porteuses de la mutation de l'exon 9 avaient des résultats similaires à ceux des patients porteurs de PIK3CA de type sauvage (88). En situation néo-adjuvante, une série de patientes (n = 92) atteintes de TNBC localisés et traités avec un régime de chimiothérapie à base d'anthracycline et une mutation de l'exon 20 de PIK3CA avaient un taux inférieur de réponse complète pathologique (pCR) ; dans cet essai, la mutation de l'exon 20 n'est survenue que chez 7 patientes (89). Hu et al. ont également suggéré que dans les cellules de TNBC et chez 50 patientes atteints de TNBC localisé, la mutation de PIK3CA induisait une chimiorésistance et favorisait la rechute (90).

Une analyse du génome du cancer PIK3CA muté a révélé une cooccurrence de multiples altérations au sein de PI3K dans environ 15 % des cas de CS et il s'agissait plus fréquemment de mutations en cis sur le même allèle. Les altérations multiples des voies conduisent à une hyper activation par rapport à une altération unique suggérant une dépendance oncogénique accrue des doubles mutations de PIK3CA et donc une possible sensibilité accrue aux inhibiteurs de PI3Kα (91).

Les récepteurs HER2-HER3 activés sollicitent la voie PI3K, ce qui suggère que les mutations de PIK3CA peuvent conférer une certaine résistance aux anti-HER2. Les données précliniques montrent que la mutation de PIKCA peut conférer une résistance au trastuzumab et au lapatinib (un inhibiteur de tyrosine kinase anti-HER2). Une résistance du trastuzumab a également été observée dans les données précliniques, avec la mutation de l'exon 20 de PIK3CA. Dans les lignées cellulaires de CS HER2-positif, Chakrabarty et al. ont pu observer dans des cellules avec la mutation de l'exon 20 une surexpression de l'héréguline, qui est un ligand d'HER3/HER4, une telle surexpression a conduit à un effet limité des anti-HER2. Dans le CS HER2-positif, la valeur prédictive ou pronostique du statut mutationnel de PIK3CA reste controverser. Dans le CS localisé, une étude n'a pas réussi à montrer un impact de la mutation PIK3CA pour le traitement par le trastuzumab lorsqu'il est administré en situation néo-adjuvante ou adjuvante. Un autre groupe mené par Loibl et al. a constaté que la mutation de PIK3CA était associée à une réduction significative de la pCR dans une méta-analyse incluant 967 patientes traitées en néo-adjuvant par trastuzumab ou par lapatinib. En situation métastatique, les résultats ne sont pas clairs. Seule une analyse rétrospective a exploré l'association potentielle de la perte de PTEN et/ou des mutations de PIK3CA avec la valeur prédictive ou pronostique du trastuzumab. Sur la base de la population de l'étude CLEOPATRA (trastuzumab plus docétaxel avec ou sans pertuzumab comme traitement de première intention pour des CS métastatiques HER2-positif), Baselga et al. ont montré, dans une analyse de biomarqueurs, que le type PIK3CA sauvage était associé à un meilleur pronostic. Avec le lapatinib ou le pertuzumab (un autre anticorps monoclonal anti-HER2), la mutation de PIK3CA n'a pas prédit un bénéfice de ces thérapies (87, 92-94).

Le traitement, in vitro, de lignées cellulaires de CS par inhibiteur de PI3Kα conduit à un arrêt de la prolifération. Donc, au lieu de mourir, les lignées cellulaires entrent plutôt dans un

état de dormance (95), et par conséquent, l'effet des inhibiteurs de PI3Kα se rapproche d'un effet cytostatique. Un effet cytotoxique direct a été rapporté avec un inhibiteur pan-PI3K ou un inhibiteur double PI3Kγ-PI3Kα. Dans la lignée cellulaire de CS RE-positif, l'apparition d'une hormono-résistance est associée à une hyper activation de la voie PI3K. L'association d'un inhibiteur de PI3Kα et d'un inhibiteur de mTOR a permis d'induire l'apoptose des cellules hormono-indépendantes et par conséquent de retarder la phase d'hormono-résistance (96). Une méta-analyse récente incluant 8 études avec 2670 patients, a montré que la mutation de PIK3CA est un bon facteur prédictif du taux de réponse objective (ORR) (odd ratio : 1,98) et de la SSP (hazard ratio = 0,65) dans le CS RE/RP-positif traité par inhibiteur de PI3K (97).

Néanmoins, l'action des inhibiteurs de PI3Kα est limitée par plusieurs mécanismes de résistance (voir dernière section), qui ne prédisent pas une activité anti-tumorale spectaculaire en monothérapie. Les biomarqueurs prédictifs de l'efficacité des inhibiteurs de PI3K sont limités et la mutation de PI3KCA est actuellement la seule. Nixon et al. ont constaté que l'association de la mutation PIK3CA avec des mutations inactivatrices de MAP3K1 pourrait prédire une meilleure réponse au buparlisib dans le CS RE-positif (98).

Le but de cette revue est d'examiner le développement de chacun des inhibiteurs de PI3K évalués dans le CS. Notre propos concernera les pan-inhibiteurs, les inhibiteurs sélectifs de p110α et leur développement dans tous les sous-types de CS. Nous passerons en revue les échecs, les succès et les perspectives possibles de cette classe thérapeutique.

Original Article

Phosphoinositide 3-kinase (PI3K) inhibitors and breast cancer, a systematic review of the literature

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I/ Introduction

1. Breast cancer

Worldwide, in 2020, breast cancer (BC) represents the first most frequent cancer in both sex with approximately 2.3 million cases and is the fourth cause of death with approximately 685 000 deaths (1). In France, between 1900 and 2018, it has been shown that the incidence is increasing approximately 1.1% per years (2). BC is an heterogeneous disease including small curable tumors or metastatic tumors with a very poor prognosis (3). In practice, clinical and pathological features are used to define the stage and the aggressiveness of the tumor. The intrinsic gene expression profile is correlated with the expression or not of three cellular receptors (estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor-2 (HER2)). There are different molecular subtypes of BC, but in clinical practice, subtypes are defined by cellular receptors expression and proliferation status which may be addressed by Ki67 (4,5). A higher histological grade is associated with a larger BC and with local or distant metastasis on diagnosis. The development of complementary deoxyribonucleic acid (cDNA) microarray introduces a new concept of molecular classification but still do not enter in clinical practice due to its good concordance with the current classification and a more expensive price (6).

The different subtypes are the following: Luminal A and Luminal B subtypes, with ER/PR-positive and HER2-negative tumors, represent the most frequent breast cancers. HER2 overexpression is found in approximately 15-20 % of tumors. If none of these receptors are expressed, then tumors are called triple negative breast cancer (TNBC) and represent approximately 10% of cases. TNBC are characterized by an aggressive disease, the younger age of patients and a less favorable outcome (7,8). Inflammatory breast cancer (IBC) represents a distinct entity and has pure clinical definition with rapid onset (<6 months) of

breast erythema, edema, and/or peau d'orange, and/or warm breast, with or without an underlying palpable mass and some pathological features such as dermal emboli. IBC is uncommon representing less than 5% of cases, and has the worst survival (9,10).

In early BC, which represents approximately 90% of cases, treatment is based on surgery, radiotherapy and, depending on subtypes, on hormonotherapy, chemotherapy and target therapy. The risk of relapse varies between 10 to 41% and depends on subtypes and other clinic-pathological characteristics (11).

In advanced and metastatic BC, the standard of care is based on systemic therapy. Concerning the HER2 overexpressed BC, the initial treatment is an association of a chemotherapy and a combination of anti-HER2 therapy (Trastuzumab and Pertuzumab) (12). Initially, the overexpression of HER2 was associated with a poor prognosis but after trastuzumab introduction and further improvements in anti-HER2 agents, a recent study showed that BC with HER2 overexpression display now the longest survival (13). For TNBC, the standard of care is chemotherapy and more recently immunotherapy with anti-PD-1 (pembrolizumab) in combination with chemotherapy has received an authorization from the Food and Drug Administration (FDA) and European Medicine Agency (EMA) for PD-L1+ (i.e., with combined positive score (CPS) equal or superior to 10 by IHC) TNBC (14). For patients whit germline BRCA1 or BRCA2 mutation, PARP inhibitors are also an option (15–18).

For ER/PR-positive/HER2-negative advanced or metastatic BC, the first line treatment is an association of an endocrine therapy (ET) and a CDK4/6 inhibitor, except if patient presents a visceral crisis (19–21). Natural history of these patients is characterized by multiple lines of hormone therapy and targeted therapy until the appearance of hormone resistance and the use of palliative chemotherapy. A meta-analysis confirmed that all patient had a benefice to CDK4/6 inhibitors therapy in first line versus ET monotherapy (22). For

premenopausal patients, ovarian suppression is systematic, and recent results from randomized studies have shown that premenopausal women treated with ET plus ovarian suppression plus CDK4/6 inhibitors had a similar progression-free survival (PFS) than postmenopausal women (23–25). Few data may suggest re-challenge to another CDK4/6 inhibitor (abemaciclib) after a previous CDK4/6 inhibitor (palbociclib) might have clinical activity (26). For patients harboring germline BRCA mutation, olaparib and talazoparib (PARP inhibitor) showed a significative benefice for PFS, but the optimal sequence of CDK4/6 and PARP inhibitors is not clear (16,27). Everolimus (mammalian target of rapamycin (mTOR) inhibitor) plus exemestane significantly improved PFS versus exemestane monotherapy, 11 months versus 4.1 months respectively in the phase III trial BOLERO-2 for patient progressing on or after aromatase inhibitors (AI) therapy (28). Advent of CDK4/6 inhibitor pushed back everolimus into the later lines. Few data explored benefice of everolimus with exemestane after CDK4/6 inhibitor, however in clinical practice, everolimus is commonly used as a second line after failure of CDK4/6 inhibitors. Chemotherapy with capecitabine, paclitaxel, eribulin are classically used in hormone resistance phase or for visceral crisis. For ER/PR-positive BC, the next step could include the use of antibody-drug conjugates (ADCs) such as trastuzumab deruxtecan (DS-8201a) for HER2 low (i.e. HER2 1+ or 2+ and hybridization in situ negative tumors), patritumab deruxtecan (HER3-DXd, U3-1402), sacituzumab govitecan or datopotamab deruxtecan.

2. PI3K pathway

The phosphatidylinositol 3-kinase (PI3K) pathway is one of the most frequently altered pathways in human tumors. This signaling network consists of PI3K, AKT and mTOR (29). PI3K belongs to the family of intracellular lipid kinases and can be divided into three groups according to their structure and function. Class I is activated by insulin or other growth factors and can be further divided into class IA and class IB. Class IA PI3K is associated with tyrosine kinase receptors (RTK) and class IB is associated with heterotrimeric G protein–coupled receptors (GPCRs). Both are composed of a catalytic subunit and a regulatory subunit. We shall continue our subject only on class IA which is the most directly involved in human carcinogenesis (30–33). For class IA PI3K, the catalytic subunit isoforms are p110α, p110β, p110γ, or p110δ. PIK3CA is located on chromosome 3q26.3 and encodes a catalytic subunit p110α. Catalytic subunit can be associated with one of five regulatory subunits (p85α, p55α, p50α encoded by PIK3R1 or p85β encoded by PIK3R2 or p55γ encoded by PIK3R3) (34,35). The catalytic subunit is composed by a helical domain and a kinase domain. The regulatory subunit is composed by 3 Src-homology-2 (SH2), 2 in the C-terminal portion and 1 in N-terminal portion, a Breakpoint Cluster Region homology (BH domain) and an inter-SH2 (35–37). Different subunits have several functions and an unequal distribution. Thus, p110α drives the activation of anabolic processes, angiogenesis, embryogenesis and the proliferation, p110γ/p110β are involved in inflammatory cells, and p110δ concerns, in particular, adaptive immunity (29,38). Regulatory subunits have three particular actions : inhibition of kinase activity of p110, stabilization of p110 and promotion of a negative retro control (34). SH2 domains is found on regularity subunits and play two key roles. Frist, SH2 allows to recruit the p85–p110 heterodimer (PI3K) to insulin receptor–IRS complex at cellular membrane and

therefore to bring PI3K closer to phosphatidylinositol 3,4-bisphosphate (PIP2). Second, SH2 binds to SH2-containing inositol 5-phosphatase (SHIP) which allows inhibition of p110 (36).

The particularity of class I PI3K is the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3). When RTK is activated by growth factors then PI3K is recruited to plasma membrane-anchored receptors and thus is activated; p110 is locked by RAS at the membrane, which allows anchoring. Activated PI3K can phosphorylate PIP2 to generate PIP3. PIP3 is one of the most important second messengers in human cells, namely by recruiting and binding AKT or other proteins with a pleckstrin-homology (PH) domain such as 3-phosphoinositide–dependent protein kinase 1 (PDK1). Then AKT is phosphorylated and activated by PDK1 and mammalian target of rapamycin complex 2 (mTORC2) (39). Activated AKT transmits the growth and triggers several phosphorylation-based signaling cascades. By generating PIP3, which brings AKT and PDK1 in contact (40), PI3K plays a central role in several cellular processes including DNA synthesis, metabolism and action on actin cytoskeleton (41,42). The tumor suppressor phosphatase and tensin homolog (PTEN) negatively regulates the action of PIP3, by 3′-phosphatase activity, transforming PIP3 to PIP2 (43), which stops the phosphorylation cascade. PIP3 can be negatively regulates by another actor, SHIP which is picked up by SH2 domain of regulatory subunit. Of note, the activity of SHIP to remove the phosphate from the 5′ position is not controlled by a tyrosine phosphorylation. Nevertheless, SHIP is unable to suppress AKT activity, due to the 5′ phosphatase activity of SHIP which does not interfere with AKT-PDK1 interaction and consequently AKT can still remain active (44,45).

3. PI3K pathway alterations human cancer

Alteration of PI3K pathway is one of the most common alteration in human cancer, estimated at 14% of all solid tumors (46). The relationship between alteration of PI3K and oncogenesis started with the discovery of the association between kinase activity and viral oncoprotein expression (47–49). Each actor of PI3K pathway can be concerned by different alterations (mutations, deletions or amplifications), with at the top of the list PIK3CA and PTEN which are respectively the second and third most highly mutated genes in human cancers (29,50,51).

The tumor suppressor gene PTEN, which was identified at the end of the 90s (52,53), is commonly inactivated in sporadic cancers. PTEN loss induces an increase of PIP3. High levels of PIP3 result in a constitutive activation of the PI3K pathway and promotes cell proliferation and cell cycle progression (51,54).

The downstream kinase AKT can be concerned by amplification and mutation. Amplification of AKT is reported in some cancers without solid implication in carcinogenesis. The E17K mutation of AKT1 is identified in BC in approximately 4% of cases. E17K mutation causes an alteration between AKT and the cellular membrane resulting in a constitutive fixation at the membrane and consequently increases activation of the pathway (55–57).

Inositol polyphosphate 4-phosphatase type II (INPP4B) is known to be a tumor suppressor in TNBC and other cancers by dephosphorylate PIP2 into PIP and then suppresses AKT signaling. Other studies reported INPP4B as an oncogene. INPP4B is strongly associated with ER-positive status and tumor grade. Recent study confirms in ER-positive BC cell lines that an increased mRNA and protein expression of INPP4B induce the tumor growth via Wnt/β-catenin activation (57,58).

In physiologic condition, tuberos sclerosis complex (TSC) 1/2 inhibit the activation of mTOR1. Mutations or haplo-insufficiency of TSC1/2 can be observed in lymphangio leiomyomatosis and tuberous sclerosis, respectively. Loss of TSC1/2 function leads to constitutive activation of mTORC1 and promotes proliferation and metabolism. Recently TSC1/2 mutations were found in hepatocellular carcinoma and have with response to sirolimus (a mTOR inhibitor) (57,59).

Mutations of PIK3CA or PIK3R1 promote cancer through multiple mechanisms, PIK3CA mutations can be found in approximately 30% of different solid tumors (60). Originally, the PIK3CA mutations, with an oncogenic potential, were identified in colorectal cancer and especially in kinase and helical domains. Samuels et al. determined 8 PI3K and 8 PI3K-like genes in human colorectal cancer cells and they analyzed the sequence of exons. PIK3CA was the only gene of this panel to carry somatic mutations, 32% of PIK3CA mutation in colorectal cancer, afterwards, they explored other cancer and PIK3CA mutations were found in 27% of glioblastomas, 25% of gastric cancers and 8% of breast cancers (61). The catalogue of somatic mutation in cancer (COSMIC) discovered that 80% of PIK3CA mutations concern only three "hotspots" and that they are all located on the kinase and helical domains of catalytic subunits. These "hotspots" H1047R, E542K, and E545K may be found in a large panel of tumors, for example breast, colorectal, glioblastoma, endometrial, cervical, etc. (62).

These "hotspot" mutations have several actions on catalytic subunits. In kinase domain, H1047R mutation on exon 20 enhances the inking of the p110 to cell membrane without the requirement of RAS. In helical domain, E542K and E545K mutations on exon 9 disturb the interaction with SH2 and consequently block the action of regulatory subunit (57,63).

PIK3CA mutations have potentially an impact on a very broad spectrum of actions at the cellular level, promote resistance to apoptosis, lead to increase invasive capacity by epithelial-to-mesenchymal transition, induce a chromosomal instability and promote an immunosuppressive environment (64–67).

PI3K pathway mutations can also cause nonsolid malignant diseases: for example the mutation of PIK3CD and PIK3R1, which encoded for p110δ catalytic subunit and p85 regulatory subunit respectively, induces primary immunodeficiency syndromes, named activating PI3Kdelta syndrome (APDS 1 and 2) (68,69). The p110δ subunit is involved in all stages of the lymphocyte development and namely in the growth of malignant B lymphocytes. Depending on the mutation localization, p110δ mutations may promote hematological malignancies (70).

Based on this rationale, the development of PI3K inhibitors targeting p110δ has been started. Successful studies have allowed to obtain FDA and EMA approvals for idelalisib as PI3Kδ inhibitor (in relapsed Chronic Lymphocytic Leukemia, relapsed Follicular B-cell non-Hodgkin Lymphoma, relapsed Small Lymphocytic Lymphoma) (71,72), copanlisib as pan-PI3K inhibitor (in relapsed follicular lymphoma) (73), duvelisib as dual PI3Kδ-PI3Kγ inhibitor (in refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, relapsed or refractory follicular lymphoma) (74,75) and umbralisib as PI3Kδ-CK1ε dual Inhibitor (in refractory chronic lymphocytic leukemia, refractory follicular lymphoma and marginal zones lymphoma) (76,77).

4. Rationale for using PI3K inhibitors in breast cancer

In BC, PI3K pathway can be deregulated by multiple alterations, for example PIK3CA mutations, PTEN dysfunctions, AKT mutations or HER2 amplifications (78). Frequently, mutations on the same pathway are mutually exclusive as it can be seen in lung cancer (79). Yet, in BC, PI3KCA mutations can be seen concomitantly with HER2 amplification, PTEN loss or AKT mutations, suggesting that an isolated mutation does not have a high oncogenic potential. Similar observations have been made in colorectal cancers with concomitant KRAS and BRAF mutations (80).

Across all BC subtypes, the prevalence of PIK3CA mutations varies between 25 and 40%. The prevalence reaches 40%, in ER-positive/HER2-negative BC (81). A meta-analysis found a positive association between PIK3CA mutation and ER expression, while for HER2 overexpression, the results are not clear and need more exploration. PIK3CA mutations have been also associated to the presence of androgen receptor (AR) in TNBC (82).

Concerning the prognostic impact of PIK3CA mutation, results are still controversial. PIK3CA mutations are associated with an improvement in recurrence-free survival in early BC patients, but have no impact on not distant disease-free survival or overall survival (OS) (83). In ER/PR-positive/HER2-negative BC, PIK3CA mutations did not predict response to hormonotherapy in early setting and results are unclear in metastatic setting. A meta-analysis including patients (n=1929) mixing all subtypes as well as early and metastatic BC found PIK3CA mutation as an independent poor prognostic factor. In this study, different PIK3CA mutations were pooled (84). Mosele et al. found that the results may vary according to BC subtypes. ER-positive/HER2-negative metastatic BC with PIK3CA mutation appeared to be less sensitive to chemotherapy and had poor survival than PIK3CA wild type (19.6 months versus 23.5 months, respectively). For TNBC, data were opposite and patients with PIK3CA mutation

had better survival than wild type patients (24 months versus 14 months, respectively). This may be due to some of TNBC that were initially ER-positive and lost ER expression when tumors acquire PIK3CA mutations, it might also be due to AR-positive TNBC, that are enriched in PIK3CA mutations and are thought to have a more indolent natural history compare to other subtypes of TNBC (82). Several studies showed a different prognostic impact between the 2 "hotspot" mutations on exon 9 and 20, results are unclear and contradictory. Exon 20 mutations on kinase domain are associated with a more favorable prognostic than exon 9 mutations on helical domain. BC with PIK3CA Kinase domain mutation are associated with better disease-free survival and OS compared to non-mutated PIK3CA and non-mutated PIK3CA are associated with better disease-free survival and OS compared to helical domain mutation (85–87). Mangone et al. explored prognostic impact of PIK3CA exon 9 or exon 20 mutation for patients with BC, approximately 75% of them having a metastatic BC. They found a poor prognosis for patients harboring PIK3CA exon 20 mutation. Patients with exon 9 mutation had similar outcome than patients with PIK3CA wild type (88). In the neo-adjuvant setting, a series of patients (n=92) with early TNBC treated with anthracycline based regimen and PIK3CA exon 20 mutation had a lower rate of pathological complete response (pCR); in this trial, exon 20 mutation occurred in only 7 patients (89). Hu et al. also suggested that in TNBC cells and in 50 patients with early TNBC, PIK3CA mutation induced chemoresistance and promoted relapse (90).

An analysis of the cancer genome mutated by PIK3CA revealed a co-occurrence of multiple PI3K alterations in approximately 15% of BC cases and they were more frequently mutations in cis on the same allele. Multiple pathway alterations lead to hyperactivation compared to a unique alteration suggesting enhanced oncogenic addiction of double PIK3CA mutations and therefore a possible increased sensitivity to PI3Kα inhibitors (91).

Activated HER2-HER3 receptors also solicit the PI3K pathway which suggests that PIK3CA mutations may confer some of resistance to anti-HER2 therapy. Pre-clinical data found that PIKCA mutation may confer resistant to trastuzumab and lapatinib. Resistance of trastuzumab was observed in pre-clinical data, with PIK3CA exon 20 mutation. In HER2-positive BC cell lines, Chakrabarty et al could observe an overexpression of heregulin, an HER3/HER4 ligand in cells with exon 20 mutation, such an overexpression led to limited effect of anti-HER2 therapy. In HER2-positive BC, the predictive or prognostic value of PIK3CA mutation status was controversial. In early BC, a study failed to show an impact of PIK3CA mutation for trastuzumab treatment when it administered in the neo-adjuvant or adjuvant setting. Another group conducted by Loibl et al. found that PIK3CA mutation was associated with a significant reduction of pCR in a meta-analysis including 967 patients treated in the neo-adjuvant setting with trastuzumab or lapatinib. In the metastatic setting, results are unclear. Only retrospective analysis explored the potential association of PTEN loss and/or PIK3CA mutations with predictive or prognostic value of trastuzumab. Based on CLEOPATRA population (metastatic HER2-positive BC tested trastuzumab plus docetaxel with or without pertuzumab as first-line treatment), Baselga et al. showed, in a biomarker analysis, that PIK3CA wild type was associated with a better prognosis. With lapatinib, a small-molecule HER2 inhibitor, or pertuzumab, another anti-HER2 monoclonal antibody, PIK3CA mutation did not predict a benefit of these therapies (87,92–94).

In vitro, the treatment of cell lines by the PI3K inhibitors leads to an arrest of proliferation. Therefore, instead of dying, cell lines enter into a dormant state (95). Hence, this was closer to a cytostatic effect of PI3Kα inhibitor. A direct cytotoxic effect was also reported with pan-PIK3 inhibitor or a dual inhibitor PI3Kγ- PI3Kα. In ER-positive BC cell line, apparition of hormone resistance was associated to a hyperactivation of PI3K pathway.

PIK3CA and mTOR inhibitor allowed to induce apoptosis of hormone-independent cell and consequently delayed hormone resistance phase (96). A recent meta-analysis including 8 studies with 2670 patients and showed that the PIK3CA mutation is a good predictive factor of objective response rate (ORR) (odd ratio: 1.98) and PFS (hazard ratio (HR) = 0.65) in ER/PR-positive BC treated by PI3K inhibitor (97).

Nevertheless, the action of PI3Kα inhibitor is limited by several mechanisms of resistance (see last section), which did not predict a dramatic anti-tumor activity in monotherapy. Predictive biomarkers of PI3K inhibitor efficacy are limited and the PI3KCA mutation is currently the only one. Nixon et al. found that association of PIK3CA mutation with an inactivating mutations of MAP3K1 may predict better response to buparlisib in ER-positive BC (98).

The aim of this review is to examine the development of each PI3K inhibitors evaluated in BC. Our purpose shall concern pan inhibitors, selective p110α inhibitors and their development in all subtypes of BC. We shall review the failures, successes, and possible futures of this therapeutic class.

II/ Pan-PI3K inhibitors

Pan-PI3K inhibitors inhibit the kinase activity of all four isoforms of class I PI3K: α, β, γ, and δ.

1. Buparlisib (BKM120)

a. Preclinical data

Anti-tumor effects induced by the pan-PI3K inhibitor, buparlisib, led to adaptive mechanisms that increase the expression of estrogen receptors in ER/PR-positive/HER2-negative BC (99). Subsequently, PI3K inhibitors (buparlisib and alpelisib) showed a synergistic effect in combination with tamoxifen (a selective estrogen receptor modulator) and promoted apoptosis in vitro and in vivo. Association with buparlisib seemed to induce a higher anti-tumor effect. Cell lines with ESR1 mutations or acquired tamoxifen resistance are still resistant to tamoxifen despite the adjunction of PI3K inhibitors (100). These observations explain how to combine PI3K inhibitors and hormonotherapy. Other studies also found a synergistic effect of CDK 4/6 inhibitors with PI3K inhibitors for ER/PR-positive/HER2-negative BC with PIK3CA mutations (101,102).

Solzak et al. interested themselves in finding a synergistic combination, from in vitro to mouse studies. They showed a synergism of buparlisib and WNT974 (WNT-pathway inhibitor). They studied a group of 40 mouses with BRCA mutations and PI3K activations. Results were very interesting with a survival rate of 80% for mice treated with the combination and only 40, 30, 0% surviving with buparlisib, placebo and WNT974 respectively (103). Van Swearingen et al. evaluated buparlisib in vitro and in vivo for TNBC brain metastases. Buparlisib and selumetinib (MEK-inhibitor) improved survival in mouses and induced a reduction in intracranial tumor burden. A model of administration of this combination for 5 days on/2 days off showed a decrease of the toxicity rate and the same efficiency (104).

Mustafi et al. showed in a mouse model of TNBC that vitamin C can sensitized TNBC cells to buparlisib. Vitamin C plays a role on epigenetic which allows a reduction of the dose of buparlisib necessary to have a therapeutic effect. On the other hand, it also acts synergistically with buparlisib to inhibit AKT phosphorylation (105). Hu et al. tested buparlisib in three multidrug resistant breast cancer cell lines with or without doxorubicin. They found a cytotoxic effect in three cell lines in vivo and in vitro of buparlisib alone, effect was observed by a blockage of PI3K pathway and lead to a diminution of NF-κB expression. Adjunction of doxorubicin demonstrated a synergistic anti tumoral effect (106).

b. Early phase studies

The first administration in human of buparlisib for advanced solid tumors appears in March 2014. The phase I study of dose-escalation and -expansion found a clinical benefit rate (CBR) (composed by a rate of complete response (CR) + partial response (PR) + stable disease (SD) for at least 6 weeks, reported as best response) of 41.0 %. Approximately 40.0 % of patient experiencing a serious adverse event (SAE) with 8.4% of hyperglycemia, 7.2 of rash, 3.6% of asthenia and 1.2% of mood disorder. The dose of 100 mg/day was the recommended dose (107) . A phase I study conducted by McRee et al. tested buparlisib in combination with capecitabine (an oral fluoropyrimidine) in twenty-five patients with all metastatic BC subtypes including 15 TNBC. Main side effects were nausea, hyperglycemia, rash, diarrhea, mucositis, depression, and anxiety. Approximately 52% of patients had a grade ≥ 3 adverse events. Despite encouraging results with a CBR at 68% (108), the development of buparlisib in association with capecitabine is stopped.

c. ER/PR-positive/HER2-negative BC

Mayer et al. confirmed the 100mg/day at maximum tolerated dose (MTD) was a safe dose for fifty-one patients during a phase Ib evaluating buparlisib in association with letrozole (109). Ma et al. were interested in a combination of buparlisib to fulvestrant and found a similar MTD and the CBR was 58.6% for thirty-one patients treated in this phase I trial (110). A phase II study, conducted by Welt et al., explored PIK3CA mutation as a predictive biomarker for patients (n=25) treated with buparlisib in association to tamoxifen in advanced BC pretreated by prior ET. PIK3CA mutation, PTEN loss (with or without PIK3CA mutation) and wild type (PIK3CA wild type and PTEN preserved) concerned 9, 3 and 13 patients respectively. Median PFS was 6.1 months for all patients and median PFS was 8.7 months for PIK3CA mutated patients. The study was prematurely stopped related to the important rate of toxicity with buparlisib, 96% of patients occurred an adverse event, of which56% of gastrointestinal disorders, 48% of mood disorders, 44% of skin rash and 32% of hepatic disorders. (111).

In BELLE-2, buparlisib was investigated for patients whose disease progressed on or after AI and had benefited at most of one previous line of chemotherapy for advanced BC. Patients (n=1147) were included to receive an association of fulvestrant with buparlisib or placebo. The final OS results did not find a significant difference: OS was 35.6 months in the buparlisib arm and 35.0 months in the placebo arm. Regarding to tolerance, 78% of patients receiving the combination experienced grade 3 or 4 adverse events versus 34% in the placebo arm. The main side effects were hyperglycemia, rash, anxiety and some severe mood disturbance (depression and suicide attempts), elevated ALAT and ASAT (112). The second phase III was BELLE-3, in which Di Leo et al. explored buparlisib versus placebo, in combination with fulvestrant for patients progressing on or after prior ET and mTOR inhibitors. Patients (n=432) were included and 289 received buparlisib. At the interim analysis for OS, there were

31% versus 32% of mortality in buparlisib and placebo group respectively. (113). The toxicity profile was similar to the one of BELLE-2.

BELLE-2 and BELLE-3 were both positive concerning their primary endpoint, median PFS by local investigator assessment for all patients with 6.9 versus 5.0 months with a HR of 0.78 (95% CI 0.67–0.89, p=0·00021) and 3.9 versus 1.8 months with a HR of 0.67, (95% CI 0.53–0.84, p=0·00030) respectively. In the group with PI3K pathway-activated of BELLE-2, median PFS with buparlisib was 6.8 months versus 4.0 months in placebo group with HR of 0.76 (95% CI 0.60–0.97) similar to the results of overall cohort. In the subgroup of PIK3CA mutated of BELLE-3, a higher median PFS was observed in buparlisib group 4.7 versus 1.4 months with a better HR of 0.39 (95% CI 0.23–0.65). Both phases III suggested focusing on the search for selective PI3K inhibitors because the clinical benefit was modest compared to the toxicity profile (113,114).

The BELLE-4, phase II/III study, tested the addition of paclitaxel to buparlisib for HER2-negative BC in first line, and did not improve PFS. The median PFS was 8.0 months in experimental arm versus 9.2 months in placebo arm with HR of 1.18 (95% CI 0.82–1.68), the study was stopped for futility (115).

We emphasize that in these studies, the PI3K pathway may be activated or not and the rate of PIK3CA mutation was 32% in BELLE-2, 39% in BELLE-3 and 35% in BELLE-4, which may suggest an underestimation of buparlisib efficiency.

All of these phase III studies contributed to stop buparlisib development in relation to an unfavorable toxicity profile (specifically because of severe diarrhea, rash, hyperglycemia and mood disorders) and modest anti tumoral activity.

d. Triple negative BC

Garrido-Castro et al. showed that buparlisib alone in TNBC was ineffective. In this phase II study, 50 patients were included, buparlisib was used in every therapeutic line with 14% of first line. CBR was 12% at 4 months with only stable disease. No response was observed and the median PFS was 1.8 months (116).

e. HER2 overexpressed BC

Buparlisib in association with trastuzumab was explored in phase Ib trial, in advanced or metastatic settings after a first line with trastuzumab. This study showed promising results with 75% of disease control rate in a population including approximately 40% of patients with activated PI3K pathway. However, 67% of SAE was observed at 100mg once a day of buparlisib, frequent adverse events were mainly hyperglycemia, rash and diarrhea. Serious mood disorders occurred for 17% of patients (117). Unfortunately, phase II failed to meet the primary endpoint which was 25% of response rate. In this study, the ORR was 10%. All population (n=50) experienced an adverse event, most common side effects were diarrhea, nausea, fatigue, hyperglycemia, rash, anxiety, and depression. Approximately, 70% of patient developed a SAE with mainly, transaminases increase (16%), rash (10%), asthenia (8%) and psychiatric disorders (14%). The development of buparlisib in association with trastuzumab for locally advanced or metastatic BC is stopped after (118). Our group evaluated association of buparlisib and lapatinib in a phase Ib for trastuzumab resistant HER2-positive advanced BC. Buparlisib at 80 mg once a day and lapatinib at 1000 mg once a day was feasible with no new safety signal. Patients (n=24) were treated independently of PIK3CA status, their CBR (CR, PR and SD for at least 24 weeks) was 29%, one patient experienced a complete response (4.17%). SAE most frequently observed were diarrhea for 21% of patients, rash for 17% of patients,

liver toxicity for 17% of patients, hyperglycemia for 8% of patients and mood disorder in 4% of patients (119). However, the association was not pursued.

NeoPHOEBE trial, a phase II randomized and double-blind study, explored the association of buparlisib, trastuzumab and paclitaxel in the neo-adjuvant setting. Patients (n=50) with early BC and HER2 overexpressed were included. IBC, bilateral BC, and metastatic BC were exclusion criteria. Only 16% of patients had PIK3CA mutations. Study was prematurely stopped after fifty inclusions (planned inclusion, n=256) due to an unacceptable liver toxicity (120).

In conclusion, buparlisib presented a modest anti-tumoral activity depending on the BC subtypes, an important toxicity rate, namely liver toxicity, rash, hyperglycemia and neuro-psy disorders. Buparlisib is not recommended for treatment but has paved the way for more selective inhibitors.

2. Pictilisib (GDC-0941)

a. Preclinical data

Pictilisib is a potent, selective, orally bioavailable inhibitor of class I PI3K, with an additional effect on mTOR. In vitro, Pictilisib induced a reversible cell cycle arrest at G1 phase, promoted apoptosis and limited endothelial cell growth (121). In ER-positive human BC cell lines and in mice model harboring PIK3CA mutation, Yang et al. found that fulvestrant plus pictilisib had a higher anti-tumoral effect than fulvestrant or pictilisib monotherapy. Furthermore, two doses schedules were explored with association. Weekly high-dose of pictilisib was shown to promote apoptosis and daily low-dose of pictilisib preferentially inhibited proliferation (122).

Zheng et al. showed that pictilisib alone had an anti-proliferative effect on different BC cell lines. In addition to block PI3K, pictilisib reduced AKT activation by mTORC2 via inhibition

of S6K1. Association of pictilisib with mTOR inhibitor promoted cell apoptosis (123). Pictilisib showed an improvement of the antitumor activity of taxanes on HER2-positive BC xenografts and also a synergistic effect with trastuzumab in term of inhibition of cell proliferation in vivo for HER2 overexpressing BC (78,124).

b. Early phase studies

The first administration in human of pictilisib was published in January 2015, in which 60 patients with solid tumors were included. Sarker et al. showed signs of antitumor activity as a single agent for doses levels ≥100 mg, and they recommended doses of 330 mg once a day. In this study, 15% of patients had a BC, but regarding this subgroup, no clinical activity data was available. Most frequent adverse events were nausea, diarrhea, vomiting and rash. SEA were represented mainly with rash in 8.3% (125).

Schöffski et al. realized a four-arm phase Ib trial made of three parts. Parts 1 and 2 included advanced BC patients (n=69) for dose escalation and cohort expansion respectively. In part 1, patient (n=20) with metastatic ER-positive BC or metastatic TNBC, received pictilisib plus paclitaxel with or without bevacizumab (antibody anti-VEGF). In part 2, all metastatic BC subtypes were included, and patients (n=39) received pictilisib plus paclitaxel and depending on BC subtypes bevacizumab or trastuzumab. Patients had a HER2 overexpression in 13% of the cases and only in the group with trastuzumab in part 2. The response rate was 26.6% in part 1 (dose escalation of pictilisib), 23.5% in part 2A, 53.8% in part 2B (with bevacizumab cohort), 33.3% in part 2C (HER2-positive cohort). In part 3, only ER-positive/HER2-negative metastatic BC were eligible, and patients (n=7) received association of pictilisib with letrozole and the ORR was 33.3%. The size of each subgroup was too small to conclude on the efficacy. All patients experienced an adverse event and the rate of SAE was 72.5%, including neutropenia, rash, peripheral neuropathy, pneumonia and venous thromboembolism (126).

c. ER/PR-positive/HER2-negative BC

The randomized, double-blind, placebo-controlled, FERGI trial evaluated pictilisib in combination with fulvestrant, for postmenopausal women with advanced or metastatic BC resistant to an AI. This study explored also apitolisib (GDC-0980, a dual PI3K-mTOR inhibitor). After 30 inclusions this arm was closed due to safety signals. The protocol design was made of two parts: the first part included all patients regardless of PIK3CA mutational status and the second part included only patients with PIK3CA-mutated tumors. This study failed to meet its primary endpoint of PFS. The median PFS was 6.6 months versus 5.1 months in part 1 and 6.5 months versus 5.1 months in part 2. No other investigation of pictilisib in this setting is ongoing (127). In the PEGGY study, a multicenter, placebo-controlled, phase II randomized trial enrolling 183 patients with locally recurrent or metastatic BC, Vuylsteke et al. showed that the addition of pictilisib with paclitaxel did not meet the primary endpoint at interim analysis and decided to stop the trial. The median PFS was 8.2 months in the pictilisib group versus 7.8 months in the placebo group. Approximately 30 patients had PIK3CA mutations in both groups and the median PFS was 7.3 months for the pictilisib group and 5.8 months for the placebo group (128).

Schmid et al. had tested the efficacy of pictilisib in association with anastrozole, versus anastrozole alone, in a comparative phase II study in the neo-adjuvant setting, enrolling 75 patients with newly diagnosed operable ER-positive and HER2-negative BC. The primary endpoint was the decrease in Ki67 as a surrogate of the decrease in cell proliferation. They found a significantly different decrease in geometric Ki67 average with 83.8% for pictilisib/anastrozole versus 66.0% for the anastrozole group (129). In 2018, Schmid et al. in the same population of newly diagnosed operable ER-positive and HER2-negative BC in the neo-adjuvant setting, found an impact of the PIK3CA mutation status. The ratio of geometric

Ki67 average suppression was 0.48 for helical domain mutations, 0.63 for PIK3CA wild types and 1.17 for kinase domain mutations. These results suggested that early BC with helical domain mutations had a poor response to anastrozole monotherapy (mean Ki67 suppression 53.9%) and that it could be importantly increased by the adjunction of pictilisib (mean Ki-67 suppression 78.1%). Conversely, BC with PIK3CA kinase domain mutations responded well to anastrozole and did not seem to benefit from pictilisib (130).

d. Triple negative BC

We found no paper published in PubMed or in google scholar evaluating pictilisib in TNBC.

e. HER2 overexpressed BC

We found no paper published in PubMed or in google scholar evaluating pictilisib in HER2 overexpressed BC.

f. Imaging

Two interesting studies explored the use of pictilisib in an imaging setting. They both used a noninvasive molecular imaging such as a positron-emission tomography (PET) tracer with a 11C-methylated pictilisib (131) and a 18F-radiolabeled drug which was based on the pictilisib structure (132). Han et al. showed that the 11C-methylated pictilisib allowed to noninvasively identify pictilisib-sensitive tumors. Altine et al. found an interesting potential of 18F-radiolabeled pictilisib analog to detect a high PI3K expression. These results suggested that a therapeutic drug like pictilisib may be used for diagnosis of PIK3CA mutations or PI3K-related diseases and could predict a response to PI3K inhibitors.

In conclusion, in all indications in which pictilisib was tested for the treatment of BC, it failed to show a clinical benefit.

3. Copanlisib (BAY 80-6946)

a. Preclinical data

Copanlisib is a potent class I PI3K inhibitor with an action targeted preferentially against p110α and p110δ as compared to p110β and p110γ (7- or 13-fold more selective for p110α). Copanlisib has multiple cellular mechanistic activities, notably, it inhibited AKT phosphorylation including both IGF-1-stimulated and basal phosphorylation (133).

In different types of solid tumor resistant to immune checkpoint inhibitor, pulsatile copanlisib inhibition had an anti-tumoral activity by converting macrophage M2 (immunosuppressive) to macrophage M1 (inflammatory) and inducing a favorable anti-tumor immune effect (134).

b. Early phase studies

Patnaik et al. published in 2016 the first in human study of intravenous copanlisib in patient (n=57) with advanced solid tumors and non-Hodgkin's lymphomas. MTD for copanlisib with three weekly administration every four weeks was 0.8mg/kg. In this study, 16 patients had a BC and 2 of them experienced a PR. Nausea and hyperglycemia were the main toxicities (135). A phase Ib trial in patients (n=64) with advanced solid tumors, showed no benefit for an association of weekly copanlisib plus refametinib (MEK inhibitor). In this trial, only 4 patients (6.4%) had BC. No objective response was observed and adverse events grade 3/4 occurred in 44 patients (68.8%) with mainly hypertension, diarrhea and rash (136).

c. ER/PR-positive/HER2-negative BC

We found no paper published in PubMed or in google scholar assessing copanlisib in ER/PR-positive/HER2-negative BC.

d. Triple negative BC

We found no paper published in PubMed or in google scholar evaluating copanlisib in TNBC.

e. HER2 overexpression BC

Keegan et al. conducted a phase Ib study involving 12 patients with metastatic HER2-positive BC who progressed after one or more lines of prior anti HER2 therapy. Patients were treated with copanlisib at 45 or 60mg intravenous (IV) in association with weekly trastuzumab. The MTD of copanlisib was 60mg and most of adverse events were hyperglycemia, fatigue, nausea, and hypertension. SD occurred in six patients (50%) with no objective response (137). Phase II studies in this indication are ongoing.

III/ PI3Kα-Specific Inhibitors

PI3Kα-Specific inhibitors are a group of selective oral inhibitors of the PI3K catalytic subunit p110α class I. Other subunits can be inhibited but all members of this class have in common a decrease in the effect on PI3Kβ, to limit the risk of side effects (138).

1. Alpelisib (BYL719)

a. Preclinical data

Alpelisib, an oral drug, is the PI3Kα-specific inhibitors with the highest selectivity for PI3Kα (139). Tolerance of alpelisib under glucose homeostasis was supposed to be better than pan-PI3K inhibitors. In monotherapy, alpelisib was shown to have a cytostatic effect on tumor cells (140). In ER/PR-positive/HER2-negative BC cell lines, alpelisib induced a higher ER expression. Expression of ESR1 was also increased. Adding fulvestrant to alpelisib increased tumor regression and provided a rationale to combine PI3K inhibitor with hormone therapy for ER/PR-positive/HER2-negative BC with PIK3CA mutation (99). In vivo, in an ER-positive BC with PIK3CA mutated on xenograft model, Fritsch et al. showed that alpelisib blocked PI3K pathway and induced a decrease of p110α protein expression. For ER-positive BC of xenograft

tumors with acquired resistance to palbociclib plus fulvestrant, O'Brien demonstrated that change of palbociclib by alpelisib restored an antitumor activity. No effect was observed if palbociclib was stopped for ribociclib and no supplementary effect was observed if palbociclib was changed for alpelisib plus ribociclib (141). In HER2-positive and PTEN loss BC cell lines, Zhang et al. showed an anti-tumoral efficacy of alpelisib in monotherapy and the effect was higher when alpelisib was associated with an anti-HER2 therapy in both in vitro and in vivo experimentation (142).

Alpelisib efficacy was limited in TNBC cell lines compared to triple positive BC cell lines by a less inhibition of p-S6. However, association to alpelisib plus a CDK4/6 inhibitor demonstrated a more potent inhibition of p-S6 associated with induction of apoptosis in TNBC cell lines (143).

PIK3CA mutation appeared to be a sensitive predictive factor of alpelisib efficacy. Nevertheless, association of PIK3CA mutation and PTEN mutation seemed to predict worse response to treatment and association of PIK3CA wild type with amplification of PIK3CA seemed to predict response (139,144). A recent genomic analysis on 440 BC found that ERα/PI3K interactions are associated with worse outcome. Alpelisib plus fulvestrant seemed to be more effective than fulvestrant alone in Erα-positive tumors in xenograft model (145).

b. Early phase studies

The first alpelisib administration in human was published in 2018. This trial explored alpelisib alone for PIK3CA-altered advanced solid tumors during the dose escalation phase. In the dose expansion phase, PIK3CA wild type and PIK3CA mutated were included. In this phase Ia study Juric et al. found, for 134 patients treated, a MTD of 400mg once a day or 150mg twice a day. Objective tumor response was observed from a dose superior or equal to 270mg once a day with at least 2 cycles of experimental treatment. Inferior dose-level at 180mg once a day showed signs of tumor growth suppression. Patients (n=4) with PIK3CA wild type had no clinical benefit of alpelisib in monotherapy. The most common toxicities noted were hyperglycemia, diarrhea, nausea, decreased appetite and vomiting (146). An in-progress phase I study, concerning ER-positive or TNBC with AR-positive and PTEN-positive, explored

the association of alpelisib with enzalutamide (a nonsteroidal antiandrogen used in prostate cancer) in metastatic setting (NCT03207529).

Baselga et al., in escalation phase I trial, explored alpelisib plus everolimus for patients (n=13) with advanced solid tumors and alpelisib plus everolimus plus exemestane for post-menopausal patients (n=7) with ER-positive advanced BC. For triple association, MTD was 200mg for alpelisib, 2.5mg for everolimus and 25mg for exemestane. SAE were mainly fatigue (29%) and transaminasitis (14%). In dose expansion of this trial, eleven patients were included in BC group. CBR (CR, PR, SD or non-CR/non-PD > 24 weeks) was 50% of which PR for 2 patients (25%). Triplet combination of alpelisib plus everolimus plus exemestane was safe with manageable and reversible side effects (147,148).

Concerning women with a progression after first-line hormonotherapy, a phase Ib study explored the association of LSZ102, a selective estrogen receptor degrader (SERD), to alpelisib or ribociclib. Independently of the PIK3CA- or ESR1-mutation status, the mPFS and CBR were respectively 1.8 months and 1.3% for LSZ102 alone (77 patients), 6.2 months and 35.1% for LSZ102/ribociclib (78 patients), 3.5 months and 20.9% for LSZ102/alpelisib (43 patients). In this study, alpelisib was used at 250 mg with 300mg of LSZ102 once a day, in arm with ribociclib, LSZ102 was used at 450mg once a day. This difference in LSZ102 dosage could be involved in the observed PFS differences. Nevertheless, the dose limiting toxicity (DLT) appeared in 5% of patients for LSZ102 alone, 3% for LSZ102/ribociclib and 19%for LSZ102/alpelisib. In LSZ102/alpelisib group, patients experienced all grade adverse events in 69.8% for diarrhea, 60.5% for nausea, 38.3% for hyperglycemia, 37.2% for vomiting, 18.6% for anemia, 16.4% for rash and 11.6% for transaminasitis (149).

c. ER/PR-positive/HER2-negative BC

In phase Ib, Mayer et al. tested alpelisib in combination with letrozole for 26 post-menopausal patients with metastatic BC, which progressed after at least one ET for metastatic disease or within 1 year of the end of ET in the adjuvant setting. Patients who received a line of chemotherapy prior to inclusion represent 31%. In combination with letrozole, the MTD of alpelisib was 300 mg once a day. Side effects were similar to the phase Ia. In this trial, CBR was

44% for PIK3CA mutated patients and 20% for PIK3CA wild type patients, they observed five objective responses and responses were not influenced by FGFR1/2 amplification and KRAS and TP53 mutations (150). Another phase Ib study, conducted by Juric et al., focused on the same population but alpelisib was associated with fulvestrant. With 87 women, they found association of alpelisib to fulvestrant was safe with a recommended dose at 300mg once a day, adverse events grade 3/4 were found in more than 10% of patients with 400 mg once a day. The median PFS was 9.1 months versus 4.7 months and the objective response rate was 29% versus 0% for patients with PIK3CA-mutated versus PIK3CA-wild BC, respectively (151). Lu et al., in a phase Ib for premenopausal patients with advanced BC, evaluated the MTD and preliminary efficacy of tamoxifen plus goserelin with or without alpelisib (16 patients) or buparlisib (13 patients). For alpelisib and buparlisib, MTD was 350mg once a day and 100mg once a day, the median PFS were 25.2 and 20.6 months respectively. In alpelisib group, all patient occurred an adverse events with mainly rash, weight loss, stomatitis, nausea, hyperglycemia, alopecia and diarrhea, grade 3/4 adverse events were found in 50% (152).

SOLAR-1 study, published in May 2019 by André et al., was a randomized, placebo-controlled, phase III trial enrolling patients with ER-positive/HER2-negative advanced BC and disease progression after a prior AI and compared alpelisib versus placebo in combination with fulvestrant. In the cohort of patients with a PIK3CA-mutated cancer, 169 patients were treated with alpelisib and 172 patients with placebo. For the primary endpoint, they found a statistically difference for the median PFS, which was 11 months in the alpelisib group and 5.7 months in the placebo group (HR 0.65, 95% CI, 0.50 to 0.85, P<0.001). Alpelisib seemed to confer a benefice for the median PFS for all subgroups. In the cohort of patients without a PIK3CA-mutated cancer, no statistical difference in PFS has been highlighted. Grade 3/4 adverse events occurred in 76% of the cases in the alpelisib group versus 35.5% in the placebo group. Most common sides effect in any grade were hyperglycemia (63.7%), diarrhea (57.7%), nausea (44.7%) and rash (35.6%) (153). Concerning hyperglycemia, rash and diarrhea median time to onset a SAE were 15 days, 13 days and 139 days respectively. These side effects were manageable, generally reversible and may be warned. Preventive treatment for rash decreases the incidence (26.7% versus 64.1%). In SOLAR-1 trial, the median dose intensity was

248mg per day. Rugo et al. showed that a median PFS of 12.5 months and 9.6 months for patients treated with alpelisib ≥ 248mg and < 248mg respectively (154). Quality of life (QoL) was also assessed in SOLAR-1 trial, no statistically difference of functional status was found for alpelisib versus placebo with an overall change from baseline at −3.50 versus 0.27 respectively. Main differences concerned diarrhea, anorexia, nausea, and asthenia. Median time to reach 10% of deterioration for QoL was not statistically difference with HR at 1.03 (155). The final analysis concerning OS of SOLAR-1, showed that the median OS was 39.3 months for the alpelisib group and 31.4 months for the placebo group (HR 0.86, 95% CI 0.64-1.15 p= 0.15). Thus, the OS results did not reach statistical significance. For patients with lung and/or liver metastases, the median OS were 37.2 months and 22.8 months, and the median time to chemotherapy were 23.3 months and 14.8 months, for the alpelisib group and the placebo group respectively. The SOLAR-1 trial led the FDA to approve "alpelisib in combination with fulvestrant for postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen" and EMA to approve "alpelisib in combination with fulvestrant for postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer after an hormonal treatment used alone has failed". In SOLAR-1, patients had received as a prior treatment CDK 4/6 inhibitors in only in 5 to 7% of the cases. However, currently, the first line treatment for advanced or metastatic ER/PR-positive/HER2-negative BC without visceral crisis is the association of hormonotherapy with CDK4/6 inhibitors. Rugo et al conducted BYLieve, a phase II multicenter, non-comparative study, for advanced BC treated with alpelisib in association to fulvestrant after previous administration of CDK 4/6 inhibitors. In this trial, the median PFS was 7.3 months, the toxicity rate of grade 3/4 was similar to SOLAR-1 with 67% of patients facing adverse events (156). Based on BYLieve population cohort, Juric et al. found that low circulating tumor DNA (ctDNA) fraction (<10% or nondetectable), a low tumor mutational burden (<10 mut/Mb) and no amplifications in chromosome 8 and/or 11 had a favorable prognostic impact in PFS, nevertheless other

patients also had a benefit from alpelisib even if benefit was lesser. Results were similar in 2 cohorts of the study, cohort A including patients with prior CDK 4/6 inhibitors plus AI and cohort B including patients with prior CDK 4/6 inhibitors plus fulvestrant. Second part of this study examined the predictive impact of alpelisib when patients had an alteration in genes known to intervene in resistance to CDK4/6 inhibitor like PTEN, RB1, NF1, or CDKN2A-C. The result supported that alpelisib would remain effective even in the presence of this resistance genes (157). Chia et al., with BYLieve cohort, found the same efficacy of alpelisib in association with ET in cohort A and B whether patients received less or more than 6 months of treatment by CDK4/6 inhibitor (158).

Bello et al., with data from the French early access program of alpelisib, explored alpelisib-fulvestrant in advanced ER-positive and HER2-negative BC with heavy pretreatment including CDK4/6 inhibitors, in real-life setting. They found a median PFS at 4.0 months with a median of 4 previous lines of systemic treatments in metastatic setting (159).

Based on the results of the association of alpelisib and ET in advanced BC, Mayer et al. explored letrozole plus alpelisib or letrozole plus placebo in the neo adjuvant setting in the NEO-ORB trial. This was a phase II randomized, with 1:1 ratio, placebo-controlled trial. In this study, postmenopausal patients (n=257) were included, 127 patients had PIK3CA mutations and 130 had PIK3CA wild type. Patients presented mainly T1b or T1c, N0 or N1. The composite primary endpoint (ORR and pCR) was not reached. ORR was 43% versus 45% for PIK3CA mutation. Surprisingly, ORR was 63% versus 61% for PIK3CA wild type BC in the alpelisib versus placebo group. The pCR rate was low and not statistically different in all groups. The pCR rate varied between 1.7% and 3.0%. Investigation of alpelisib in the neo adjuvant setting stopped and, also in this study, PIK3CA status showed no predictive value for the response to alpelisib (160). In a pooled analysis of SAFIR02-BREAST and SAFIR-PI3K, phase II randomized studies, including 1462 patients with metastatic HER2-negative BC and testing the maintenance of target therapy (including alpelisib) with fulvestrant guided by genomics versus chemotherapy. Patients with endocrine resistant disease had advanced BC with PIK3CA- mutated status which did not progress after 6-8 cycles of first- or second-line chemotherapy and patient were not exposed to targeted therapy. Study found a significative lounger PFS for patient (n=115) with

the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) I or II. Median PFS was 9.1 months in maintenance target therapy versus 2.4 months in maintenance chemotherapy group (HR 0.41; p<0.001). For all patients, median PFS of two groups were not significatively different with HR of 0.77 (95%CI: 0.56-1.06, p=0.109) (161).

d. Triple negative BC

Alpelisib in association with Nab-paclitaxel for 43 patients with metastatic TNBC was explored during a phase I/II study. Sharma et al. found an ORR of 59%, including 7% of CR. The median PFS was 8.7 months. Patients (40%) with a PIK3CA mutation had a median PFS of 11.9 months versus 7.5 months for patients withPIK3CA wild type status. These results suggested a predictive impact of PIK3CA mutation to alpelisib treatment in metastatic TNBC. They also found a higher median PFS for patients without prediabetic or diabetic metabolic status with 11.9 versus 7.5 months (162).

In an ongoing study, a phase III, randomized, double blind, placebo-controlled trial is testing the efficiency of alpelisib in association with nab-paclitaxel in first- or second-line therapy for advanced TNBC with PIK3CA mutations or with PTEN loss if no PIK3CA mutation is found (NCT04251533) (163).

In the neo adjuvant setting, an ongoing phase II trial, conducted by Damodaran et al., is evaluating alpelisib and nab-paclitaxel in association, in patients with refractory or suboptimal response to initial anthracycline-based chemotherapy and BC displaying PIK3CA or PTEN alterations (164).

e. HER2 overexpressed BC

Jain et al. reported the safety and activity of alpelisib in combination with trastuzumab emtansine (TDM-1), in a phase I trial, for 17 patients with metastatic BC after at least 3 lines of prior therapy. ORR and CBR were respectively 43% and 71% for all patients, 30% and 60% for patients resistant to prior TDM-1. The median PFS was 8.1 months, which suggests a central position of the PI3K pathway in the mechanisms of resistance to anti-HER2 treatment. PIK3CA mutation was observed in 30% of patients (165). Another phase I study including

HER2-positive BC with PIK3CA mutations, investigated alpelisib in combination with trastuzumab and LJM716 (a HER3-targeted antibody). Unfortunately, this study underlined an important gastrointestinal toxicity for the triple association and was stopped prematurely (166).

A phase III trial, multicenter, randomized, double-blind, placebo-controlled, evaluating maintenance Alpelisib in association to trastuzumab and pertuzumab is engaged for metastatic BC with PIK3CA mutation (167).

2. Taselisib (GDC-0032)

a. Preclinical data

Taselisib is a potent dual PI3Kα/PI3Kδ inhibitor. Taselisib was tested alone and in combination with taxane, hormonotherapy and anti HER2 therapy in eleven different cells lines of BC with different PIK3CA mutation. Taselisib had a limited activity in monotherapy. In combination with other therapy, efficacy was improved. Triple association of taselisib plus trastuzumab with docetaxel or pertuzumab showed in vivo durable anti tumoral response (168). In preclinical study examining BC cell lines, PIK3CA mutations appeared to be a predictive factor of response to taselisib. Response was independent of HER2-status. ESR1 with PIK3CA mutation did not limit effect of taselisib with or without fulvestrant (169).

b. Early phase studies

The phase I trial of taselisib for advanced solid tumors was published by Juric et al. in July 2017. DLT were observed from 12 mg to 16mg. The antitumor activity seemed to be observed since 3 mg of taselisib. Side effects were similar to those of alpelisib with diarrhea, hyperglycemia, decreased appetite, nausea, rash, stomatitis, and vomiting. On 32 patients of this phase I trial, 39% of tumor had PIK3CA mutations and for them ORR was 36%, while no response was observed in patients with PIK3CA wild type tumors. Especially, 4 BC had

objective response at 3mg. This study suggested an antitumor efficiency of taselisib in BC with PIK3CA "hotspot" mutations (170). Jhaveri et al. published a large phase I trial of 166 patients with PIK3CA mutated cancers. The ORR was 9% which consequently stopped the drug development. Only 17 patients in all cohort had a TNBC, in this subgroup the ORR was 5.9%. Nevertheless, they found a higher response rate for helical domain mutations. Mutations on TP53 and PTEN seemed be to associated with a resistance to taselisib (171).

A phase Ib explored taselisib in combination to tamoxifen in patients (n=30) with ER-positive metastatic BC whose progress after at least one prior line of ET. Dose escalation phase tested 2 then 4 mg of taselisib. Frequent adverse events observed were diarrhea (43%), mucositis (33%) and hyperglycemia (27%). ORR was 24% and 40% of patients had a SD at 6 months or more. Dose of taselisib at 4mg once daily every day was the recommended dose for further studies (172).

Phase Ib dose escalation and dose expansion trial conducted by Abramson et al. evaluated the association of taselisib plus taxane in metastatic BC and non-small cell lung cancer (NSCLC). Seventy patients had BC, seven had NSCLC and one had both. SAE occurred in 90.5% (fatigue, diarrhea, nausea, and neutropenia) with 14.5% of adverse events leading to death. ORR was 35% in docetaxel arm and 20.4% with paclitaxel arm. With docetaxel, MTD of taselisib was 3mg (once daily for 21 days). In paclitaxel arm, with the maximal expected dose of taselisib at 6 mg for 5 days on/2 days off, no limited toxicities appeared. Despite interesting activity signals, toxicity limited further development of these association (173).

c. ER/PR-positive/HER2-negative BC

A phase Ib trial for hormone sensitive heavily pretreated advanced BC evaluated taselisib with letrozole in 28 patients. The ORR was 38% in the PIK3CA mutated group and 9%

in the PIK3CA wild type group. Patients experienced diarrhea, hyperglycemia and mucosal inflammation grade 3 or 4 adverse events, in 14%, 7% and 7% respectively (174). No further study was realized to explore the association of taselisib and letrozole in metastatic BC.

LORELEI trial was a phase II, multicenter, randomized, double-blind, placebo-controlled study of letrozole in association to taselisib at 4mg versus letrozole with placebo for early ER-positive/HER2-negative BC in the neo adjuvant setting. In the patients included (n=334), 46% had PIK3CA mutations, 77% of patients had T2, 65% had N0 and 89% of all cohort had a stage 2. This study showed a significant difference in only one of the two coprimary endpoints (ORR and pCR). The ORR was 50% in the taselisib group versus 39% in the placebo group (p=0.049) and the pCR rate was 2% in the taselisib group versus 1% in the placebo group experienced. An adverse event $\geq$ grade 3 occurred in 12% of patients, mainly with digestive toxicity or infection. LORELEI did not change the clinical practice and only allowed to observe an anti-tumor activity (175).

Taselisib was investigated at 6mg in combination to fulvestrant in postmenopausal women with advanced ER-positive/HER2-negative BC. In a non-comparative phase II study enrolling 87 patients, the CBR was 29.5%. For patients with PIK3CA-mutated BC, the CBR was 38.5% versus 23.8% for PIK3CA wild type. Approximately 50% of patients experienced a grade 3 or more adverse event, which was colitis in 13% of the cases. Of note, 21% of patients harbored both ESR1 and PIK3CA mutations (176,177). This study suggested a clinical activity of taselisib plus fulvestrant relatively dependent of the PI3KCA status and led to a phase III study, the SANDPIPER trial for PIK3CA-mutant advanced ER-positive/HER2-negative BC resistant to ET.

Dent et al. conducted the SANDPIPER trial which assessed the efficiency of taselisib at 4mg with fulvestrant, with 631 patients. Patients were randomly selected in the experimental

arm (n=430) and in the placebo arm (n=176). Prior treatments with CDK4/6 inhibitors and chemotherapy were noted for <4% and approximately 30% of patients, respectively. The toxicity rate of SAE was 49.5% in the taselisib arm versus 16.4% in the placebo arm. The most frequent adverse events were diarrhea, hyperglycemia, rash, stomatitis, and colitis. For the population of the study, including only PIK3CA mutated patients, the primary endpoint was the investigator-assessed PFS, and a statistical difference was observed with 7.4months for the taselisib arm versus 5.4months for the placebo arm (HR 0.70, p=0.0037). The ORR was increased with taselisib to 28.0%, versus 11.9% with placebo. Despite an improvement in PFS, the adjunction of taselisib had no clinical utility compared to the SOLAR-1 trial in which the mPFS was 11 months in the alpelisib arm versus 5.7 months in the placebo arm (178). Conducted by Oliveira et al., a multicenter, randomized phase II trial. Patients (n=152) with metastatic BC whose progress after at least one prior line of ET were included for received tamoxifen in association with taselisib at 4mg or placebo. The primary endpoint was a unstratified median PFS. Median PFS was 3.2 months in placebo arm and 4.8 months in taselisib arm (unstratified HR 0.62, 95%CI 0.43-0.93). Approximately 24% patients harbored a PIK3CA mutation in this trial. CBR (CR + PR + SD at 6 months) was 14.5% versus 22.4%. The toxicity rate of grade ≥3 adverse events was 44% for the taselisib arm with no new safety signal versus 5% for the placebo arm (179).

d. Triple negative BC

Lehmann et al. conducted a phase Ib/II study on patients with metastatic AR-positive to evaluate enzalutamide with or without taselisib at 4mg. Phase I included patients (n=13) with ER/PR-positive BC and TNBC, phase II included patients (n=17) with only TNBC. PIK3CA mutated occurred in 50% of all patients. Phase I determined the dose at 4mg of taselisib for

phase II. The phase II primary endpoint was the CBR (CR+PR+SD at 16 weeks). Four patients in this study developed a limited toxicity which led to treatment discontinuation, these four patients were removed of activity analysis. For efficacy, TNBC treated in phase Ib were included. CBR was 35.7% in taselisib arm versus 0% in placebo arm. CBR was 42.9% in PIK3CA mutated patients versus 28.6% in PIK3CA wild type, the difference was not due to small sample size of subgroups. CBR was 75% in luminal androgen receptor (LAR) subgroups of TNBC versus 12.5% in other subgroups, this difference was statically significant (p=0.06). In association with enzalutamide at 160mg, DLT with taselisib occurred at 8mg. The study was stopped prematurely related to SANDPIPPER trial results (180).

e. HER2 overexpressed BC

Few clinical studies explored taselisib in HER2-positive BC. Metzger Filho et al. conducted a study in 2 parts. A first part included a preclinical trial concerning mouse model with transgenic mammary carcinomas driven by HER2, with or without a PIK3CA exon 20 mutation, and a resistance to T-DM1. Results showed that the addition of taselisib to T-DM1 restored the activity of an anti-HER2 therapy in both subgroups. The other part of this study was a phase Ib clinical trial on metastatic HER2-positive BC. The median age of including patients (n=26) was 57 years. Patients received a prior therapy with T-DM1 in 38.5% of cases, 58% had ER-positive and 23% had PIK3CA mutations. The toxicity rate seemed to be similar to those observed in other studies, except for the rate of pneumonitis in four patients including 3 pneumocystis, and for a higher rate of thrombocytopenia grade 3 or 4 adverse events at 19.2%. The ORR was 33% in all groups, 30% versus 36% if patients received prior T-DM1 or not, respectively, and 40% versus 22% if patients had BC displaying PIK3CA mutations or not, respectively. For all patients, the median PFS was 7.6months. This study seemed to show some

interesting activity signals for this combination, and pneumocystis prophylaxis was probably necessary with the combination (181).

3. Inavolisib (GDC-0077)

a. Preclinical data

Based on taselisib structure, inavolisib was developed with a higher PI3Kα isoform selectivity and a lower PI3Kδ isoform selectivity. Concerning GDC-0032 (taselisib) and GDC-0077 (Inavolisib), it has been discovered, with pre-clinical and clinical trials, a positive additional effect of these 2 drugs. Beside the inhibition of PIK3CA, which lead to block PI3K pathway and to anti-tumor activity as we see with alpelisib, taselisib and inavolisib inhibited more potently PIK3CA, they promote the degradation of mutant p110α proteins with E545K (exon 9) and H1047R (exon 20) mutations in cells and this removal of mutant p110α appears to limit feedback-induced reactivation of the PI3K pathway in cells. Taselisib and inavolisib also induced a degradation of HER2 (RTK), which makes it possible to counter negative feedback of which increased the RTK activity and limited the drug activity. This new effects of PI3Kα-Specific Inhibitor suggested a higher anti-tumor effect (182).

b. Early phase studies

A first in human, phase I dose escalation, multi arms trial of inavolisib was published in February 2020 and included patients with advanced or metastatic tumors which harbored PIK3CA mutations. In the first arm of 20 patients, inavolisib was given as a monotherapy, 19 patients presented an ER-positive BC and one a colorectal cancer. Principal toxicities of grade ≥3 were hyperglycemia, lymphopenia, fatigue, nausea, and weight loss with 9 mg once a day of inavolisib, which was the MTD. The CBR was estimated at 45% with approximately 20% of

patients with PR. This single agent arm demonstrated an interesting anti-tumor activity (183). The other arms of this phase I were an association of inavolisib at 9mg to letrozole, with or without palbociclib (CDK4/6 inhibitors), (respectively G+L and G+L+P group). No DLT was observed at the recommended dose of inavolisib which was 9mg once a day in both arms. Major SAE were hyperglycemia/fatigue/hypokalemia and hyperglycemia / neutropenia / leukopenia / thrombocytopenia for G+L and G+L+P groups respectively. The CBR/PR were 35%/8% and 76%/36% respectively. A pharmacokinetic exploration did not find any interaction between the 3 drugs in G+L+P groups and a pharmacodynamics study found an important downregulation of the PI3K pathway by reduction of phosphorylated AKT (183).

c. ER/PR-positive/HER2-negative BC

Kalinsky et. al conducted, a phase Ib trial with an association of inavolisib with fulvestrant in postmenopausal women with PIK3CA-mutated metastatic BC. In this trial, 20 patients were enrolled, the toxicity profile was similar to those previously described, except for a higher rate of hyperamylasemia and hyperlipasemia. The CBR (CR+PR+SD at 24 weeks) was estimated at 60%, with 36% of patients achieving PR (184). Bedard et al. addressed, in a phase Ib trial, inavolisib at 9 mg in association with fulvestrant and palbociclib for PIK3CA-mutated ER-positive/HER2-negative metastatic BC. The population was divided in two arms. Arm E (n=13) had no prior treatment with PI3K or CDK4/6 inhibitors and with only ≤ 1 prior chemotherapy authorized. Arm F (n=15) had no restriction on prior therapies. The recommended dose of inavolisib was also 9 mg once a day, the grade ≥3 toxicities rate was similar in both groups with a majority of hyperglycemia (47%) and neutropenia (47%). The CBR (CR+PR+SD at 24 weeks) was evaluated at 61% in both arms in the population who received

prior fulvestrant, and 28% of patients had a PR (185). A phase II study is underway in the indications mentioned above (NCT03006172).

A phase III trial is ongoing and try to assess the efficacy of inavolisib in association with palbociclib and fulvestrant for advanced or metastatic ER-positive/HER2-negative BC with PIK3CA mutation. This is a randomized 1:1, placebo-controlled, stratified by visceral disease, primary versus secondary hormonotherapy resistance and geographical region trial. The primary endpoint is investigator-assessed and the pre-analyzed plan is to include approximately 400 patients (NCT04191499).

d. Triple negative BC

We found no paper published in PubMed or in google scholar evaluating inavolisib in TNBC.

e. HER2 overexpressed BC

Phase II studies are engaged for PIK3CA-mutated metastatic HER2-positive BC. An experimental association (arm G) composed of inavolisib with trastuzumab and pertuzumab (NCT03006172) is evaluated.

4. Serabelisib (TAK-117)

a. Preclinical data

Serabelisib was initially develop for vascular malformations disease. In contrary to other PI3Kα, serabelisib was not particularly potent against PI3Kα (67).

b. Early phase studies

The first in human, phase I trial of serabelisib was published in September 2017. In this study, 71 patients were included, and serabelisib alone was tested in advanced solid tumors with continuous or two discontinuous regimens. The rate of grade ≥3 adverse events was between 22% and 35% depending on drug regimens. The most frequent adverse events were

ALAT/ASAT elevation and hyperglycemia. The response rate was very low with 3 PR with continuous regimen and 1 PR with discontinuous regimen. To have a tolerated dose of serabelisib an intermittent schedule was necessary. The use of serabelisib as a single agent at a tolerated dose had a limited potential efficiency and the development in monotherapy was stopped (186).

The association of TAK-228 (oral mTORC1/2 inhibitor) and serabelisib showed a synergistic effect in a cohort of metastatic bladder cancer (187). This association was named PIKTOR.

Starks et al. conducted a phase I trial to assess the MTD of serabelisib. The safety and preliminary efficacy of the triple association of serabelisib-TAK-228 and paclitaxel, was evaluated in patients with advanced ovarian, endometrial, or BC. Patients (n=19) were included in 6 escalation cohorts, the ORR was estimated at 37%, no CR was observed for BC, but 2 CR occurred in endometrioid endometrial adenocarcinoma. The ORR was 47% in all cohorts for patients achieved 3 cycles and the mPFS was approximately 11 months. The proportion of drug related grade ≥3 adverse events was 9% (188). Phase II should start soon.

c. ER/PR-positive/HER2-negative BC

We found no paper published in PubMed or in google scholar assessing serabelisib in ER/PR-positive/HER2-negative BC.

d. Triple negative BC

PIKTOR (association of serabelisib and TAK-228) was also tested in metastatic TNBC. An American group made the hypothesis that a treatment with PIKTOR can increase the tumor genomic instability and consequently increase the TNBC sensitivity to chemotherapy and immunotherapy. In this small study of 10 patients with TNBC, the median age was 51 years and median prior chemotherapy regimens was 3 lines. PIKTOR showed 1PR, 3 SD and 6 PD.

Durable responses to pembrolizumab after progression with PIKTOR concerned 3 out of 10 patients and all had received carboplatine in prior treatments. This study suggested that PIKTOR could influence the tumor by making it more sensitive to subsequent treatments (189).

e. HER2 overexpressed BC

We found no paper published in PubMed or in google scholar evaluating serabelisib in HER2 overexpressed BC.

Table 1 summarized phase III of PIK3CA inhibitor in breast cancer.

IV/ Future perspectives

1. PIK3CA inhibitors in association with CDK4/6 inhibitors

A meta-analysis conducted by Han et al. showed by an indirect comparison that the use of CDK4/6 inhibitors with an ET is probably better as it significantly improves the median PFS compared to PIK3CA inhibitors with an ET. This study included randomized trials evaluating benefit and toxicity of CDK4/6 inhibitors or PI3K/AKT/mTOR inhibitors with ET between 2010 to 2019. A large cohort of 9771 patients were analyzed in meta-analysis. They used a generic inverse variance method for estimated indirectly the pooled HR and then they used a bayes framework to validate models with Markov Chain Monte Carlo methods and with the JAGS software version 4.3.0

The pooled HR was 1.43 (95% CI, 1.12-1.61) when CDK4/6 inhibitors were compared with PI3K inhibitors. Benefits were observed in all subgroups, all metastatic lines and in both visceral and bone only diseases. The benefit of CDK4/6 inhibitors was also observed in OS with a pooled HR at 0.78 (95% CI, 0.65-0.94) when CDK4/6 inhibitors were compared in face to face with PI3K and mTOR inhibitors. A risk ratio (RR) was used to evaluate grade ≥3 adverse events. Cytopenia had a higher rate with CDK4/6 inhibitors. For cytopenia, risk ratio (RR) was significantly different in favor of abemaciclib versus palbociclib (RR 0.024) and ribociclib (RR 0.018). Hyperglycemia had a higher rate with PI3K and mTOR inhibitors. RR was similar in CDK4/6 and PI3K/AKT/mTOR inhibitors groups (190). A second meta-analysis identified 79 phase II/III studies including postmenopausal women, with ER-positive/HER2-negative BC, which progressed after a first line treatment with AI or ET and explored CDK4/6 inhibitors or PI3K/AKT/mTOR inhibitors in association with fulvestrant. For analysis, only 8 studies were included. To be able to compare studies, they used cumulative ranking curve and calculated surface under curve. They showed that CDK4/6 inhibitors (abemaciclib, palbociclib and

ribociclib) were superior in PFS, ORR and OS compare to PI3K/AKT/mTOR inhibitors (pictilisib, alpelisib and buparlisib) (191).

Robust pre-clinical data suggested a synergistic effect to the combination of CDK4/6 inhibitors with PIK3CA inhibitors (buparlisib and alpelisib) in ER/PR-positive/HER2-negative BC. In mouse model, O'Brien et al. demonstrated that the association of CDK4/6 inhibitors to an ET significantly inhibited tumor growth compared to ET alone. Moreover, the adjunction of PIK3CA inhibitors induced tumor regression and one CR was also observed (192). In an in vitro and in vivo study, of TNBC cell lines with PIK3CA mutations, Asghar et al. found a synergistic effect of CDK4/6 inhibitors with PIK3CA inhibitors (193).

Concerning ER/PR-positive/HER2-negative metastatic BC, a phase Ib trial tested the safety and preliminary efficiency of the association to ribociclib (continuous versus discontinuous) and fulvestrant with/without alpelisib or buparlisib. Both arms with triple associations were suspended due to unacceptable toxicity and were not continued in the phase II investigations (194). Alpelisib was also explored in association to ribociclib and letrozole in a phase Ib/II trial with post-menopausal women. Three arms in which 41 patients were included, A1: letrozole/ribociclib, A2: letrozole/alpelisib and A3: letrozole/ribociclib/ alpelisib. Thirty-six patients were in A3, 22% had SD and 19% had PD. The safety profile was acceptable with triple association, grade 3/4 adverse events occurred in 22% for neutropenia, 17% for hyperglycemia, 11% for fatigue and 6% for nausea. The arm A3 showed a considerable reduction in Ki76 staining on tumor tissue compared to A1 or A2 (195). These results must be validated in a large, randomized trial. The triple association of palbociclib, taselisib, and fulvestrant was also explored in a phase Ib trial, conducted by Pascual et al., in patients with PIK3CA-mutated, ER-positive/HER2-negative advanced BC. In this population with a median of 3 prior systemic therapy lines for advanced diseases, the ORR was 37.5%. The high baseline

cyclin E1 expression and early detection of ctDNA were associated with shorter PFS. With the triple association, the most frequent grade 3/4 adverse events were neutropenia (47.4%) and leucopenia (16.7%) (196).

Concerning the association of CDK4/6 inhibitors and PIK3CA inhibitors in TNBC, no trial was published. A pre-clinical study showed a synergistic effect including a complete and durable response to combined CDK 4/6 and PIK3CA inhibitors in mouse model (197).

For HER2-positive BC, several studies demonstrated a favorable impact of CDK4/6 inhibitors and PIK3CA inhibitors but, their association was not evaluated (198).

2. Resistance to PIK3CA inhibitors and possible solutions

Despite the central role in tumorigenesis of PI3K, only a modest benefit of PIK3CA inhibitors was observed in clinical trials for both pan-PIK3CA and PIK3CAα-specific inhibitors. Thus, the clinical benefit could be limited by several resistance mechanisms.

In BC and in prostate cancers, the role of one family of protein kinases, the proviral integration of Moloney virus (PIM), has been highlighted. Song et al. found that the PIM1 kinase promotes resistance and prevent cell death by decreasing the cellular level of ROS, which consequently attenuates the toxicity of PI3K inhibitors. The action on ROS was AKT-independent (199). Furthermore, PIM1 conferred an acquired resistance to PI3K inhibitors, indeed, it appeared that the PIM1 overexpression and PIK3CA mutations were mutually exclusive for treatment-naïve BC. PIM1 was overexpressed for patients with a progression after receiving PI3K inhibitors. This is confirmed by biopsies at disease progression (200). Based on the above-mentioned data, IBL-302, a PIM/PI3K/mTOR inhibitor was developed. Pre-clinical data in BC cell lines demonstrated anti-tumor efficacy in monotherapy and also in combination with trastuzumab for HER2-positive BC cell line with trastuzumab-resistance,

compared to IBL-302 alone (201). In BC cell lines, Litchfield et al. reported that abemaciclib can inhibit mTOR by blocking both PIM kinases and CDK4/6, which resulted in blocking the PI3K/Akt/mTOR pathway and reducing cell growth. When abemaciclib was associated to alpelisib in PIK3CA mutated ER-positive BC, it had a synergistic effect in neutralizing mTOR activation and increasing the effects on the cellular proliferation. In fact, mTOR may be activated by three different pathways which were independent of each other, Akt via PI3K, PIM kinase and CDK4. These results suggested a potential novel approach to counteract acquired resistance mechanisms to PI3K inhibitors (202).

A network-based mathematical model, on ER-positive PIK3CA mutated BC cell lines, predict in vitro efficacy of alpelisib in combination to MCL1 inhibitors. A novel resistance mechanism was identified as FOXO3 downregulation. These data suggested the importance of using mathematical models to investigate resistance mechanisms and efficacy of drug combination to overcome this resistance (203).

Higher activity of alpelisib was associated with complete inhibition of mTORC1. mTOR1 appeared to increase in BC cell lines with PIK3CA mutation which progress during alpelisib. Association of mTOR inhibitor to alpelisib seemed to reverse resistance (204). Cai et al., using a whole genome screen on ER-positive PIK3CA mutated BC cell lines, found several gene (TSC1, TSC2, TBC1D7, AKT1S1, STK11…) which negatively regulate mTORC1. Loss of these negative regulators appeared to confer resistance to PI3K inhibitors and confirmed mTOR inhibition may overcome the resistance. Genomic alterations of mTORC1 regulator were found in 15% in ER-positive PIK3CA mutated breast cancer and seemed to be mutually exclusive (205). Razavi et al. search resistance mechanism to alpelisib with AI. PTEN loss and ESR1 mutation were associated to resistance (206). PTEN loss was an acquired resistance mechanism, Juric et al. analyzed progressive metastatic sites of patients whose die after treatment by alpelisib.

Compared to first biopsy, all sites harbored PTEN loss. Moreover, PTEN alterations were different depending on sites and all genomic alterations of PTEN lead to resistance (207). For patients with PIK3CA mutated head and neck and esophageal squamous cell carcinomas, Elkabets et al. showed a novel acquired resistance mechanism to alpelisib. Patients which progressed after alpelisib presented an overexpression of AXL.AXL activated the epidermal growth factor receptor (EGFR) by dimerization and phosphorylation and consequently activation of EGFR lead to activate mTOR (208).

Hyperglycemia was one of the most frequent adverse events found with PIK3CA inhibitors, 64% in SOLAR-1 (153), 43% in BELLE-2 (112), 37% in BELLE-3 (113), 40% in SANDPIPER trial (178). For patients in which alpelisib was stopped due to unacceptable toxicity, hyperglycemia represented approximately 6%. Rugo et al. tried to establish guidelines for this new therapeutic class. For any patients implement lifestyle modification is necessary for prevention of hyperglycemia. Before starting Alpelisib, one have to identify risk factors for developing hyperglycemia, for example hypertension or family history of type 2 diabetes mellitus. If patient had no risk factor, alpelisib can be started alone and if patient had at least 1 risk factor, alpelisib could be started with metformin at 500mg once daily. The same treatment is used in grade 1 hyperglycemia. For grade 2, dose of metformin is increased, and we can use a second line treatment (SGLT2 inhibitor, DPP-4 inhibitors, Thiazolidinediones, GLP-1 receptor agonists and a-Glucosidase inhibitors) in association with metformin. If grade 2 hyperglycemia persist, a third line treatment (Sulfonylureas, Meglitinides or exogenous insulin) could be introduced with association of metformin and a second line treatment. For grade 3, to the same support, we add alpelisib interruption until recovery to grade 1, then decrease the dose and addressee patient to an endocrinologist. For grade 4 or durable grade3, discontinuation of alpelisib is to be discussed (209).

Hopkins et al. made the hypothesis that the limited efficiency observed with all PIK3CA inhibitors was the consequence of hyperglycemia and that “insulin feedback” led to reactivate the PI3K pathway, which could directly decrease the clinical benefits. Indeed, the inhibition of PIK3CA led to an increase in glucose uptakes by tumors, a decrease in glucose uptakes by muscles and fat tissues and the activation of glycogenolysis, which itself led to an acute hyperglycemia. Hyperglycemia is sensed by the pancreas which produces a massive amount of insulin and restores glucose homeostasis. In mouse model, hyperinsulinemia (insulin feedback) has been shown to be able to reactivate PI3K pathways, even in the presence of PI3K inhibitors. These results showed the importance of glucose homeostasis to efficacy with PIK3CA inhibitors and highlights the response variability that may be related to the degree of insulin resistance in general population. Metformin showed a little effect in mouse models for reducing blood insulin levels during a PI3K inhibitors therapy. Therefore, exogenous insulin seemed, at the light of this data, to promote the “insulin feedback”. A ketogenic diet and sodium–glucose cotransporter 2 (SGLT2) inhibitors were 2 potentials approach for limited “insulin feedback” which successfully limited hyperglycemia in preclinical tumor models. Their efficiency must be proven in clinical trials (42,210,211). The ketogenic diet consists in suppressing carbohydrates of the alimentation and acts by limiting the liver glycogenolysis potential due to the absence of carbohydrates and then prevents an increase of the glucose level. SGLT2 inhibitors blocked the reabsorption of glucose and sodium in the renal proximal tubule so they induced glycosuria. SGLT2 inhibitors was a new therapeutic class with growing importance due to its effects on blood pressure, weight loss, action on diabetes mellitus, corrected anemia, nephroprotection, reduction of morbidity, and mortality, both generally and in particular cardiovascular deaths for patients with heart failure (212,213).

A phase II study in progress “Alpelisib, Fulvestrant and Dapagliflozin for the Treatment of ER-positive, HER2-negative, PIK3CA Mutant Metastatic Breast Cancer” includes the same population than SOLAR-1 trial to establish if the adjunction of dapagliflozin, a SGLT-2 inhibitor, could significantly reduce hyperglycemia of any grade (NCT05025735). Another phase II in the same population, examined if the association of dapagliflozin and metformin could reduce grade 3 hyperglycemia (NCT04899349). A Phase Ib/II study of serabelisib in combination with canagliflozin (a SGLT-2 inhibitor), in advanced solid tumors with PIK3CA mutations or KRAS mutations, including BC, is testing the efficiency of this association (NCT04073680). A phase II trial “Preventing High Blood Sugar in People Being Treated for Metastatic Breast Cancer” with 3 experimental arms in a similar population as SOLAR-1 is exploring the rate of hyperglycemia grade 3 with ketogenic diet, low carbohydrate diet or canagliflozin in combination with alpelisib and fulvestrant (NCT05090358).

B. Cohort treated with Alpelisib and Fulvestrant under ATU French early access program

I. Description of the patient population at Institut Paoli Calmettes

1. Background

SOLAR-1 trial showed a significant increase in median PFS from 5.7 months in placebo group to 11 months in alpelisib group (HR 0.65, 95% CI, 0.50 to 0.85, P<0.001). Nevertheless, only 5.9% of patients had received prior CDK4/6 inhibitors and consequently the patient population did not represent patients in current clinical practice. Afterwards, a French early access program (EAP) opened and allowed patients to benefit from alpelisib before reimbursement by the health authorities. Thus, patients, treated with alpelisib in this EAP, actually represented a real-life population. We shall describe here, a population of women with metastatic HR-positive/HER2-negative BC and resistance to previous endocrine therapy, receiving fulvestrant + alpelisib at the Institut Paoli-Calmettes, within this EAP. Our purpose is to describe the efficacy and safety of alpelisib in association with fulvestrant, based on a retrospective real-life cohort.

2. Methods

From prospective data collected within the framework of the EAP, data regarding 40 consecutive women from our institution were extracted. Patients who were allowed to receive alpelisib within this EAP, accepted at the same time the collection of data. Inclusion criteria were as follows: post-menopausal patients with ER-positive HER2-negative advanced or metastatic BC with PIK3CA mutation whose disease progressed after at least 2 prior line of treatment one of which included AI and CDK4/6 inhibitor (except if not eligible to this treatment) who were treated with alpelisib in EAP between 11.2018 and 12.2020. Symptomatic visceral progression and IBC were excluded criteria.

Alpelisib was initiated at 300mg once daily. Dose reduction and suspension were allowed. Minimal dose of alpelisib were 100mg once daily and if toxicity still unacceptable treatment was discontinued. Grade 1/2 hyperglycemia was first managed with metformin and persistent grade 2 or grade 3 were managed with insulin therapy. Grade 1 rash was treated with dermocorticoid, grade 2 with H2 antihistamine treatment and grade 3 with association of H2 antihistamine treatment and corticosteroid. Positron emission tomography (PET) or tomography scan was performed every 3 or 4 months to evaluated treatment response. If patients presented brain metastasis, cerebral magnetic resonance imaging (MRI) was performed.

Primary objective was to evaluate the efficacy of alpelisib plus fulvestrant in terms of PFS. We used the Kaplan-Meier method to estimate the probabilities of PFS in all patients of the cohort. Secondary objective was to evaluate the safety of the association. Exploratory analysis evaluated PFS whether rash occurred or not, and whether hyperglycemia occurred or not and their pointwise 95% confidence intervals. The Log rank non-parametric tests for comparison of survival distributions were used to compare PFS differences between groups. The alpha risk was set to 5.0%. We also conducted a univariate analysis of clinical and pathological parameters associated with PFS. A ratio of PFS on alpelisib treatment (PFSa) to either PFS on the immediate previous treatment (PFSpre) or the prior everolimus treatment (PFSe) was calculated. A ratio ≥ 1.3 was considered as a non-ambiguous sign of activity for the new treatment, relative to previously received treatments (214).

The statistical analysis was performed with R software.

3. Results

Forty patients were treated in EAP, the median age was 61 years. In our cohort, only 1 patient did not receive prior CDK4/6 inhibitors and no hormonotherapy in metastatic setting (only adjuvant hormonotherapy), and 92.5% received prior chemotherapy, 65% of patients had received 4 or more lines of previous treatment in metastatic settings. The repartition of PIK3CA mutations is presented in figure 1, no patient harbored double mutation and figure 2 shows the sample used for the characterization of PIK3CA. Baseline characteristics of patients were summarized in table 2.

The median duration of follow-up was 7 months (1-19). The 3- and 6-month PFS were 67.0% (95% CI: 49.2-79.7) and 31.0% (95% CI: 16.0-47.3), respectively. Median PFS was 4.0 months and figure 3 represents PFS for all cohort. We examined the efficacy of alpelisib-fulvestrant combination according to prior treatment with everolimus and found that CBR was 79% in everolimus-pretreated patients versus 40% in non-pretreated (p=0.045, Fisher's exact test). Nevertheless, groups were too small to formally compare PFS using log-rank test.

Of note, there was a statistically significant difference in median PFS according to the occurrence of rash or not: 6.0 months versus 2.0 months respectively (p=0.002). The 3-month PFS was 40.0% (95% CI: 19.3-60.0) and 92.9% (95% CI: 59.1-99.0) if rash was absent or present, respectively. In univariate analysis, no other factor reached a statistical significance including prior sensitivity versus hormono-resistance (p 0.29) or histology (p 0.69). Yet, there was a non-significant trend for a longer PFS in patients exposed to prior fulvestrant therapies: median PFS was 6.1 months in fulvestrant pre-treated versus 2.8 months in patients not pre-treated with fulvestrant, with an HR at 0.4 (95% CI: 0.1-1.2) and a p-value of 0.0766. A similar trend was also observed for a longer PFS (6.2 months versus 3.3 months) when hyperglycemia occurred with HR 0.4 (95CI, 0.2-1.2, p 0.089). Table 3 summarize univariate analysis.

We examined for each individual patient the PFS observed during immediate prior treatment or the prior everolimus treatment and during alpelisib combination and calculated PFS ratio (PFSa/PFSpre and PFSa/PFSe respectively). Figures 4 and 5 show PFSpre or PFSe follow by PFSa. PFS was higher on alpelisib than on prior treatment in 10 patients and PFS ratio was $\geq$ 1.3 in 25% of patients. We performed similar comparison between PFSa and PFSe: PFS ratio was $\geq$ 1.3 in 14.8% of patients.

All grade adverse events occurred in 87.5% of the cases. Hyperglycemia was the most frequent adverse event, 60% all grade and 12.5% grade 3. Metformin was used in 40% of the cases in monotherapy and allowed to continue the therapy with glycemic control. The exogenous insulin was needed in association to metformin for 7.5% of patients, these 3 patients had a PFS at 5, 11 and 12 months. Other frequent adverse events included rash (42.5%), nausea (32.5%), weight loss (50%). Figure 6 summarized principal adverse events. Regarding to treatment exposures, 45% of patients had a dose reduction, 32.5% had transitory suspensions of alpelisib due to toxicity and 10 patients (25%) discontinued alpelisib due to unacceptable toxicity.

4. Discussion

Our cohort showed interesting results concerning the PFS in a population heavily pretreated, with metastatic ER/PR-positive/HER2-negative BC and resistance to endocrine therapy, in the context of the French EAP. This population is closer to real life patients than most of the previous prospective studies. No new safety signal with treatment by alpelisib in association to fulvestrant appeared and this association was manageable and safe. Pre-treatment with everolimus did not seem to impact the efficacy of alpelisib + fulvestrant. Moreover, our results suggested a trend for better PFS in patients with prior fulvestrant or presence of hyperglycemia, but our cohort was too small to identify a significant difference.

These trends for better PFS in case of prior exposure to fulvestrant or everolimus may indicate a higher benefit for alpelisib + fulvestrant in patients who have been previously identified by clinicians as good candidate to receive multiples lines of endocrine therapy. Our results also suggested a favorable impact in terms of PFS if patients developed rash or hyperglycemia. These data were contradictory with pre-clinical and clinical data which suggested that hyperglycemia was a factor of acquired resistance to alpelisib due to “insulin feedback”. We hypothesized that, patients with hyperglycemia had a modest “insulin feedback” and consequently did not overcome inhibition of PIK3CA, however this supposition need to be prospectively evaluated by dosage of insulin level before administration and at several time of alpelisib treatment. Alternatively, a longer PFS in patients with hyperglycemia may be due to a higher drug exposure and/or pharmacodynamics effect in this subgroup.

Nevertheless, regarding to the absence of benefit in OS in the final results of SOLAR-1 trial and the low number of patients pre-treated with CDK4/6 inhibitor in this study, the French health authorities (Haute autorité de santé) in January 2021 gave an unfavorable opinion for reimbursement which led to the discontinuation of alpelisib prescribing in this indication. This decision is discussable. First, OS was a secondary endpoint in SOLAR-1 and the study could have been underpowered to demonstrate a significant difference in favor of alpelisib. Numerically, median OS in patients treated with alpelisib plus fulvestrant (39.3 months) was higher than patients treated with placebo plus fulvestrant (31.4 months), HR was 0.86 (95% CI, 0.64-1.15; p=0.15). Numerically difference was also observed patients with lung and/or liver metastases (37.2 months for alpelisib and 22.8 months for placebo) and median times to chemotherapy (23.3 months for alpelisib and 14.8 months for placebo). In addition, BYLieve study suggested that results could be transposable to ER-positive HER2-negative

advanced or metastatic BC with PIK3CA mutation whose progressed on or after ET plus CDK4/6 inhibitor.

An Improved management of toxicities related to alpelisib may increase treatment time and maintain the highest dose possible of treatment. Improvement goes through the realization of standardized recommendations and the involvement of different specialists, for example endocrinologist for hyperglycemia.

Alpelisib inhibits PI3K, a central actor of multiple pathways in cell, and these inhibition lead to adaptative mechanism of cancer cells to escape the anti-tumor effect. The discovery of new predictive biomarkers beyond PIK3CA mutations for alpelisib efficacy may allow to improve the efficacy/toxicity ratio and to select the patients who could most benefit t from treatment. Two different associations of alpelisib with other anti-tumor drugs are possible: for example, MCL1 inhibitors which increased anti-tumor activity but may alter the tolerance profile; alpelisib may also be combined with an SGLT2 inhibitor, for example, which thus makes it possible to counteract one of the resistance mechanisms and limit toxicity.

II. Presentation “Alpelisib and fulvestrant efficiency in HR-positive HER2-negative PIK3CA-mutant advanced breast cancer: data from the French early access program”

Our cohort was used in a national analysis of all patients in French EAP. We presented results in figure 7.

C. Conclusion

In conclusion, the therapeutic class of PI3K inhibitors, including pan-inhibitors and selective-inhibitors, are at the beginning of their development in breast cancer. Although currently they have led to few authorizations, their field of evolution is considerable. Pan-inhibitors have not shown the expected efficacy, but they have nevertheless opened the way to PI3Kα-specific inhibitors. Despite the central role of PI3K in oncogenesis, only modest anti-tumor activity was observed and the toxicity profile that should not be overlooked. All breast cancer subtypes have their own metabolic pathway, and we need to better understand the mechanisms of resistance to these drugs in each subtype to adapt our therapeutic strategies. Learning to manage these drugs to facilitate their use and discovering predictive biomarkers of responses are the new challenges we must meet.

En conclusion, la classe thérapeutique des inhibiteurs de PI3K, comprenant les pan-inhibiteurs et les inhibiteurs sélectifs de la sous unité p110α, a fait l'objet d'un développement intense dans le domaine des cancers du sein. Bien qu'actuellement ils n'aient donné lieu qu'à peu d'autorisations, leur champ d'évolution reste considérable. Les pan-inhibiteurs n'ont pas montré l'efficacité attendue, mais ils ont néanmoins ouvert la voie aux inhibiteurs spécifiques de PI3Kα. Malgré le rôle central de PI3K dans l'oncogenèse, seule une activité anti-tumorale modeste a été observée avec un profil de toxicité non négligeable. Tous les sous-types de cancer du sein ont leur propre voie métabolique, et nous devons mieux comprendre les mécanismes de résistance à ces médicaments au sein de chaque sous-type pour adapter nos stratégies thérapeutiques. Apprendre à gérer ces médicaments afin de faciliter leur utilisation pour augmenter les durées de traitement et découvrir des nouveaux biomarqueurs prédictifs de réponse sont actuellement les nouveaux défis auxquels nous devons faire face.

D. Bibliographie

1. WHO. GLOBOCAN 2020 [Internet]. Available from: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf
2. INCA. Epidémiologie des cancers : Le cancer du sein. https://www.e-cancer.fr/Professionnels-de-sante/Les-chiffres-du-cancer-en-France/Epidemiologie-des-cancers/Les-cancers-les-plus-frequents/Cancer-du-sein;
3. Tao Z, Shi A, Lu C, Song T, Zhang Z, Zhao J. Breast Cancer: Epidemiology and Etiology. Cell Biochem Biophys [Internet]. 2015 Jun [cited 2021 Sep 28];72(2):333–8. Available from: http://link.springer.com/10.1007/s12013-014-0459-6
4. Verma R, Bowen RL, Slater SE, Mihaimeed F, Jones JL. Pathological and epidemiological factors associated with advanced stage at diagnosis of breast cancer. British Medical Bulletin [Internet]. 2012 Sep 1 [cited 2021 Sep 28];103(1):129–45. Available from: https://academic.oup.com/bmb/article-lookup/doi/10.1093/bmb/lds018
5. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature [Internet]. 2000 Aug [cited 2021 Sep 28];406(6797):747–52. Available from: http://www.nature.com/articles/35021093
6. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn H-J. Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Annals of Oncology [Internet]. 2011 Aug [cited 2021 Sep 30];22(8):1736–47. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753419384145
7. Park SY, Lee HE, Li H, Shipitsin M, Gelman R, Polyak K. Heterogeneity for Stem Cell-Related Markers According to Tumor Subtype and Histologic Stage in Breast Cancer. Clinical Cancer Research [Internet]. 2010 Feb 1 [cited 2021 Sep 28];16(3):876–87. Available from: http://clincancerres.aacrjournals.org/cgi/doi/10.1158/1078-0432.CCR-09-1532
8. Morris PG, Murphy CG, Mallam D, Accordino M, Patil S, Howard J, et al. Limited Overall Survival in Patients with Brain Metastases from Triple Negative Breast Cancer: Breast Cancer, Brain Metastases, and Survival. The Breast Journal [Internet]. 2012 Jul [cited 2021 Sep 28];18(4):345–50. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1524-4741.2012.01246.x
9. Cristofanilli M, Valero V, Buzdar AU, Kau S-W, Broglio KR, Gonzalez-Angulo AM, et al. Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. Cancer. 2007 Oct;110(7):1436–44.
10. Dawood S, Merajver SD, Viens P, Vermeulen PB, Swain SM, Buchholz TA, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol. 2011 Mar;22(3):515–23.
11. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med [Internet]. 2017 Nov 9 [cited 2021 Sep 28];377(19):1836–46. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1701830
12. Baselga J, Cortés J, Kim S-B, Im S-A, Hegg R, Im Y-H, et al. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. N Engl J Med [Internet]. 2012 Jan 12 [cited 2021 Sep 28];366(2):109–19. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1113216
13. Taskindoust M, Thomas SM, Sammons SL, Fayanju OM, DiLalla G, Hwang ES, et al.

Survival Outcomes Among Patients with Metastatic Breast Cancer: Review of 47,000 Patients. Ann Surg Oncol [Internet]. 2021 May 28 [cited 2021 Sep 30]; Available from: https://link.springer.com/10.1245/s10434-021-10227-3

14. Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im S-A, Yusof MM, et al. KEYNOTE-355: Randomized, double-blind, phase III study of pembrolizumab + chemotherapy versus placebo + chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer. JCO [Internet]. 2020 May 20 [cited 2020 Jun 15];38(15_suppl):1000–1000. Available from: https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.1000
15. Turner NC, Telli ML, Rugo HS, Mailliez A, Ettl J, Grischke E-M, et al. A Phase II Study of Talazoparib after Platinum or Cytotoxic Nonplatinum Regimens in Patients with Advanced Breast Cancer and Germline *BRCA1/2* Mutations (ABRAZO). Clin Cancer Res [Internet]. 2019 May 1 [cited 2020 Apr 26];25(9):2717–24. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-18-1891
16. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee K-H, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation. N Engl J Med [Internet]. 2018 Aug 23 [cited 2020 Apr 26];379(8):753–63. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1802905
17. Sammons S, Tan TJY, Traina TA, Kim S-B, Im Y-H, Bachelder C, et al. Dora: A randomized phase II multicenter maintenance study of olaparib alone or olaparib in combination with durvalumab in platinum responsive advanced triple-negative breast cancer (aTNBC). JCO [Internet]. 2019 May 20 [cited 2022 Mar 14];37(15_suppl):TPS1113–TPS1113. Available from: http://ascopubs.org/doi/10.1200/JCO.2019.37.15_suppl.TPS1113
18. Eikesdal HP, Yndestad S, Elzawahry A, Llop-Guevara A, Gilje B, Blix ES, et al. Olaparib monotherapy as primary treatment in unselected triple negative breast cancer. Annals of Oncology [Internet]. 2021 Feb [cited 2022 Mar 14];32(2):240–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753420431643
19. Finn RS, Martin M, Rugo HS, Jones SE, Im S-A, Gelmon KA, et al. PALOMA-2: Primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in postmenopausal women with ER+/HER2– advanced breast cancer (ABC). JCO [Internet]. 2016 May 20 [cited 2021 Sep 28];34(15_suppl):507–507. Available from: http://ascopubs.org/doi/10.1200/JCO.2016.34.15_suppl.507
20. O'Shaughnessy J, Petrakova K, Sonke GS, Conte P, Arteaga CL, Cameron DA, et al. Ribociclib plus letrozole versus letrozole alone in patients with de novo HR+, HER2− advanced breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat [Internet]. 2018 Feb [cited 2021 Sep 28];168(1):127–34. Available from: http://link.springer.com/10.1007/s10549-017-4518-8
21. Johnston S, Martin M, Di Leo A, Im S-A, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. npj Breast Cancer [Internet]. 2019 Dec [cited 2021 Sep 28];5(1):5. Available from: http://www.nature.com/articles/s41523-018-0097-z
22. Rossi V, Berchialla P, Giannarelli D, Nisticò C, Ferretti G, Gasparro S, et al. Should All Patients With HR-Positive HER2-Negative Metastatic Breast Cancer Receive CDK 4/6 Inhibitor As First-Line Based Therapy? A Network Meta-Analysis of Data from the PALOMA 2, MONALEESA 2, MONALEESA 7, MONARCH 3, FALCON, SWOG and FACT Trials. Cancers [Internet]. 2019 Oct 26 [cited 2022 Feb 13];11(11):1661. Available from:

https://www.mdpi.com/2072-6694/11/11/1661
23. Tripathy D, Im S-A, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. The Lancet Oncology [Internet]. 2018 Jul [cited 2022 Feb 13];19(7):904–15. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204518302924
24. Loibl S, Turner NC, Ro J, Cristofanilli M, Iwata H, Im S-A, et al. Palbociclib Combined with Fulvestrant in Premenopausal Women with Advanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results. The Oncologist [Internet]. 2017 Sep 1 [cited 2022 Feb 13];22(9):1028–38. Available from: https://academic.oup.com/oncolo/article/22/9/1028/6444567
25. Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2− Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. JCO [Internet]. 2017 Sep 1 [cited 2022 Feb 13];35(25):2875–84. Available from: https://ascopubs.org/doi/10.1200/JCO.2017.73.7585
26. dos Anjos CH, Razavi P, Herbert J, Colon J, Gill K, Modi S, et al. A large retrospective analysis of CDK 4/6 inhibitor retreatment in ER+ metastatic breast cancer (MBC). JCO [Internet]. 2019 May 20 [cited 2022 Feb 13];37(15_suppl):1053–1053. Available from: http://ascopubs.org/doi/10.1200/JCO.2019.37.15_suppl.1053
27. Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation. N Engl J Med [Internet]. 2017 Aug 10 [cited 2020 Apr 26];377(6):523–33. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1706450
28. Yardley DA, Noguchi S, Pritchard KI, Burris HA, Baselga J, Gnant M, et al. Everolimus Plus Exemestane in Postmenopausal Patients with HR+ Breast Cancer: BOLERO-2 Final Progression-Free Survival Analysis. Adv Ther [Internet]. 2013 Oct [cited 2022 Feb 13];30(10):870–84. Available from: http://link.springer.com/10.1007/s12325-013-0060-1
29. Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. Nat Rev Drug Discov [Internet]. 2014 Feb [cited 2021 Sep 16];13(2):140–56. Available from: https://www.nature.com/articles/nrd4204
30. Jia S, Roberts TM, Zhao JJ. Should individual PI3 kinase isoforms be targeted in cancer? Current Opinion in Cell Biology [Internet]. 2009 Apr [cited 2021 Sep 21];21(2):199–208. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0955067409000118
31. Courtney KD, Corcoran RB, Engelman JA. The PI3K pathway as drug target in human cancer. J Clin Oncol. 2010 Feb 20;28(6):1075–83.
32. Yuan TL, Cantley LC. PI3K pathway alterations in cancer: variations on a theme. Oncogene [Internet]. 2008 Sep [cited 2021 Sep 21];27(41):5497–510. Available from: http://www.nature.com/articles/onc2008245
33. Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat Rev Genet [Internet]. 2006 Aug [cited 2021 Sep 21];7(8):606–19. Available from: http://www.nature.com/articles/nrg1879
34. Backer JM. The Regulation of Class IA PI 3-Kinases by Inter-Subunit Interactions. In: Rommel C, Vanhaesebroeck B, Vogt PK, editors. Phosphoinositide 3-kinase in Health and Disease [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2021 Sep 26]. p. 87–114. (Current Topics in Microbiology and Immunology; vol. 346). Available

from: http://link.springer.com/10.1007/82_2010_52
35. Burke JE, Williams RL. Synergy in activating class I PI3Ks. Trends in Biochemical Sciences [Internet]. 2015 Feb [cited 2021 Sep 26];40(2):88–100. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0968000414002205
36. Vadas O, Burke JE, Zhang X, Berndt A, Williams RL. Structural Basis for Activation and Inhibition of Class I Phosphoinositide 3-Kinases. Sci Signal [Internet]. 2011 Oct 18 [cited 2021 Sep 26];4(195):re2–re2. Available from: https://stke.sciencemag.org/lookup/doi/10.1126/scisignal.2002165
37. Fruman DA. Regulatory Subunits of Class IA PI3K. In: Rommel C, Vanhaesebroeck B, Vogt PK, editors. Phosphoinositide 3-kinase in Health and Disease [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2022 Feb 4]. p. 225–44. (Current Topics in Microbiology and Immunology; vol. 346). Available from: http://link.springer.com/10.1007/82_2010_39
38. Bi L, Okabe I, Bernard DJ, Wynshaw-Boris A, Nussbaum RL. Proliferative Defect and Embryonic Lethality in Mice Homozygous for a Deletion in the p110α Subunit of Phosphoinositide 3-Kinase. Journal of Biological Chemistry [Internet]. 1999 Apr [cited 2021 Sep 25];274(16):10963–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0021925819735959
39. Toker A. Achieving specificity in Akt signaling in cancer. Advances in Biological Regulation [Internet]. 2012 Jan [cited 2021 Sep 26];52(1):78–87. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0065257111000689
40. Luo J, Sobkiw CL, Hirshman MF, Logsdon MN, Li TQ, Goodyear LJ, et al. Loss of class IA PI3K signaling in muscle leads to impaired muscle growth, insulin response, and hyperlipidemia. Cell Metabolism [Internet]. 2006 May [cited 2021 Sep 25];3(5):355–66. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1550413106001227
41. Vanhaesebroeck B, Leevers SJ, Ahmadi K, Timms J, Katso R, Driscoll PC, et al. Synthesis and Function of 3-Phosphorylated Inositol Lipids. Annu Rev Biochem [Internet]. 2001 Jun [cited 2021 Sep 21];70(1):535–602. Available from: http://www.annualreviews.org/doi/10.1146/annurev.biochem.70.1.535
42. Goncalves MD, Hopkins BD, Cantley LC. Phosphatidylinositol 3-Kinase, Growth Disorders, and Cancer. N Engl J Med [Internet]. 2018 Nov 22 [cited 2020 Dec 8];379(21):2052–62. Available from: http://www.nejm.org/doi/10.1056/NEJMra1704560
43. Maehama T, Dixon JE. The Tumor Suppressor, PTEN/MMAC1, Dephosphorylates the Lipid Second Messenger, Phosphatidylinositol 3,4,5-Trisphosphate. Journal of Biological Chemistry [Internet]. 1998 May [cited 2021 Sep 25];273(22):13375–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0021925819577663
44. Rohrschneider LR, Fuller JF, Wolf I, Liu Y, Lucas DM. Structure, function, and biology of SHIP proteins. Genes Dev. 2000 Mar 1;14(5):505–20.
45. Choi Y, Zhang J, Murga C, Yu H, Koller E, Monia BP, et al. PTEN, but not SHIP and SHIP2, suppresses the PI3K/Akt pathway and induces growth inhibition and apoptosis of myeloma cells. Oncogene [Internet]. 2002 Aug [cited 2022 Feb 4];21(34):5289–300. Available from: http://www.nature.com/articles/1205650
46. Zhang Y, Kwok-Shing Ng P, Kucherlapati M, Chen F, Liu Y, Tsang YH, et al. A Pan-Cancer Proteogenomic Atlas of PI3K/AKT/mTOR Pathway Alterations. Cancer Cell [Internet]. 2017 Jun [cited 2021 Sep 30];31(6):820-832.e3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S153561081730168X

47. Hunter T, Sefton BM. Transforming gene product of Rous sarcoma virus phosphorylates tyrosine. Proc Natl Acad Sci USA [Internet]. 1980 Mar [cited 2021 Sep 25];77(3):1311–5. Available from: http://www.pnas.org/lookup/doi/10.1073/pnas.77.3.1311
48. Graziani A, Gramaglia D, Cantley LC, Comoglio PM. The tyrosine-phosphorylated hepatocyte growth factor/scatter factor receptor associates with phosphatidylinositol 3-kinase. Journal of Biological Chemistry [Internet]. 1991 Nov [cited 2021 Sep 25];266(33):22087–90. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0021925818545361
49. Samuels Y, Waldman T. Oncogenic Mutations of PIK3CA in Human Cancers. In: Rommel C, Vanhaesebroeck B, Vogt PK, editors. Phosphoinositide 3-kinase in Health and Disease [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2021 Sep 28]. p. 21–41. (Current Topics in Microbiology and Immunology; vol. 347). Available from: http://link.springer.com/10.1007/82_2010_68
50. Lawrence MS, Stojanov P, Mermel CH, Robinson JT, Garraway LA, Golub TR, et al. Discovery and saturation analysis of cancer genes across 21 tumour types. Nature [Internet]. 2014 Jan [cited 2021 Sep 25];505(7484):495–501. Available from: http://www.nature.com/articles/nature12912
51. Keniry M, Parsons R. The role of PTEN signaling perturbations in cancer and in targeted therapy. Oncogene [Internet]. 2008 Sep [cited 2021 Sep 25];27(41):5477–85. Available from: http://www.nature.com/articles/onc2008248
52. Li J. PTEN, a Putative Protein Tyrosine Phosphatase Gene Mutated in Human Brain, Breast, and Prostate Cancer. Science [Internet]. 1997 Mar 28 [cited 2021 Sep 25];275(5308):1943–7. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.275.5308.1943
53. Teng DH, Hu R, Lin H, Davis T, Iliev D, Frye C, et al. MMAC1/PTEN mutations in primary tumor specimens and tumor cell lines. Cancer Res. 1997 Dec 1;57(23):5221–5.
54. Álvarez-Garcia V, Tawil Y, Wise HM, Leslie NR. Mechanisms of PTEN loss in cancer: It's all about diversity. Seminars in Cancer Biology [Internet]. 2019 Dec [cited 2021 Sep 25];59:66–79. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1044579X18300592
55. Kim MS, Jeong EG, Yoo NJ, Lee SH. Mutational analysis of oncogenic AKT E17K mutation in common solid cancers and acute leukaemias. Br J Cancer [Internet]. 2008 May [cited 2022 Feb 13];98(9):1533–5. Available from: http://www.nature.com/articles/6604212
56. Carpten JD, Faber AL, Horn C, Donoho GP, Briggs SL, Robbins CM, et al. A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. Nature. 2007 Jul 26;448(7152):439–44.
57. Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K Pathway in Human Disease. Cell [Internet]. 2017 Aug [cited 2021 Sep 26];170(4):605–35. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0092867417308656
58. Rodgers SJ, Ooms LM, Oorschot VMJ, Schittenhelm RB, Nguyen EV, Hamila SA, et al. INPP4B promotes PI3Kα-dependent late endosome formation and Wnt/β-catenin signaling in breast cancer. Nat Commun. 2021 May 25;12(1):3140.
59. Wei J, Ye L, Song L, Tang H, Zhang T, Fu B, et al. TSC1/2 mutations-a unique type of mutation suitable for liver transplantation of Hepatocellular carcinoma. J Gastrointest Oncol. 2021 Jun;12(3):1074–85.
60. Samuels Y, Ericson K. Oncogenic PI3K and its role in cancer: Current Opinion in Oncology [Internet]. 2006 Jan [cited 2021 Sep 26];18(1):77–82. Available from: http://journals.l

ww.com/00001622-200601000-00013
61. Samuels Y. High Frequency of Mutations of the PIK3CA Gene in Human Cancers. Science [Internet]. 2004 Apr 23 [cited 2021 Sep 25];304(5670):554–554. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.1096502
62. Sanger Institute. The catalogue of somatic mutation in cancer (COSMIC) [Internet]. Available from: https://cancer.sanger.ac.uk/cosmic/gene/analysis?ln=PIK3CA #distribution
63. Karakas B, Bachman KE, Park BH. Mutation of the PIK3CA oncogene in human cancers. Br J Cancer [Internet]. 2006 Feb [cited 2021 Sep 27];94(4):455–9. Available from: http://www.nature.com/articles/6602970
64. Samuels Y, Diaz LA, Schmidt-Kittler O, Cummins JM, DeLong L, Cheong I, et al. Mutant PIK3CA promotes cell growth and invasion of human cancer cells. Cancer Cell [Internet]. 2005 Jun [cited 2021 Sep 30];7(6):561–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1535610805001601
65. Bonelli MA, Cavazzoni A, Saccani F, Alfieri RR, Quaini F, La Monica S, et al. Inhibition of PI3K Pathway Reduces Invasiveness and Epithelial-to-Mesenchymal Transition in Squamous Lung Cancer Cell Lines Harboring *PIK3CA* Gene Alterations. Mol Cancer Ther [Internet]. 2015 Aug [cited 2021 Sep 30];14(8):1916–27. Available from: http://mct.aacrjournals.org/lookup/doi/10.1158/1535-7163.MCT-14-0892
66. Biswas SK. Metabolic Reprogramming of Immune Cells in Cancer Progression. Immunity [Internet]. 2015 Sep [cited 2021 Sep 30];43(3):435–49. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1074761315003611
67. Vanhaesebroeck B, Perry MWD, Brown JR, André F, Okkenhaug K. PI3K inhibitors are finally coming of age. Nat Rev Drug Discov [Internet]. 2021 Oct [cited 2021 Oct 4];20(10):741–69. Available from: https://www.nature.com/articles/s41573-021-00209-1
68. Lucas CL, Chandra A, Nejentsev S, Condliffe AM, Okkenhaug K. PI3Kδ and primary immunodeficiencies. Nat Rev Immunol [Internet]. 2016 Nov [cited 2021 Sep 27];16(11):702–14. Available from: http://www.nature.com/articles/nri.2016.93
69. Dornan GL, Siempelkamp BD, Jenkins ML, Vadas O, Lucas CL, Burke JE. Conformational disruption of PI3Kδ regulation by immunodeficiency mutations in *PIK3CD* and *PIK3R1*. Proc Natl Acad Sci USA [Internet]. 2017 Feb 21 [cited 2021 Sep 27];114(8):1982–7. Available from: http://www.pnas.org/lookup/doi/10.1073/pnas.1617244114
70. Seiler T, Hutter G, Dreyling M. The Emerging Role of PI3K Inhibitors in the Treatment of Hematological Malignancies: Preclinical Data and Clinical Progress to Date. Drugs [Internet]. 2016 Apr [cited 2021 Sep 27];76(6):639–46. Available from: http://link.springer.com/10.1007/s40265-016-0565-4
71. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med [Internet]. 2014 Mar 13 [cited 2021 Sep 27];370(11):997–1007. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1315226
72. Miller BW, Przepiorka D, de Claro RA, Lee K, Nie L, Simpson N, et al. FDA Approval: Idelalisib Monotherapy for the Treatment of Patients with Follicular Lymphoma and Small Lymphocytic Lymphoma. Clin Cancer Res [Internet]. 2015 Apr 1 [cited 2021 Sep 27];21(7):1525–9. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-14-2522
73. Matasar MJ, Capra M, Özcan M, Lv F, Li W, Yanez E, et al. Copanlisib + rituximab versus

rituximab + placebo in patients with relapsed follicular (FL) or marginal zone lymphoma (MZL): Subset analysis from the phase III CHRONOS-3 trial. JCO [Internet]. 2021 May 20 [cited 2021 Sep 27];39(15_suppl):7510–7510. Available from: https://ascopubs.org/doi/10.1200/JCO.2021.39.15_suppl.7510

74. Flinn I, Jäger U, Offner F, Cymbalista F, Hallek M, Caligaris-Cappio F, et al. DUO: A phase 3 trial of the PI3K-δ,γ inhibitor IPI-145 versusofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. JCO [Internet]. 2014 May 20 [cited 2021 Sep 27];32(15_suppl):TPS7122–TPS7122. Available from: http://ascopubs.org/doi/10.1200/jco.2014.32.15_suppl.tps7122
75. Rodrigues DA, Sagrillo FS, Fraga CAM. Duvelisib: A 2018 Novel FDA-Approved Small Molecule Inhibiting Phosphoinositide 3-Kinases. Pharmaceuticals [Internet]. 2019 May 6 [cited 2021 Sep 27];12(2):69. Available from: https://www.mdpi.com/1424-8247/12/2/69
76. Gribben JG, Jurczak W, Jacobs RW, Grosicki S, Giannopoulos K, Wrobel T, et al. Umbralisib Plus Ublituximab (U2) Is Superior to Obinutuzumab Plus Chlorambucil (O+Chl) in Patients with Treatment Naïve (TN) and Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): Results from the Phase 3 Unity-CLL Study. Blood [Internet]. 2020 Nov 5 [cited 2021 Sep 30];136(Supplement 1):37–9. Available from: https://ashpublications.org/blood/article/136/Supplement%201/37/470297/Umbralisib-Plus-Ublituximab-U2-Is-Superior-to
77. Ghosh N, Zinzani PL, Samaniego F, Jurczak W, Derenzini E, Reeves JA, et al. IBCL-203: Umbralisib, a PI3Kδ/CK1ε Dual Inhibitor Demonstrates Marked Clinical Activity in Patients with Relapsed or Refractory Indolent Non-Hodgkin Lymphoma (iNHL): Results from the Phase 2 Global UNITY-NHL Trial. Clinical Lymphoma Myeloma and Leukemia [Internet]. 2021 Sep [cited 2021 Sep 30];21:S404. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2152265021019121
78. Junttila TT, Akita RW, Parsons K, Fields C, Lewis Phillips GD, Friedman LS, et al. Ligand-independent HER2/HER3/PI3K complex is disrupted by trastuzumab and is effectively inhibited by the PI3K inhibitor GDC-0941. Cancer Cell. 2009 May 5;15(5):429–40.
79. Gainor JF, Varghese AM, Ou S-HI, Kabraji S, Awad MM, Katayama R, et al. *ALK* Rearrangements Are Mutually Exclusive with Mutations in *EGFR* or *KRAS* : An Analysis of 1,683 Patients with Non–Small Cell Lung Cancer. Clin Cancer Res [Internet]. 2013 Aug 1 [cited 2021 Oct 4];19(15):4273–81. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-13-0318
80. Midthun L, Shaheen S, Deisch J, Senthil M, Tsai J, Hsueh C-T. Concomitant KRAS and BRAF mutations in colorectal cancer. J Gastrointest Oncol. 2019 Jun;10(3):577–81.
81. Mollon LE, Anderson EJ, Dean JL, Warholak TL, Aizer A, Platt EA, et al. A Systematic Literature Review of the Prognostic and Predictive Value of PIK3CA Mutations in HR+/HER2− Metastatic Breast Cancer. Clinical Breast Cancer [Internet]. 2020 Jun [cited 2020 Dec 6];20(3):e232–43. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1526820919306706
82. Mosele F, Stefanovska B, Lusque A, Tran Dien A, Garberis I, Droin N, et al. Outcome and molecular landscape of patients with PIK3CA-mutated metastatic breast cancer. Annals of Oncology [Internet]. 2020 Mar [cited 2022 Feb 25];31(3):377–86. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753419390945
83. Pang B, Cheng S, Sun S-P, An C, Liu Z-Y, Feng X, et al. Prognostic role of PIK3CA mutations and their association with hormone receptor expression in breast cancer: a meta-

analysis. Sci Rep [Internet]. 2015 May [cited 2021 Oct 4];4(1):6255. Available from: http://www.nature.com/articles/srep06255
84. Sobhani N, Roviello G, Corona SP, Scaltriti M, Ianza A, Bortul M, et al. The prognostic value of PI3K mutational status in breast cancer: A meta-analysis. J Cell Biochem [Internet]. 2018 Jun [cited 2022 Feb 25];119(6):4287–92. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jcb.26687
85. Barbareschi M, Buttitta F, Felicioni L, Cotrupi S, Barassi F, Del Grammastro M, et al. Different Prognostic Roles of Mutations in the Helical and Kinase Domains of the *PIK3CA* Gene in Breast Carcinomas. Clin Cancer Res [Internet]. 2007 Oct 15 [cited 2021 Oct 4];13(20):6064–9. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-07-0266
86. Zhao L, Vogt PK. Helical domain and kinase domain mutations in p110 of phosphatidylinositol 3-kinase induce gain of function by different mechanisms. Proceedings of the National Academy of Sciences [Internet]. 2008 Feb 19 [cited 2021 Oct 4];105(7):2652–7. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.0712169105
87. Mukohara T. PI3K mutations in breast cancer: prognostic and therapeutic implications. Breast Cancer (Dove Med Press). 2015;7:111–23.
88. Mangone F, Bobrovnitchaia I, Salaorni S, Manuli E, Nagai M. PIK3CA exon 20 mutations are associated with poor prognosis in breast cancer patients. Clinics [Internet]. 2012 Nov 7 [cited 2022 Feb 26];67(11):1285–90. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3488987/?report=classic
89. Guo S, Loibl S, von Minckwitz G, Darb-Esfahani S, Lederer B, Denkert C. PIK3CA H1047R Mutation Associated with a Lower Pathological Complete Response Rate in Triple-Negative Breast Cancer Patients Treated with Anthracycline-Taxane-Based Neoadjuvant Chemotherapy. Cancer Res Treat. 2020 Jul;52(3):689–96.
90. Hu H, Zhu J, Zhong Y, Geng R, Ji Y, Guan Q, et al. PIK3CA mutation confers resistance to chemotherapy in triple-negative breast cancer by inhibiting apoptosis and activating the PI3K/AKT/mTOR signaling pathway. Ann Transl Med. 2021 Mar;9(5):410.
91. Vasan N, Razavi P, Johnson JL, Shao H, Shah H, Antoine A, et al. Double PIK3CA mutations in cis increase oncogenicity and sensitivity to PI3Kα inhibitors. Science. 2019 Nov 8;366(6466):714–23.
92. Chakrabarty A, Rexer BN, Wang SE, Cook RS, Engelman JA, Arteaga CL. H1047R phosphatidylinositol 3-kinase mutant enhances HER2-mediated transformation by heregulin production and activation of HER3. Oncogene [Internet]. 2010 Sep [cited 2022 Feb 26];29(37):5193–203. Available from: http://www.nature.com/articles/onc2010257
93. Baselga J, Cortés J, Im S-A, Clark E, Ross G, Kiermaier A, et al. Biomarker Analyses in CLEOPATRA: A Phase III, Placebo-Controlled Study of Pertuzumab in Human Epidermal Growth Factor Receptor 2–Positive, First-Line Metastatic Breast Cancer. JCO [Internet]. 2014 Nov 20 [cited 2022 Mar 2];32(33):3753–61. Available from: http://ascopubs.org/doi/10.1200/JCO.2013.54.5384
94. Loibl S, Majewski I, Guarneri V, Nekljudova V, Holmes E, Bria E, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2016 Aug;27(8):1519–25.
95. Morris JZ, Tissenbaum HA, Ruvkun G. A phosphatidylinositol-3-OH kinase family

member regulating longevity and diapause in Caenorhabditis elegans. Nature [Internet]. 1996 Aug [cited 2021 Oct 4];382(6591):536–9. Available from: http://www.nature.com/articles/382536a0
96. Miller TW, Hennessy BT, González-Angulo AM, Fox EM, Mills GB, Chen H, et al. Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor–positive human breast cancer. J Clin Invest [Internet]. 2010 Jul 1 [cited 2020 Dec 22];120(7):2406–13. Available from: http://www.jci.org/articles/view/41680
97. Wang M, Li J, Huang J, Luo M. The Predictive Role of PIK3CA Mutation Status on PI3K Inhibitors in HR+ Breast Cancer Therapy: A Systematic Review and Meta-Analysis. Biomed Res Int. 2020;2020:1598037.
98. Nixon MJ, Formisano L, Mayer IA, Estrada MV, González-Ericsson PI, Isakoff SJ, et al. PIK3CA and MAP3K1 alterations imply luminal A status and are associated with clinical benefit from pan-PI3K inhibitor buparlisib and letrozole in ER+ metastatic breast cancer. npj Breast Cancer [Internet]. 2019 Dec [cited 2021 Oct 8];5(1):31. Available from: http://www.nature.com/articles/s41523-019-0126-6
99. Bosch A, Li Z, Bergamaschi A, Ellis H, Toska E, Prat A, et al. PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor–positive breast cancer. Sci Transl Med [Internet]. 2015 Apr 15 [cited 2021 Jan 5];7(283):283ra51-283ra51. Available from: https://stm.sciencemag.org/lookup/doi/10.1126/scitranslmed.aaa4442
100. Chen I-C, Hsiao L-P, Huang I-W, Yu H-C, Yeh L-C, Lin C-H, et al. Phosphatidylinositol-3 Kinase Inhibitors, Buparlisib and Alpelisib, Sensitize Estrogen Receptor-positive Breast Cancer Cells to Tamoxifen. Sci Rep [Internet]. 2017 Dec [cited 2021 Oct 8];7(1):9842. Available from: http://www.nature.com/articles/s41598-017-10555-z
101. Vora SR, Juric D, Kim N, Mino-Kenudson M, Huynh T, Costa C, et al. CDK 4/6 inhibitors sensitize PIK3CA mutant breast cancer to PI3K inhibitors. Cancer Cell. 2014 Jul 14;26(1):136–49.
102. Herrera-Abreu MT, Palafox M, Asghar U, Rivas MA, Cutts RJ, Garcia-Murillas I, et al. Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor–Positive Breast Cancer. Cancer Res [Internet]. 2016 Apr 15 [cited 2021 Oct 8];76(8):2301–13. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/0008-5472.CAN-15-0728
103. Solzak JP, Atale RV, Hancock BA, Sinn AL, Pollok KE, Jones DR, et al. Dual PI3K and Wnt pathway inhibition is a synergistic combination against triple negative breast cancer. npj Breast Cancer [Internet]. 2017 Dec [cited 2021 Oct 9];3(1):17. Available from: http://www.nature.com/articles/s41523-017-0016-8
104. Van Swearingen AED, Sambade MJ, Siegel MB, Sud S, McNeill RS, Bevill SM, et al. Combined kinase inhibitors of MEK1/2 and either PI3K or PDGFR are efficacious in intracranial triple-negative breast cancer. Neuro-Oncology [Internet]. 2017 Oct 19 [cited 2021 Oct 10];19(11):1481–93. Available from: http://academic.oup.com/neuro-oncology/article/19/11/1481/3806770
105. Mustafi S, Camarena V, Qureshi R, Sant DW, Wilkes Z, Bilbao D, et al. Vitamin C sensitizes triple negative breast cancer to PI3K inhibition therapy. Theranostics [Internet]. 2021 [cited 2021 Oct 9];11(8):3552–64. Available from: https://www.thno.org/v11p3552.htm
106. Hu Y, Guo R, Wei J, Zhou Y, Ji W, Liu J, et al. Effects of PI3K inhibitor NVP-BKM120 on overcoming drug resistance and eliminating cancer stem cells in human breast cancer

cells. Cell Death Dis. 2015 Dec 17;6:e2020.
107. Rodon J, Braña I, Siu LL, De Jonge MJ, Homji N, Mills D, et al. Phase I dose-escalation and -expansion study of buparlisib (BKM120), an oral pan-Class I PI3K inhibitor, in patients with advanced solid tumors. Invest New Drugs [Internet]. 2014 Aug [cited 2021 Oct 8];32(4):670–81. Available from: http://link.springer.com/10.1007/s10637-014-0082-9
108. McRee AJ, Marcom PK, Moore DT, Zamboni WC, Kornblum ZA, Hu Z, et al. A Phase I Trial of the PI3K Inhibitor Buparlisib Combined With Capecitabine in Patients With Metastatic Breast Cancer. Clinical Breast Cancer [Internet]. 2018 Aug [cited 2021 Oct 8];18(4):289–97. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1526820917303130
109. Mayer IA, Abramson VG, Isakoff SJ, Forero A, Balko JM, Kuba MG, et al. Stand up to cancer phase Ib study of pan-phosphoinositide-3-kinase inhibitor buparlisib with letrozole in estrogen receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2014 Apr 20;32(12):1202–9.
110. Ma Y, Aymeric L, Locher C, Mattarollo SR, Delahaye NF, Pereira P, et al. Contribution of IL-17–producing γδ T cells to the efficacy of anticancer chemotherapy. The Journal of Experimental Medicine [Internet]. 2011 Mar [cited 2020 Feb 23];208(3):491–503. Available from: https://rupress.org/jem/article/208/3/491/41042/Contribution-of-IL17producing-%CE%B3%CE%B4-T-cells-to-the
111. Welt A, Wiesweg M, Theurer S, Abenhardt W, Groschek M, Müller L, et al. Buparlisib in combination with tamoxifen in pretreated patients with hormone receptor-positive, HER2-negative advanced breast cancer molecularly stratified for PIK3CA mutations and loss of PTEN expression. Cancer Med. 2020 Jul;9(13):4527–39.
112. Campone M, Im S-A, Iwata H, Clemons M, Ito Y, Awada A, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant for postmenopausal, hormone receptor-positive, human epidermal growth factor receptor 2-negative, advanced breast cancer: Overall survival results from BELLE-2. European Journal of Cancer [Internet]. 2018 Nov [cited 2021 Oct 8];103:147–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0959804918311122
113. Di Leo A, Johnston S, Lee KS, Ciruelos E, Lønning PE, Janni W, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology [Internet]. 2018 Jan [cited 2021 Jan 7];19(1):87–100. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204517306885
114. Baselga J, Im S-A, Iwata H, Cortés J, De Laurentiis M, Jiang Z, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology [Internet]. 2017 Jul [cited 2022 Mar 6];18(7):904–16. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204517303765
115. Martín M, Chan A, Dirix L, O'Shaughnessy J, Hegg R, Manikhas A, et al. A randomized adaptive phase II/III study of buparlisib, a pan-class I PI3K inhibitor, combined with paclitaxel for the treatment of HER2– advanced breast cancer (BELLE-4). Annals of Oncology [Internet]. 2017 Feb [cited 2021 Oct 8];28(2):313–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753419322094
116. Garrido-Castro AC, Saura C, Barroso-Sousa R, Guo H, Ciruelos E, Bermejo B, et al. Phase 2 study of buparlisib (BKM120), a pan-class I PI3K inhibitor, in patients with metastatic

triple-negative breast cancer. Breast Cancer Res [Internet]. 2020 Dec [cited 2021 Oct 9];22(1):120. Available from: https://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-020-01354-y
117. Saura C, Bendell J, Jerusalem G, Su S, Ru Q, De Buck S, et al. Phase Ib Study of Buparlisib plus Trastuzumab in Patients with HER2-Positive Advanced or Metastatic Breast Cancer That Has Progressed on Trastuzumab-Based Therapy. Clin Cancer Res [Internet]. 2014 Apr 1 [cited 2021 Oct 10];20(7):1935–45. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-13-1070
118. Pistilli B, Pluard T, Urruticoechea A, Farci D, Kong A, Bachelot T, et al. Phase II study of buparlisib (BKM120) and trastuzumab in patients with HER2+ locally advanced or metastatic breast cancer resistant to trastuzumab-based therapy. Breast Cancer Res Treat [Internet]. 2018 Apr [cited 2021 Oct 10];168(2):357–64. Available from: http://link.springer.com/10.1007/s10549-017-4596-7
119. Guerin M, Rezai K, Isambert N, Campone M, Autret A, Pakradouni J, et al. PIKHER2: A phase IB study evaluating buparlisib in combination with lapatinib in trastuzumab-resistant HER2-positive advanced breast cancer. European Journal of Cancer [Internet]. 2017 Nov [cited 2021 Oct 11];86:28–36. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0959804917312509
120. Loibl S, de la Pena L, Nekljudova V, Zardavas D, Michiels S, Denkert C, et al. Neoadjuvant buparlisib plus trastuzumab and paclitaxel for women with HER2+ primary breast cancer: A randomised, double-blind, placebo-controlled phase II trial (NeoPHOEBE). European Journal of Cancer [Internet]. 2017 Nov [cited 2021 Oct 11];85:133–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0959804917312443
121. Folkes AJ, Ahmadi K, Alderton WK, Alix S, Baker SJ, Box G, et al. The Identification of 2-(1 *H* -Indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2- *d*]pyrimidine (GDC-0941) as a Potent, Selective, Orally Bioavailable Inhibitor of Class I PI3 Kinase for the Treatment of Cancer. J Med Chem [Internet]. 2008 Sep 25 [cited 2022 Feb 14];51(18):5522–32. Available from: https://pubs.acs.org/doi/10.1021/jm800295d
122. Yang W, Hosford SR, Dillon LM, Shee K, Liu SC, Bean JR, et al. Strategically Timing Inhibition of Phosphatidylinositol 3-Kinase to Maximize Therapeutic Index in Estrogen Receptor Alpha–Positive, *PIK3CA* -Mutant Breast Cancer. Clin Cancer Res [Internet]. 2016 May 1 [cited 2022 Feb 14];22(9):2250–60. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-15-2276
123. Zheng J, Zou X, Yao J. The Antitumor Effect of GDC-0941 Alone and in Combination with Rapamycin in Breast Cancer Cells. Chemotherapy [Internet]. 2012 [cited 2022 Feb 14];58(4):273–81. Available from: https://www.karger.com/Article/FullText/341812
124. Wallin JJ, Guan J, Prior WW, Lee LB, Berry L, Belmont LD, et al. GDC-0941, a Novel Class I Selective PI3K Inhibitor, Enhances the Efficacy of Docetaxel in Human Breast Cancer Models by Increasing Cell Death *In Vitro* and *In Vivo*. Clin Cancer Res [Internet]. 2012 Jul 15 [cited 2021 Oct 11];18(14):3901–11. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-11-2088
125. Sarker D, Ang JE, Baird R, Kristeleit R, Shah K, Moreno V, et al. First-in-Human Phase I Study of Pictilisib (GDC-0941), a Potent Pan–Class I Phosphatidylinositol-3-Kinase (PI3K) Inhibitor, in Patients with Advanced Solid Tumors. Clin Cancer Res [Internet]. 2015 Jan 1 [cited 2021 Oct 11];21(1):77–86. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-14-0947

126. Schöffski P, Cresta S, Mayer IA, Wildiers H, Damian S, Gendreau S, et al. A phase Ib study of pictilisib (GDC-0941) in combination with paclitaxel, with and without bevacizumab or trastuzumab, and with letrozole in advanced breast cancer. Breast Cancer Res [Internet]. 2018 Dec [cited 2021 Oct 11];20(1):109. Available from: https://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-018-1015-x
127. Krop IE, Mayer IA, Ganju V, Dickler M, Johnston S, Morales S, et al. Pictilisib for oestrogen receptor-positive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Oncology [Internet]. 2016 Jun [cited 2021 Oct 11];17(6):811–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204516001066
128. Vuylsteke P, Huizing M, Petrakova K, Roylance R, Laing R, Chan S, et al. Pictilisib PI3Kinase inhibitor (a phosphatidylinositol 3-kinase [PI3K] inhibitor) plus paclitaxel for the treatment of hormone receptor-positive, HER2-negative, locally recurrent, or metastatic breast cancer: interim analysis of the multicentre, placebo-controlled, phase II randomised PEGGY study. Annals of Oncology [Internet]. 2016 Nov [cited 2021 Oct 16];27(11):2059–66. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753419358375
129. Schmid P, Pinder SE, Wheatley D, Macaskill J, Zammit C, Hu J, et al. Phase II Randomized Preoperative Window-of-Opportunity Study of the PI3K Inhibitor Pictilisib Plus Anastrozole Compared With Anastrozole Alone in Patients With Estrogen Receptor–Positive Breast Cancer. JCO [Internet]. 2016 Jun 10 [cited 2021 Oct 16];34(17):1987–94. Available from: https://ascopubs.org/doi/10.1200/JCO.2015.63.9179
130. Schmid P, Pinder S, Wheatley D, Zummit C, Macaskill E, Hu J, et al. Abstract P2-08-02: Interaction of PIK3CA mutation subclasses with response to preoperative treatment with the PI3K inhibitor pictilisib in patients with estrogen receptor-positive breast cancer. In: Poster Session Abstracts [Internet]. American Association for Cancer Research; 2019 [cited 2021 Oct 16]. p. P2-08-02-P2-08–02. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.SABCS18-P2-08-02
131. Han N, Jiang Y, Gai Y, Liu Q, Yuan L, Wang Y, et al. 11 C-Labeled Pictilisib (GDC-0941) as a Molecular Tracer Targeting Phosphatidylinositol 3-Kinase (PI3K) for Breast Cancer Imaging. Contrast Media & Molecular Imaging [Internet]. 2019 Nov 3 [cited 2021 Oct 16];2019:1–11. Available from: https://www.hindawi.com/journals/cmmi/2019/1760184
132. Altine B, Gai Y, Han N, Jiang Y, Ji H, Fang H, et al. Preclinical Evaluation of a Fluorine-18 (^{18} F)-Labeled Phosphatidylinositol 3-Kinase Inhibitor for Breast Cancer Imaging. Mol Pharmaceutics [Internet]. 2019 Nov 4 [cited 2021 Oct 16];16(11):4563–71. Available from: https://pubs.acs.org/doi/10.1021/acs.molpharmaceut.9b00690
133. Scott WJ, Hentemann MF, Rowley RB, Bull CO, Jenkins S, Bullion AM, et al. Discovery and SAR of Novel 2,3-Dihydroimidazo[1,2- *c*]quinazoline PI3K Inhibitors: Identification of Copanlisib (BAY 80-6946). ChemMedChem [Internet]. 2016 Jul 19 [cited 2022 Feb 14];11(14):1517–30. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cmdc.201600148
134. Glaeske S, Huebner F, Anurin A, Janzer A, Zitzmann-Kolbe S, Paul J, et al. Abstract LB-123: Pulsatile inhibition of PI3K converts immune suppression by T $_{reg}$ s and M2-TAM to anti-tumor immune response in animal models insensitive or resistant to the monotherapies of PI3K and checkpoint inhibitors. In: Immunology [Internet]. American Association for Cancer Research; 2018 [cited 2022 Feb 14]. p. LB-123-LB-123. Available

from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.AM2018-LB-123
135. Patnaik A, Appleman LJ, Tolcher AW, Papadopoulos KP, Beeram M, Rasco DW, et al. First-in-human phase I study of copanlisib (BAY 80-6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas. Annals of Oncology [Internet]. 2016 Oct [cited 2022 Feb 14];27(10):1928–40. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753419359113
136. Ramanathan RK, Von Hoff DD, Eskens F, Blumenschein G, Richards D, Genvresse I, et al. Phase Ib Trial of the PI3K Inhibitor Copanlisib Combined with the Allosteric MEK Inhibitor Refametinib in Patients with Advanced Cancer. Targ Oncol [Internet]. 2020 Apr [cited 2022 Feb 14];15(2):163–74. Available from: https://link.springer.com/10.1007/s11523-020-00714-0
137. Keegan NM, Furney SJ, Walshe JM, Gullo G, Kennedy MJ, Smith D, et al. Phase Ib Trial of Copanlisib, A Phosphoinositide-3 Kinase (PI3K) Inhibitor, with Trastuzumab in Advanced Pre-Treated HER2-Positive Breast Cancer "PantHER." Cancers [Internet]. 2021 Mar 11 [cited 2021 Nov 28];13(6):1225. Available from: https://www.mdpi.com/2072-6694/13/6/1225
138. Heffron TP, Wei B, Olivero A, Staben ST, Tsui V, Do S, et al. Rational Design of Phosphoinositide 3-Kinase α Inhibitors That Exhibit Selectivity over the Phosphoinositide 3-Kinase β Isoform. J Med Chem [Internet]. 2011 Nov 24 [cited 2022 Feb 17];54(22):7815–33. Available from: https://pubs.acs.org/doi/10.1021/jm2007084
139. Furet P, Guagnano V, Fairhurst RA, Imbach-Weese P, Bruce I, Knapp M, et al. Discovery of NVP-BYL719 a potent and selective phosphatidylinositol-3 kinase alpha inhibitor selected for clinical evaluation. Bioorganic & Medicinal Chemistry Letters [Internet]. 2013 Jul [cited 2022 Feb 14];23(13):3741–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0960894X13005908
140. Fritsch C, Pfister E, Ebel N, Guthy D, Schnell C, Hofmann F. Abstract 3934: Determination of the PI3Kα selective inhibitor alpelisib mechanism of action and efficacy in ER+/ PIK3CA mutant breast cancer preclinical models. In: Experimental and Molecular Therapeutics [Internet]. American Association for Cancer Research; 2018 [cited 2022 Feb 14]. p. 3934–3934. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.AM2018-3934
141. O'Brien NA, Conklin D, Luo T, Ayala R, Issakhanian S, Kalous O, et al. Abstract 4150: Anti-tumor activity of the PI3K/mTOR pathway inhibitors alpelisib (BYL719) and everolimus (RAD001) in xenograft models of acquired resistance to CDK-4/6 targeted therapy. In: Experimental and Molecular Therapeutics [Internet]. American Association for Cancer Research; 2017 [cited 2022 Feb 14]. p. 4150–4150. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.AM2017-4150
142. Zhang C, Xu B, Liu P. Addition of the p110α inhibitor BYL719 overcomes targeted therapy resistance in cells from Her2-positive-PTEN-loss breast cancer. Tumor Biol [Internet]. 2016 Nov [cited 2022 Feb 15];37(11):14831–9. Available from: http://link.springer.com/10.1007/s13277-016-5381-7
143. Yuan Y, Wen W, Yost SE, Xing Q, Yan J, Han ES, et al. Combination therapy with BYL719 and LEE011 is synergistic and causes a greater suppression of p-S6 in triple negative breast cancer. Sci Rep [Internet]. 2019 Dec [cited 2022 Feb 15];9(1):7509. Available from: http://www.nature.com/articles/s41598-019-43429-7

144. Fritsch C, Huang A, Chatenay-Rivauday C, Schnell C, Reddy A, Liu M, et al. Characterization of the Novel and Specific PI3Kα Inhibitor NVP-BYL719 and Development of the Patient Stratification Strategy for Clinical Trials. Mol Cancer Ther [Internet]. 2014 May [cited 2020 Dec 14];13(5):1117–29. Available from: http://mct.aacrjournals.org/lookup/doi/10.1158/1535-7163.MCT-13-0865
145. Jacquemetton J, Kassem L, Poulard C, Dahmani A, De Plater L, Montaudon E, et al. Analysis of genomic and non-genomic signaling of estrogen receptor in PDX models of breast cancer treated with a combination of the PI3K inhibitor alpelisib (BYL719) and fulvestrant. Breast Cancer Res [Internet]. 2021 Dec [cited 2022 Feb 14];23(1):57. Available from: https://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-021-01433-8
146. Juric D, Rodon J, Tabernero J, Janku F, Burris HA, Schellens JHM, et al. Phosphatidylinositol 3-Kinase α–Selective Inhibition With Alpelisib (BYL719) in *PIK3CA* -Altered Solid Tumors: Results From the First-in-Human Study. JCO [Internet]. 2018 May 1 [cited 2020 Dec 22];36(13):1291–9. Available from: https://ascopubs.org/doi/10.1200/JCO.2017.72.7107
147. Baselga J, Curigliano G, Martín M, André F, Beck JT, Tortora G, et al. Abstract CT061: A phase Ib study of alpelisib (BYL719) + everolimus ± exemestane in patients with advanced solid tumors or HR+/HER2-breast cancer. In: Clinical Trials [Internet]. American Association for Cancer Research; 2016 [cited 2022 Feb 17]. p. CT061–CT061. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.AM2016-CT061
148. Curigliano G, Martin M, Jhaveri K, Beck JT, Tortora G, Fazio N, et al. Alpelisib in combination with everolimus ± exemestane in solid tumours: Phase Ib randomised, open-label, multicentre study. European Journal of Cancer [Internet]. 2021 Jul [cited 2022 Feb 17];151:49–62. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0959804921002094
149. Jhaveri K, Juric D, Yap Y-S, Cresta S, Layman RM, Duhoux FP, et al. A Phase I Study of LSZ102, an Oral Selective Estrogen Receptor Degrader, with or without Ribociclib or Alpelisib, in Patients with Estrogen Receptor–Positive Breast Cancer. Clin Cancer Res [Internet]. 2021 Nov 1 [cited 2021 Nov 28];27(21):5760–70. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-21-1095
150. Mayer IA, Abramson VG, Formisano L, Balko JM, Estrada MV, Sanders ME, et al. A Phase Ib Study of Alpelisib (BYL719), a PI3Kα-Specific Inhibitor, with Letrozole in ER^{+}/$HER2^{-}$ Metastatic Breast Cancer. Clin Cancer Res [Internet]. 2017 Jan 1 [cited 2020 Nov 14];23(1):26–34. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-16-0134
151. Juric D, Janku F, Rodón J, Burris HA, Mayer IA, Schuler M, et al. Alpelisib Plus Fulvestrant in *PIK3CA* -Altered and *PIK3CA* -Wild-Type Estrogen Receptor–Positive Advanced Breast Cancer: A Phase 1b Clinical Trial. JAMA Oncol [Internet]. 2019 Feb 14 [cited 2020 Nov 14];5(2):e184475. Available from: http://oncology.jamanetwork.com/article.aspx?doi=10.1001/jamaoncol.2018.4475
152. Lu Y-S, Lee KS, Chao T-Y, Tseng L-M, Chitapanarux I, Chen S-C, et al. A Phase Ib Study of Alpelisib or Buparlisib Combined with Tamoxifen Plus Goserelin in Premenopausal Women with HR-Positive HER2-Negative Advanced Breast Cancer. Clin Cancer Res [Internet]. 2021 Jan 15 [cited 2021 Oct 22];27(2):408–17. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-20-1008

153. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for *PIK3CA* -Mutated, Hormone Receptor–Positive Advanced Breast Cancer. N Engl J Med [Internet]. 2019 May 16 [cited 2020 Nov 14];380(20):1929–40. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1813904
154. Rugo HS, André F, Yamashita T, Cerda H, Toledano I, Stemmer SM, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. Annals of Oncology [Internet]. 2020 Aug [cited 2022 Mar 3];31(8):1001–10. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753420397982
155. Ciruelos EM, Rugo HS, Mayer IA, Levy C, Forget F, Delgado Mingorance JI, et al. Patient-Reported Outcomes in Patients With *PIK3CA* -Mutated Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer From SOLAR-1. JCO [Internet]. 2021 Jun 20 [cited 2022 Mar 3];39(18):2005–15. Available from: https://ascopubs.org/doi/10.1200/JCO.20.01139
156. Rugo HS, Lerebours F, Ciruelos E, Drullinsky P, Ruiz-Borrego M, Neven P, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. The Lancet Oncology [Internet]. 2021 Apr [cited 2021 Oct 22];22(4):489–98. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204521000346
157. Juric D, Turner N, Prat A, Chia S, Ciruelos E. Abstract P5-13-03: Alpelisib + endocrine therapy (ET) in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2- negative (HER2–), PIK3CA-mutated advanced breast cancer (ABC) previously treated with cyclin-dependent kinase 4/6 inhibitor (CDK4/6i): Biomarker analyses from the Phase II BYLieve study. San Antonio Breast Cancer Symposium 2021. 2021 Dec 7;
158. Chia S, Ciruelos E, Rugo H, Lerebours F. Abstract P1-18-08: Effect of Duration of Prior Cyclin-Dependent Kinase 4/6 Inhibitor (CDK4/6i) Therapy (≤6 mo or >6 mo) on Alpelisib Benefit in Patients With Hormone Receptor- Positive (HR+), Human Epidermal Growth Factor Receptor 2-Negative (HER2–), PIK3CA-Mutated Advanced Breast Cancer (ABC) From BYLieve. San Antonio Breast Cancer Symposium 2021. 2021 Dec 7;(P1-18–08).
159. Bello D, Bertucci A, De La Motte Rouge T, Blonz C, Akla S, Grenier J, et al. Alpelisib and fulvestrant efficacy in HR-positive HER2-negative *PIK3CA* -mutant advanced breast cancer: Data from the French early access program. JCO [Internet]. 2021 May 20 [cited 2021 Oct 22];39(15_suppl):1064–1064. Available from: https://ascopubs.org/doi/10.1200/JCO.2021.39.15_suppl.1064
160. Mayer IA, Prat A, Egle D, Blau S, Fidalgo JAP, Gnant M, et al. A Phase II Randomized Study of Neoadjuvant Letrozole Plus Alpelisib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer (NEO-ORB). Clin Cancer Res [Internet]. 2019 May 15 [cited 2021 Oct 22];25(10):2975–87. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-18-3160
161. André F, Goncalves A, Filleron T, Dalenc F. Clinical utility of molecular tumor profiling: Results from the randomized trial SAFIR01-BREAST. Presented at SABCS 2021. 2021 Dec 7;
162. Sharma P, Abramson VG, O'Dea A, Nye L, Mayer I, Pathak HB, et al. Clinical and Biomarker Results from Phase I/II Study of PI3K Inhibitor Alpelisib plus Nab-paclitaxel in HER2-Negative Metastatic Breast Cancer. Clin Cancer Res [Internet]. 2021 Jul 15 [cited

2021 Oct 22];27(14):3896–904. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-20-4879
163. Sharma P, Farooki A, Fasching PA, Loi S, Peterson K, Prat A, et al. 349TiP EPIK-B3: A phase III, randomised, double-blind (DB), placebo (PBO)-controlled study of alpelisib (ALP) + nab-paclitaxel (nab-PTX) in advanced triple-negative breast cancer (TNBC) with either PIK3CA mutation or phosphatase and tensin homolog (PTEN) loss without PIK3CA mutation. Annals of Oncology [Internet]. 2020 Sep [cited 2021 Oct 22];31:S387–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753420404478
164. Damodaran S, Litton JK, Hess KR, Eppig CT, Grzegorzewski KJ, Meric-Bernstam F, et al. Abstract OT2-06-01: A phase-2 trial of neoadjuvant alpelisib and nab-paclitaxel in anthracycline refractory triple negative breast cancers with PIK3CA or PTEN alterations. In: Ongoing Clinical Trials [Internet]. American Association for Cancer Research; 2020 [cited 2021 Oct 25]. p. OT2-06-01-OT2-06–01. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.SABCS19-OT2-06-01
165. Jain S, Shah AN, Santa-Maria CA, Siziopikou K, Rademaker A, Helenowski I, et al. Phase I study of alpelisib (BYL-719) and trastuzumab emtansine (T-DM1) in HER2-positive metastatic breast cancer (MBC) after trastuzumab and taxane therapy. Breast Cancer Res Treat [Internet]. 2018 Sep [cited 2020 Nov 14];171(2):371–81. Available from: http://link.springer.com/10.1007/s10549-018-4792-0
166. Jhaveri K, Drago JZ, Shah PD, Wang R, Pareja F, Ratzon F, et al. A Phase I Study of Alpelisib in Combination with Trastuzumab and LJM716 in Patients with *PIK3CA* -Mutated HER2-Positive Metastatic Breast Cancer. Clin Cancer Res [Internet]. 2021 Jul 15 [cited 2021 Oct 25];27(14):3867–75. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-21-0047
167. Hurvitz SA, Chia SKL, Ciruelos EM, Hu X, Im S-A, Janni W, et al. 352TiP EPIK-B2: A phase III study of alpelisib (ALP) as maintenance therapy with trastuzumab (T) and pertuzumab (P) in patients (pts) with PIK3CA-mutated (mut) human epidermal growth factor receptor-2–positive (HER2+) advanced breast cancer (ABC). Annals of Oncology [Internet]. 2020 Sep [cited 2022 Feb 10];31:S389–90. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753420404508
168. Sampath D, Nannini M, Jane G, Hong R, Parsons K, Belvin M, et al. Abstract P4-15-02: The PI3K inhibitor GDC-0032 enhances the efficacy of standard of care therapeutics in PI3K alpha mutant breast cancer models. In: Poster Session Abstracts [Internet]. American Association for Cancer Research; 2013 [cited 2022 Feb 17]. p. P4-15-02-P4-15–02. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/0008-5472.SABCS13-P4-15-02
169. Moore HM, Savage HM, O'Brien C, Zhou W, Sokol ES, Goldberg ME, et al. Predictive and Pharmacodynamic Biomarkers of Response to the Phosphatidylinositol 3-Kinase Inhibitor Taselisib in Breast Cancer Preclinical Models. Mol Cancer Ther [Internet]. 2020 Jan [cited 2022 Feb 17];19(1):292–303. Available from: http://mct.aacrjournals.org/lookup/doi/10.1158/1535-7163.MCT-19-0284
170. Juric D, Krop I, Ramanathan RK, Wilson TR, Ware JA, Sanabria Bohorquez SM, et al. Phase I Dose-Escalation Study of Taselisib, an Oral PI3K Inhibitor, in Patients with Advanced Solid Tumors. Cancer Discov [Internet]. 2017 Jul [cited 2021 Oct 25];7(7):704–15. Available from: http://cancerdiscovery.aacrjournals.org/lookup/doi/10.1158/2159-8290.CD-16-1080
171. Jhaveri K, Chang MT, Juric D, Saura C, Gambardella V, Melnyk A, et al. Phase I Basket

Study of Taselisib, an Isoform-Selective PI3K Inhibitor, in Patients with *PIK3CA* -Mutant Cancers. Clin Cancer Res [Internet]. 2021 Jan 15 [cited 2021 Oct 25];27(2):447–59. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-20-2657

172. Baird RD, van Rossum AGJ, Oliveira M, Beelen K, Gao M, Schrier M, et al. POSEIDON Trial Phase 1b Results: Safety, Efficacy and Circulating Tumor DNA Response of the Beta Isoform-Sparing PI3K Inhibitor Taselisib (GDC-0032) Combined with Tamoxifen in Hormone Receptor Positive Metastatic Breast Cancer Patients. Clin Cancer Res [Internet]. 2019 Nov 15 [cited 2022 Feb 10];25(22):6598–605. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-19-0508
173. Abramson VG, Oliveira M, Cervantes A, Wildiers H, Patel MR, Bauer TM, et al. A phase Ib, open-label, dose-escalation study of the safety and pharmacology of taselisib (GDC-0032) in combination with either docetaxel or paclitaxel in patients with HER2-negative, locally advanced, or metastatic breast cancer. Breast Cancer Res Treat [Internet]. 2019 Nov [cited 2022 Feb 17];178(1):121–33. Available from: http://link.springer.com/10.1007/s10549-019-05360-3
174. Saura C, Sachdev J, Patel MR, Cervantes A, Juric D, Infante JR, et al. Abstract PD5-2: Ph1b study of the PI3K inhibitor taselisib (GDC-0032) in combination with letrozole in patients with hormone receptor-positive advanced breast cancer. In: Poster Discussion Abstracts [Internet]. American Association for Cancer Research; 2015 [cited 2021 Oct 25]. p. PD5-2-PD5-2. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.SABCS14-PD5-2
175. Saura C, Hlauschek D, Oliveira M, Zardavas D, Jallitsch-Halper A, de la Peña L, et al. Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with oestrogen receptor-positive, HER2-negative, early-stage breast cancer (LORELEI): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Oncology [Internet]. 2019 Sep [cited 2021 Oct 25];20(9):1226–38. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204519303341
176. Dickler M, Saura C, Oliveira M, Richards D, Krop I, Cervantes A, et al. Abstract P6-12-01: Phase II study of taselisib (GDC-0032) plus fulvestrant in HER2-negative, hormone receptor-positive advanced breast cancer: Analysis by *PIK3CA* and *ESR1* mutation status from circulating tumor DNA. In: Poster Session Abstracts [Internet]. American Association for Cancer Research; 2017 [cited 2021 Oct 25]. p. P6-12-01-P6-12–01. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.SABCS16-P6-12-01
177. Dickler MN, Saura C, Richards DA, Krop IE, Cervantes A, Bedard PL, et al. Phase II Study of Taselisib (GDC-0032) in Combination with Fulvestrant in Patients with HER2-Negative, Hormone Receptor–Positive Advanced Breast Cancer. Clin Cancer Res [Internet]. 2018 Sep 15 [cited 2021 Oct 25];24(18):4380–7. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-18-0613
178. Dent S, J. C, Im Y-H, Diéras V, Harbeck N, Krop IE, et al. Phase III randomized study of taselisib or placebo with fulvestrant in estrogen receptor-positive, PIK3CA-mutant, HER2-negative, advanced breast cancer: the SANDPIPER trial. Annals of Oncology [Internet]. 2021 Feb [cited 2021 Nov 7];32(2):197–207. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753420431242
179. Oliveira M, Baird RD, Voorthuis RAB, De Boo L, van Rossum AGJ, Garrigos Cubells L, et al. LBA18 POSEIDON randomized phase II trial: Tamoxifen (TAM) + taselisib or placebo

(PLA) in patients (pts) with hormone receptor positive (HR+)/HER2- metastatic breast cancer (MBC). Annals of Oncology [Internet]. 2021 Sep [cited 2022 Feb 10];32:S1291–2. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753421043957

180. Lehmann BD, Abramson VG, Sanders ME, Mayer EL, Haddad TC, Nanda R, et al. TBCRC 032 IB/II Multicenter Study: Molecular Insights to AR Antagonist and PI3K Inhibitor Efficacy in Patients with AR $^{+}$ Metastatic Triple-Negative Breast Cancer. Clin Cancer Res [Internet]. 2020 May 1 [cited 2022 Feb 10];26(9):2111–23. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-19-2170
181. Metzger Filho O, Goel S, Barry WT, Hamilton EP, Tolaney SM, Yardley DA, et al. A mouse-human phase I co-clinical trial of taselisib in combination with TDM1 in advanced HER2-positive breast cancer (MBC). JCO [Internet]. 2017 May 20 [cited 2021 Nov 7];35(15_suppl):1030–1030. Available from: http://ascopubs.org/doi/10.1200/JCO.2017.35.15_suppl.1030
182. Song KW, Edgar KA, Hanan EJ, Hafner M, Oeh J, Merchant M, et al. RTK-dependent inducible degradation of mutant PI3Kα drives GDC-0077 (Inavolisib) efficacy [Internet]. Cancer Biology; 2021 May [cited 2021 Nov 7]. Available from: http://biorxiv.org/lookup/doi/10.1101/2021.05.12.442687
183. Juric D, Kalinsky K, Oliveira M, Cervantes A, Bedard P, Krop I, et al. Abstract OT1-08-04: A first-in-human phase Ia dose escalation study of GDC-0077, a p110a-selective and mutant-degrading PI3K inhibitor, in patients with *PIK3CA* -mutant solid tumors. In: Ongoing Clinical Trials [Internet]. American Association for Cancer Research; 2020 [cited 2021 Nov 8]. p. OT1-08-04-OT1-08–04. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.SABCS19-OT1-08-04
184. Kalinsky K, Juric D, Bedard PL, Oliveira M, Cervantes A, Hamilton E, et al. Abstract CT109: A phase I/Ib study evaluating GDC-0077 plus fulvestrant in patients with *PIK3CA* -mutant, hormone receptor-positive/HER2-negative breast cancer. In: Tumor Biology [Internet]. American Association for Cancer Research; 2020 [cited 2021 Nov 8]. p. CT109–CT109. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.AM2020-CT109
185. Bedard PL, Jhaveri K, Cervantes A, Gambardella V, Hamilton E, Italiano A, et al. Abstract PD1-02: A phase I/Ib study evaluating GDC-0077 + palbociclib (palbo) + fulvestrant in patients (pts) with *PIK3CA* -mutant (mut), hormone receptor-positive/HER2-negative metastatic breast cancer (HR+/HER2- mBC). In: Poster Spotlight Session Abstracts [Internet]. American Association for Cancer Research; 2021 [cited 2021 Nov 8]. p. PD1-02-PD1-02. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.SABCS20-PD1-02
186. Juric D, de Bono JS, LoRusso PM, Nemunaitis J, Heath EI, Kwak EL, et al. A First-in-Human, Phase I, Dose-Escalation Study of TAK-117, a Selective PI3Kα Isoform Inhibitor, in Patients with Advanced Solid Malignancies. Clin Cancer Res [Internet]. 2017 Sep 1 [cited 2021 Nov 17];23(17):5015–23. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-16-2888
187. Hernández-Prat A, Rodriguez-Vida A, Juanpere-Rodero N, Arpi O, Menéndez S, Soria-Jiménez L, et al. Novel Oral mTORC1/2 Inhibitor TAK-228 Has Synergistic Antitumor Effects When Combined with Paclitaxel or PI3Kα Inhibitor TAK-117 in Preclinical Bladder Cancer Models. Mol Cancer Res [Internet]. 2019 Sep [cited 2021 Nov 17];17(9):1931–44. Available from: http://mcr.aacrjournals.org/lookup/doi/10.1158/1541-7786.MCR-18-0923

188. Starks D, Rojas-Espaillat LA, Dey N, De P, Leyland-Jones B, Williams CB. Final results of phase 1 evaluation of the safety and clinical activity of sapanisertib in combination with serabelisib and paclitaxel in patients with advanced ovarian, endometrial, or breast cancer. JCO [Internet]. 2021 May 20 [cited 2021 Nov 17];39(15_suppl):5569–5569. Available from: https://ascopubs.org/doi/10.1200/JCO.2021.39.15_suppl.5569
189. O'Shaughnessy J, Rodriguez ESR, Ontiveros P, Wenstrup R, Pramparo T, Lang J, et al. Abstract PS11-25: Pilot trial of priming with oral TAK-228 and TAK-117 (PIKTOR) to increase DNA damage repair deficiency (DDRD) followed by cisplatin (cis) and nab paclitaxel (nab pac) in chemotherapy-pretreated metastatic triple negative breast cancer (metTNBC) pts. In: Poster Session Abstracts [Internet]. American Association for Cancer Research; 2021 [cited 2021 Nov 26]. p. PS11-25-PS11-25. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.SABCS20-PS11-25
190. Han Y, Wang J, Wang Z, Xu B. Comparative efficacy and safety of CDK4/6 and PI3K/AKT/mTOR inhibitors in women with hormone receptor-positive, HER2-negative metastatic breast cancer: a systematic review and network meta-analysis. Current Problems in Cancer [Internet]. 2020 Dec [cited 2021 Nov 26];44(6):100606. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0147027220300933
191. Leung JH, Leung HWC, Wang S-Y, Huang S-S, Chan ALF. Efficacy and safety of CDK4/6 and PI3K/AKT/mTOR inhibitors as second-line treatment in postmenopausal patients with hormone receptor-positive, HER-2-negative metastatic breast cancer: a network meta-analysis. Expert Opinion on Drug Safety [Internet]. 2021 Aug 3 [cited 2021 Oct 11];20(8):949–57. Available from: https://www.tandfonline.com/doi/full/10.1080/14740338.2021.1931116
192. O'Brien NA, Tomaso ED, Ayala R, Tong L, Issakhanian S, Linnartz R, et al. Abstract 4756: In vivo efficacy of combined targeting of CDK4/6, ER and PI3K signaling in ER+ breast cancer. In: Endocrinology [Internet]. American Association for Cancer Research; 2014 [cited 2021 Nov 26]. p. 4756–4756. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.AM2014-4756
193. Asghar US, Barr AR, Cutts R, Beaney M, Babina I, Sampath D, et al. Single-Cell Dynamics Determines Response to CDK4/6 Inhibition in Triple-Negative Breast Cancer. Clin Cancer Res [Internet]. 2017 Sep 15 [cited 2021 Nov 26];23(18):5561–72. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-17-0369
194. Tolaney SM, Im Y-H, Calvo E, Lu Y-S, Hamilton E, Forero-Torres A, et al. Phase Ib Study of Ribociclib plus Fulvestrant and Ribociclib plus Fulvestrant plus PI3K Inhibitor (Alpelisib or Buparlisib) for HR $^{+}$ Advanced Breast Cancer. Clin Cancer Res [Internet]. 2021 Jan 15 [cited 2021 Nov 26];27(2):418–28. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-20-0645
195. Juric D, Ismail-Khan R, Campone M, García-Estévez L, Becerra C, De Boer R, et al. Abstract P3-14-01: Phase Ib/II study of ribociclib and alpelisib and letrozole in ER+, HER2– breast cancer: Safety, preliminary efficacy and molecular analysis. In: Poster Session Abstracts [Internet]. American Association for Cancer Research; 2016 [cited 2021 Nov 26]. p. P3-14-01-P3-14–01. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/1538-7445.SABCS15-P3-14-01
196. Pascual J, Lim JSJ, Macpherson IR, Armstrong AC, Ring A, Okines AFC, et al. Triplet Therapy with Palbociclib, Taselisib, and Fulvestrant in *PIK3CA* -Mutant Breast Cancer and Doublet Palbociclib and Taselisib in Pathway-Mutant Solid Cancers. Cancer Discov [Internet]. 2021 Jan [cited 2021 Dec 11];11(1):92–107. Available from:

http://cancerdiscovery.aacrjournals.org/lookup/doi/10.1158/2159-8290.CD-20-0553
197. Teo ZL, Versaci S, Dushyanthen S, Caramia F, Savas P, Mintoff CP, et al. Combined CDK4/6 and PI3Kα Inhibition Is Synergistic and Immunogenic in Triple-Negative Breast Cancer. Cancer Res [Internet]. 2017 Nov 15 [cited 2021 Nov 28];77(22):6340–52. Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/0008-5472.CAN-17-2210
198. Agostinetto E, Debien V, Marta GN, Lambertini M, Piccart-Gebhart M, de Azambuja E. CDK4/6 and PI3K inhibitors: A new promise for patients with HER2-positive breast cancer. Eur J Clin Invest [Internet]. 2021 Jul [cited 2021 Dec 11];51(7). Available from: https://onlinelibrary.wiley.com/doi/10.1111/eci.13535
199. Song JH, Singh N, Luevano LA, Padi SKR, Okumura K, Olive V, et al. Mechanisms Behind Resistance to PI3K Inhibitor Treatment Induced by the PIM Kinase. Mol Cancer Ther [Internet]. 2018 Dec [cited 2021 Dec 11];17(12):2710–21. Available from: http://mct.aacrjournals.org/lookup/doi/10.1158/1535-7163.MCT-18-0374
200. Le X, Antony R, Razavi P, Treacy DJ, Luo F, Ghandi M, et al. Systematic Functional Characterization of Resistance to PI3K Inhibition in Breast Cancer. Cancer Discov [Internet]. 2016 Oct [cited 2021 Dec 11];6(10):1134–47. Available from: http://cancerdiscovery.aacrjournals.org/lookup/doi/10.1158/2159-8290.CD-16-0305
201. Kennedy SP, O'Neill M, Cunningham D, Morris PG, Toomey S, Blanco-Aparicio C, et al. Preclinical evaluation of a novel triple-acting PIM/PI3K/mTOR inhibitor, IBL-302, in breast cancer. Oncogene [Internet]. 2020 Apr 2 [cited 2021 Dec 11];39(14):3028–40. Available from: http://www.nature.com/articles/s41388-020-1202-y
202. Litchfield LM, Boehnke K, Brahmachary M, Mur C, Bi C, Stephens JR, et al. Combined inhibition of PIM and CDK4/6 suppresses both mTOR signaling and Rb phosphorylation and potentiates PI3K inhibition in cancer cells. Oncotarget [Internet]. 2020 Apr 28 [cited 2021 Dec 11];11(17):1478–92. Available from: https://www.oncotarget.com/lookup/doi/10.18632/oncotarget.27539
203. Gómez Tejeda Zañudo J, Mao P, Alcon C, Kowalski K, Johnson GN, Xu G, et al. Cell Line-Specific Network Models of ER+ Breast Cancer Identify Potential PI3Kα Inhibitor Resistance Mechanisms and Drug Combinations. Cancer Res. 2021 Sep 1;81(17):4603–17.
204. Elkabets M, Vora S, Juric D, Morse N, Mino-Kenudson M, Muranen T, et al. mTORC1 Inhibition Is Required for Sensitivity to PI3K p110α Inhibitors in *PIK3CA* -Mutant Breast Cancer. Sci Transl Med [Internet]. 2013 Jul 31 [cited 2022 Feb 15];5(196). Available from: https://www.science.org/doi/10.1126/scitranslmed.3005747
205. Cai Y, Xu G, Wu F, Michelini F, Chan C, Qu X, et al. Genomic Alterations in PIK3CA-Mutated Breast Cancer Result in mTORC1 Activation and Limit the Sensitivity to PI3Kα Inhibitors. Cancer Res. 2021 May 1;81(9):2470–80.
206. Razavi P, Dickler MN, Shah PD, Toy W, Brown DN, Won HH, et al. Alterations in PTEN and ESR1 promote clinical resistance to alpelisib plus aromatase inhibitors. Nat Cancer. 2020 Apr;1(4):382–93.
207. Juric D, Castel P, Griffith M, Griffith OL, Won HH, Ellis H, et al. Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. Nature. 2015 Feb 12;518(7538):240–4.
208. Elkabets M, Pazarentzos E, Juric D, Sheng Q, Pelossof RA, Brook S, et al. AXL mediates resistance to PI3Kα inhibition by activating the EGFR/PKC/mTOR axis in head and neck and esophageal squamous cell carcinomas. Cancer Cell. 2015 Apr 13;27(4):533–46.
209. Rugo HS, Lacouture ME, Goncalves MD, Masharani U, Aapro MS, O'Shaughnessy JA. A

multidisciplinary approach to optimizing care of patients treated with alpelisib. Breast. 2022 Feb;61:156–67.
210. Hopkins BD, Pauli C, Du X, Wang DG, Li X, Wu D, et al. Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. Nature [Internet]. 2018 Aug [cited 2021 May 17];560(7719):499–503. Available from: http://www.nature.com/articles/s41586-018-0343-4
211. Hopkins BD, Goncalves MD, Cantley LC. Insulin–PI3K signalling: an evolutionarily insulated metabolic driver of cancer. Nature Reviews Endocrinology [Internet]. 2020 May 1;16(5):276–83. Available from: https://doi.org/10.1038/s41574-020-0329-9
212. Docherty KF, Curtain JP, Anand IS, Bengtsson O, Inzucchi SE, Køber L, et al. Effect of dapagliflozin on anaemia in DAPA-HF. Eur J Heart Fail [Internet]. 2021 Apr [cited 2021 Dec 12];23(4):617–28. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2132
213. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. The Lancet [Internet]. 2020 Sep [cited 2021 Dec 12];396(10254):819–29. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673620318249
214. Von Hoff DD, Stephenson JJ, Rosen P, Loesch DM, Borad MJ, Anthony S, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. J Clin Oncol. 2010 Nov 20;28(33):4877–83.

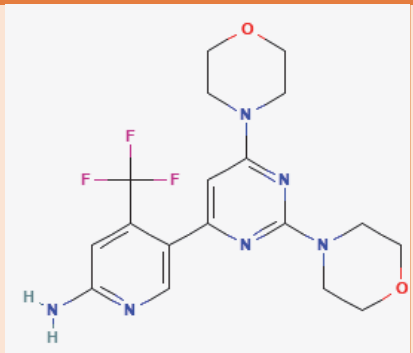
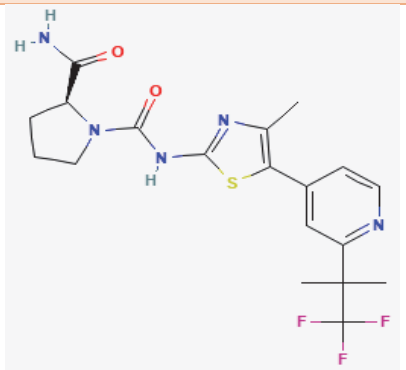
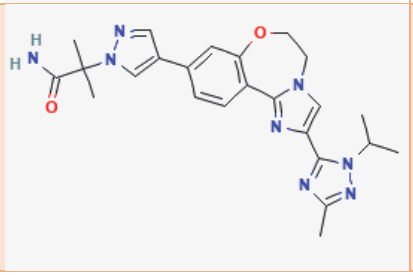
Molecule	Chemical structure	PIK3CA subunit target	Phase III	Patients	Drug	Results	Approval (FDA/EMA)
Buparlisib		Pan PI3K Inhibitor	BELLE-2 *n=1147* BELLE-3 *n=432* BELLE-4 n=416	ER-positive HER2-negative ABC pts who progressed on or after AI and a maximum of one previous line of CT ER-positive HER2- negative ABC pts who progressed on or after prior ET and mTOR inhibitors ER-positive HER2-negative ABC receiving first-line CT	Fulvestrant with buparlisib or placebo Fulvestrant with buparlisib or placebo Paclitaxel with buparlisib or placebo	mPFS 6.9m vs 5.0m HR 0.78 (95% CI 0.67–0.89, p=0·00021) mPFS 3.9m vs 1.8m HR 0.67 (95% CI 0.53–0.84, p=0·00030) mPFS 8.0m for buparlisib vs 9.2m for placebo HR 1.18 (95% CI 0.82–1.68)	No approval for this drug
Alpelisib		p110α selective PI3K inhibitor	SOLAR-1 *n=341*	ER-positive HER2-negative ABC with PIK3CA mutation and disease progression on or after prior AI	Fulvestrant with alpelisib or placebo	mPFS 11.0m for alpelisib vs 5.7m for placebo HR 0.65 (95% CI, 0.50 to 0.85; p<0.001)	FDA approval for ER-positive HER2-negative ABC PI3K-mutated who had received ET previously EMA approval for ER-positive HER2-negative ABC PI3K-mutated who had received ET alone previously
Taselisib		Dual p110α and p100δ selective PI3K inhibitor	SANDPIPER *n=631*	ER-positive HER2-negative PIK3CA mutated ABC resistant to ET	Fulvestrant with taselisib or placebo	mPFS 7.4m for taselisib vs 5.4m for placebo HR 0.70 (95% CI, 0.56-0.89 p=0.0037)	No approval for this drug

Table 1. Main PI3K inhibitor in breast cancer, chemical structure, specificity, phase III, results and approvals

FDA: food and drug administration; EMA: European medicine agency; HR: hazard ratio; ER: estrogen receptor; HER2: human epidermal receptor 2; ABC: advanced breast cancer; mPFS: median progression-free survival; CI: confidence interval; vs: versus; AI: aromatase inhibitor; ET: endocrine therapy; CT: chemotherapy

Variable	Cohort, N = 40
Age at diagnosis, years (range)	60 (37-89)
ECOG-PS	
0	9 (22,5%)
1	22 (55%)
2	9 (22,5%)
Menopause	
Yes	38 (95%)
No	2 (5%)
Nb of previous lines of treatment (either ET or CT)	
2	3 (7,5%)
3	11 (27,5%)
> 3	26 (65%)
AI	
Yes	17 (42,5%)
No	23 (57,5%)
Previous AI+CDK4/6i	
Yes	9 (22,5%)
No	31 (77,5%)
Prior fulvestrant	
Yes	30 (75%)
No	10 (25%)
Prior fulvestrant+CDK4/6i	
Yes	30 (75%)
No	10 (25%)
CT for metastatic disease	
Yes	37 (92,5%)
No	3 (7,5%)
AI+everolimus	
Yes	30 (75%)
No	10 (25%)
Adjuvant hormonotherapy	
Yes	28 (70%)
No	9 (22,5%)
NA	3 (7,5%)
Type of adjuvant hormonotherapy	
Anti-aromatase	18 (45%)
Tamoxifene	18 (45%)
Previous hormonal sensitivity in early BC (n=26)	
Sensibility	10 (38,5%)
Primary resistance	2 (7,5%)
Secondary resistance	14 (54%)
Previous hormonal sensitivity in metastatic BC	

Variable	Cohort, N = 40
Sensibility	17 (42,5%)
Resistance	23 (57,5%)
HER2 expression	
0	16 (40%)
1+	10 (25%)
2+fish-	12 (30%)
NA	2 (5%)
Dose reduction	
Yes	19 (47,5%)
No	21 (52,5%)
Transient interruption	
Yes	13 (32,5%)
No	27 (67,5%)
Reasons for definitive discontinuation	
Progression	24 (60%)
Toxicity	10 (25%)
NA	6 (15%)
Number of metastatic sites	
1	10 (25%)
2	8 (20%)
3	11 (27,5%)
4	9 (22,5%)
5	2 (5%)
Nature of metastatic site	
Lung/pleura	14 (35%)
Bone	33 (82,5%)
Liver	18 (45%)
Soft tissue	3 (7,5%)
Other	26 (65%)
Best objective response	
PD	10 (25,6%)
SD	11 (28,2%)
PR	11 (28,2%)
CR	2 (5,1%)
DR	1 (2.6%)
NA	4 (10,3%)

Table 2. Characteristics of patients in all cohort

ECOG-PS: Eastern Cooperative Oncology Group-performans status; AI: aromatase inhibitor; ET: endocrine therapy; CT: chemotherapy; CDK4/6i: CDK4/6 inhibitor; BC: breast cancer; PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response; DR: dissociative response; NA: not available.

variables	class	N	Events	median survival [CI95]	Hazard Ratio [CI95]	test	unadjusted p-value
subtype	AUTRE		1	69 [.-.]	1	Log-Rank	0.0687
	CANALAIREL		9	206 [89-.]	0.1 [0-1.2]		
	LOBULAIRE		9	147 [82-.]	0.3 [0-2.6]		
	NA's	21	-	-	-		
Her2	Her2-		10	187 [89-.]	1	Log-Rank	0.5527
	Her2+		14	124.5 [93-362]	0.8 [0.3-1.8]		
	NA's	15	-	-	-		
fulvestrant	NON		21	147 [93-206]	1	Log-Rank	0.4801
	OUI		3	226 [20-.]	0.6 [0.2-2.2]		
	NA's	14	-	-	-		
fulvestrant_CDK4/6 inhibitor	NON		4	84 [0-.]	1	Log-Rank	0.0766
	OUI		20	187 [123-245]	0.4 [0.1-1.2]		
	NA's	14	-	-	-		
hyperglycemia	NON		7	99.5 [89-.]	1	Log-Rank	0.0887
	OUI		17	189 [123-350]	0.4 [0.2-1.2]		
	NA's	14	-	-	-		
hormonosensibility	NON		12	91 [75-.]	1	Log-Rank	0.2946
	OUI		6	215 [187-.]	0.6 [0.2-1.6]		
	NA's	22	-	-	-		
PIK3CA	tumeur_primitive		5	106 [82-.]	1	Log-Rank	0.22
	sang		1	63.5 [10-.]	1 [0.1-9]		
	tumeur_metastatique		18	189 [123-334]	0.4 [0.1-1.2]		
	NA's	14	-	-	-		
CBR	non		5	93 [89-.]	1	Log-Rank	0.0047
	oui		17	189 [147-350]	0.2 [0.1-0.7]		
	NA's	16	-	-	-		
prior_fulvestrant	NON		4	84 [0-.]	1	Log-Rank	0.0766
	OUI		20	187 [123-245]	0.4 [0.1-1.2]		
	NA's	14	-	-	-		

Table 3. Univariate analysis of progression free survival

CBR: clinical benefice rate (CBR= complete response + partial response + stable disease)

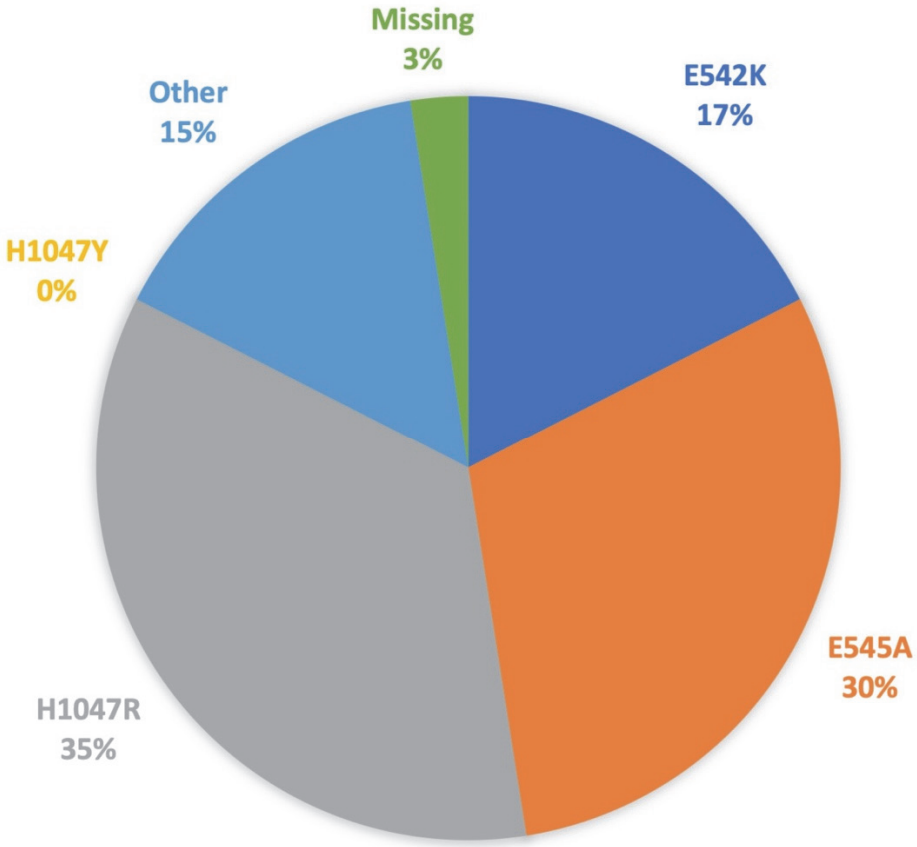


Figure 1. Differents PIK3CA mutations
E542K and E545A: exon 9
H1047R: exon 20

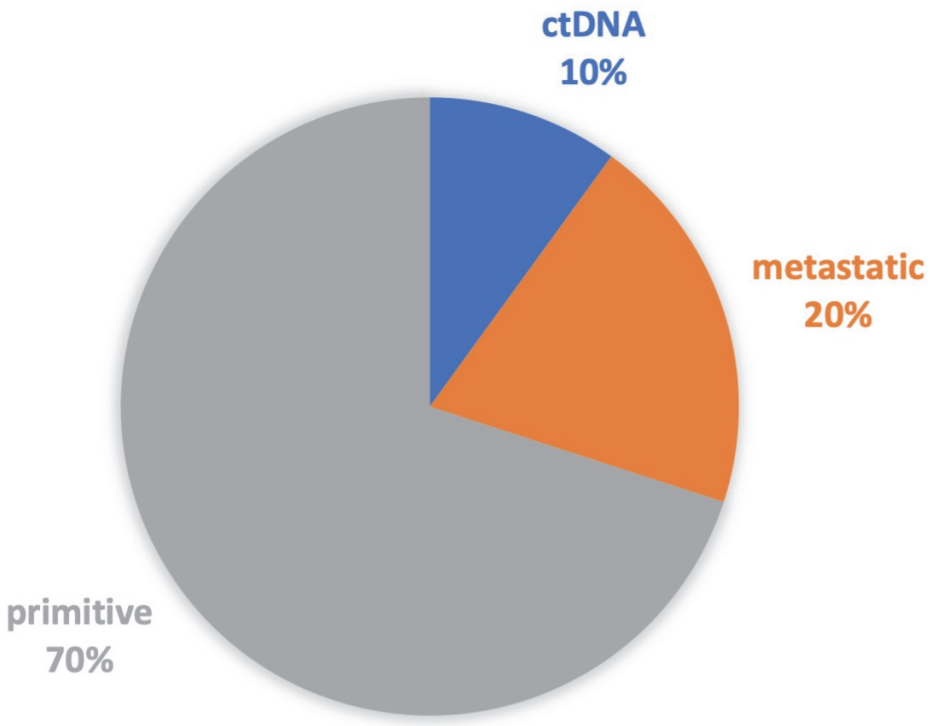


Figure 2. Sample of PIK3CA mutation identification
ctDNA: circulating tumor DNA

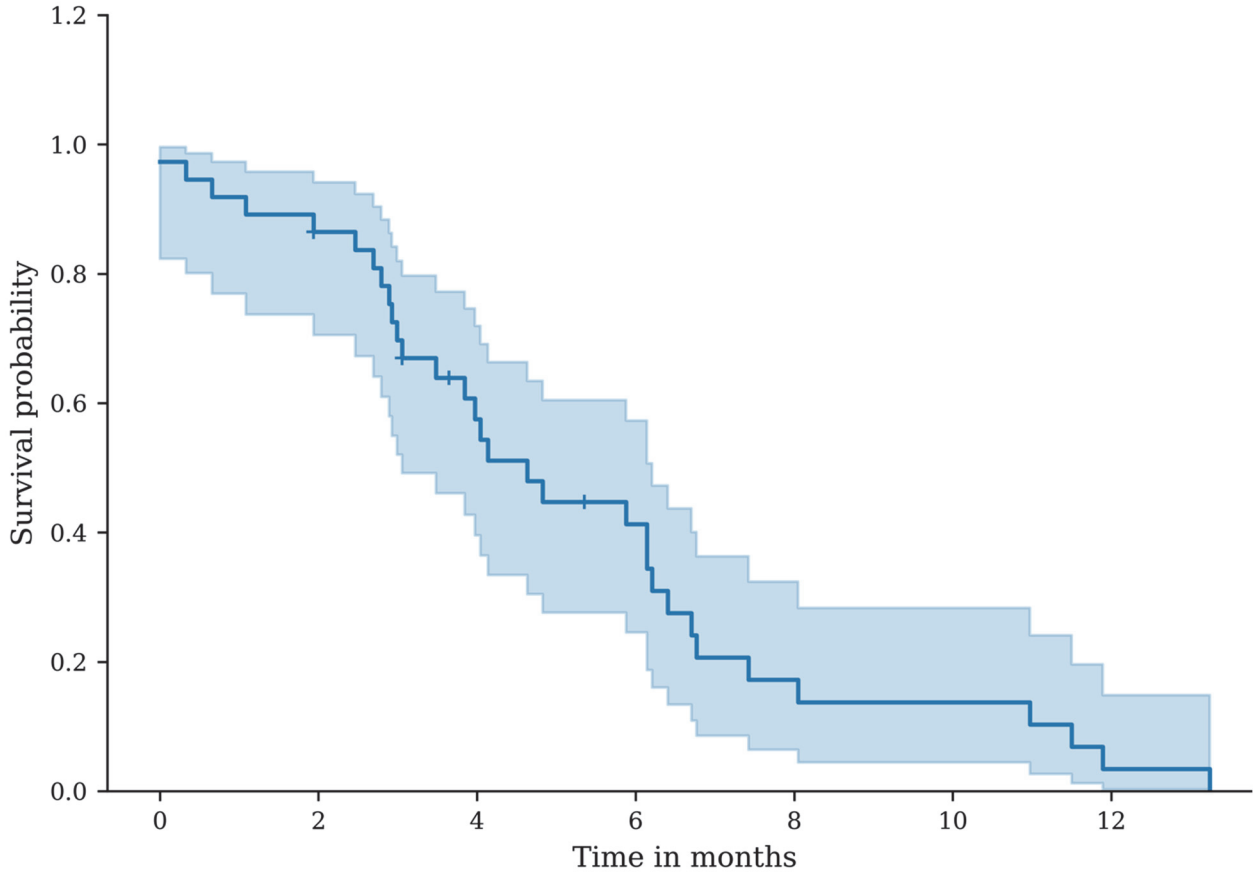


Figure 3. Progression free survival of all cohort treated with alpelisib and fulvestrant

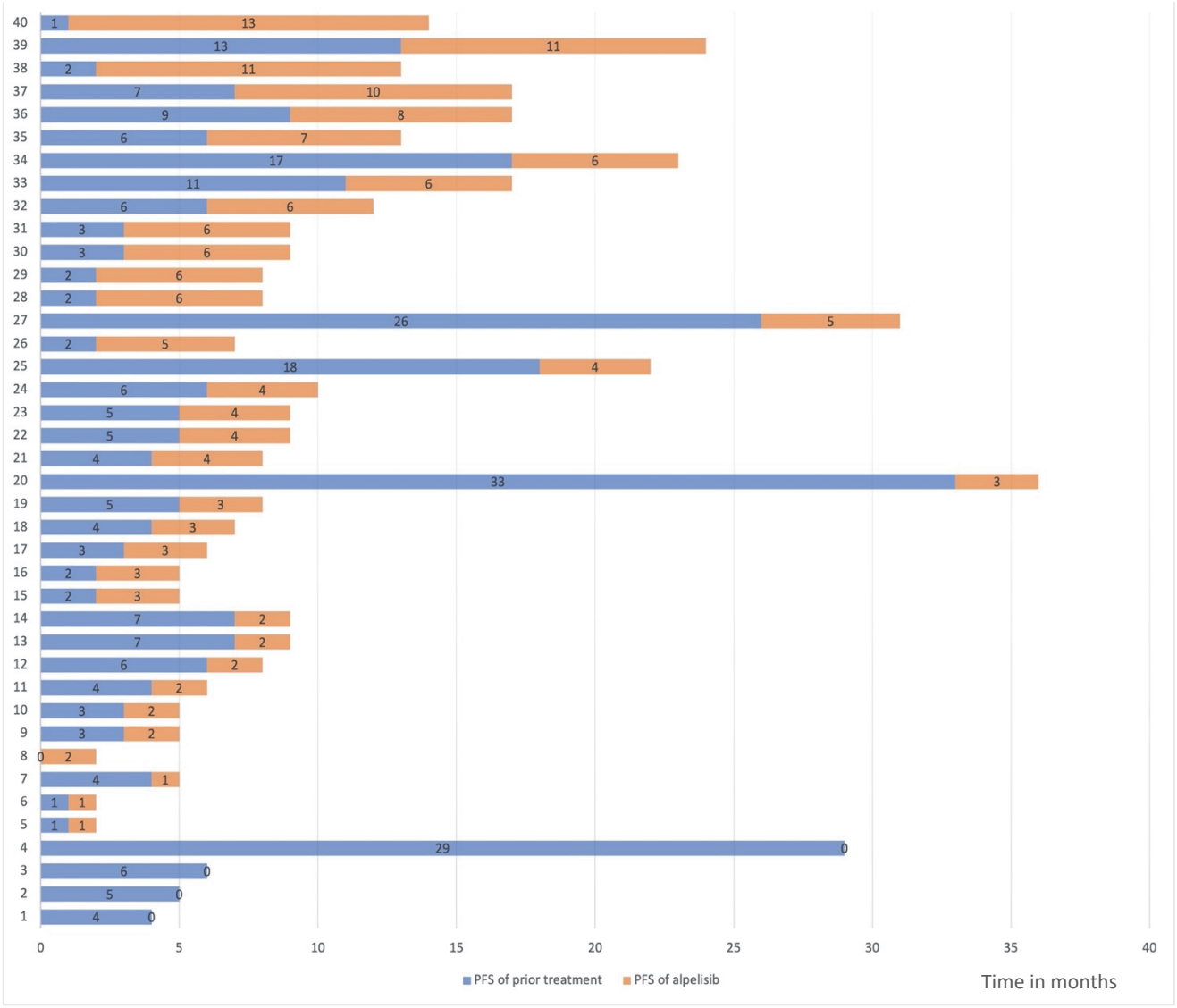


Figure 4. Progression free survival of prior treatment then progression free survival of alpelisib

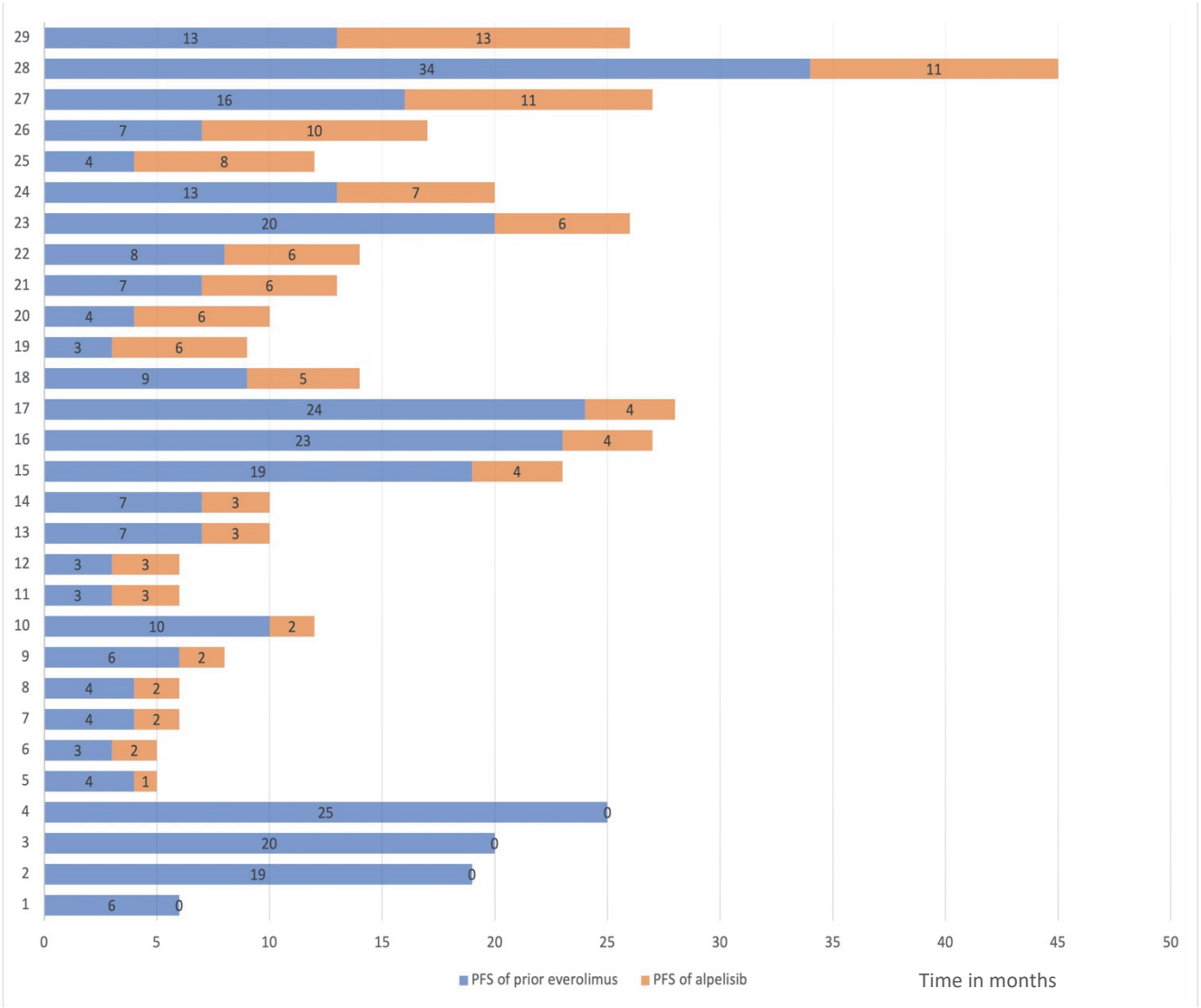


Figure 5. Progression free survival of prior everolimus then progression free survival of alpelisib

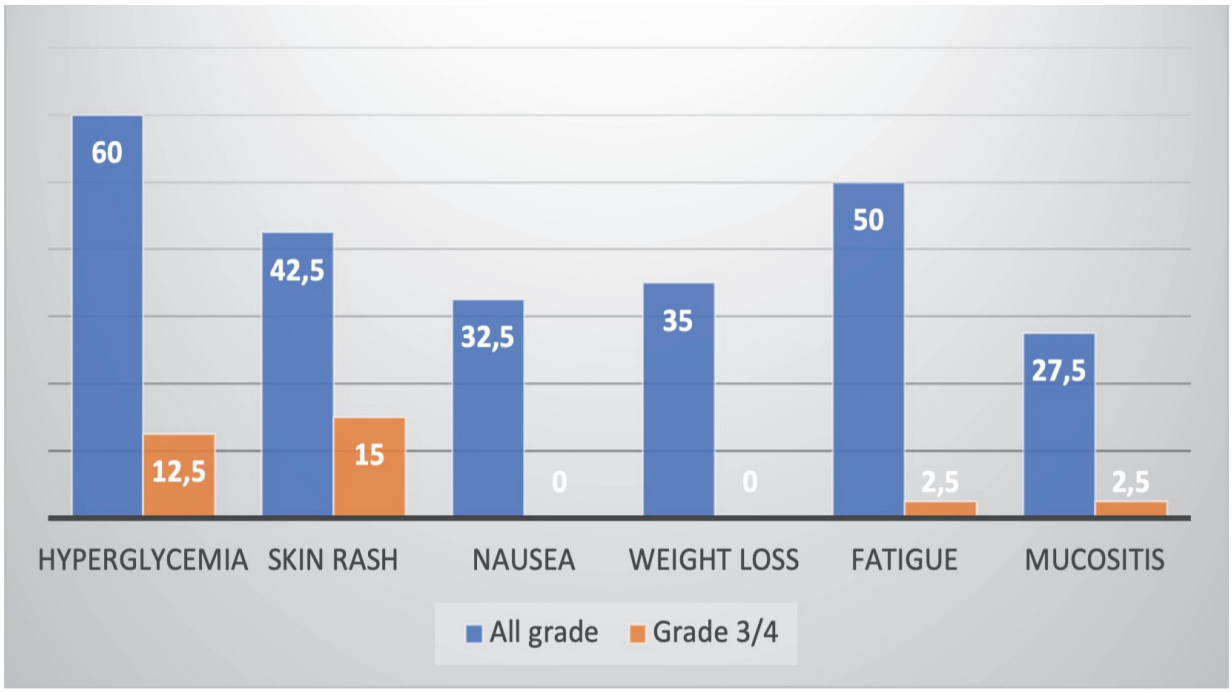


Figure 6. Safety profile of alpelisib in association to fulvestrant

Alpelisib and fulvestrant efficacy in HR-positive HER2-negative PIK3CA-mutant advanced breast cancer: data from the French early access program

Bello Roufai D[1], Bertucci A[2], De La Motte Rouge T[3], Blonz C[4], Akla S[5], Grenier J[6], Bailleux C[7], Gligorov J[8], Simon H[9], Desmoulins I[10], Tharin Z[10], Renaud E[9], Benderra MA[8], Delaloge S[5], Bertho M[4], Robert L[3], Cottu P[1], Gonçalves A[2], Bidard FC[1], Lerebours F[1]

1: Institut Curie, 2: Institut Paoli Calmettes, 3: Centre Eugène Marquis, 4: Institut de Cancérologie de l'Ouest, 5: Institut Gustave Roussy, 6: Institut Sainte-Catherine, 7:Centre Antoine Lacassagne, 8: Centre hospitalo-universitaire de Tenon; 9: centre hospitalo-universitaire de Brest, 10: Centre Georges-François Leclerc

Background

SOLAR-1 trial:

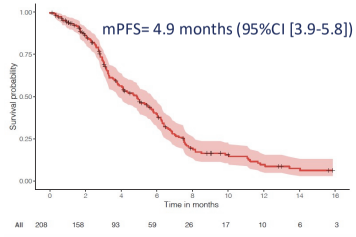
- Showed improved PFS of fulvestrant+alpelisib in an endocrine resistant PI3KCA mutated population
- Included only 5.9% of patients pretreated with CDK4/6 inhibitors

Methods

A French early access program (EAP) opened between 11.2018 and 10.2020.
Data regarding 209 consecutive women from 10 centers were extracted.
Inclusion criteria: at least one previous systemic treatment including an aromatase inhibitor and a CDK4/6 inhibitor.
Objective: to assess the efficacy and safety of alpelisib+fulvestrant in the post CDK4/6 inhibitor setting based a on retrospective, real-life study.

Clinical efficacy summary

Figure 1. Progression free survival



ORR= 35.4% of 164 evaluable patients
CBR (Clinical benefit rate) at 6 months= 39.6%

Patients' characteristics and prognostic factors

Table 1. Baseline characteristics and prognostic impact on PFS

	N (%) All=209	HR (CI95%)	p value	HR (CI95%)	p value
Median age (range)	62 (30-84)				
Age (years) <60 ≥60	 92 (44) 117 (56)	 0.91 (0.65-1.27)	 0.57		
Performance status 0-2 3	 202 (98.5) 3 (1.5)	 0.07 (0.02-0.25)	 <0.001	 0.08 (0.02-0.29)	 <0.0001
Tumor subtype ILC IC of NST	 47 (23.3) 146 (72.3)	 0.96 (0.64-1.43)	 0.25		
PR PR+ PR-	 125 (65.4) 13 (34,6)	 1,57 (0.64-3.8)	 0.31		
HER2 0 1+ 2+ FISH-	 111 (53.6) 50 (24.2) 39 (18.8)	 1.02 (0.69-1.52) 1.18 (0.77-1.81)	 0.88		
De novo metastasis No Yes	 184 (76.4) 24 (23.6)	 0.67 (0.94-2.40)	 0.09		
Median number of previous systemic therapies (range)	4 (1-14)				
Prior fulvestrant Yes No	 163 (78) 46 (22)	 0.52 (0.34-0.79)	 0.003	 0.53 (0.35-0.82)	 0.005
Prior everolimus Yes No	 116 (55.5) 93 (44.5)	 0.87 (0.62 -1.23)	 0.66		
Chemotherapy No Yes	 49 (23.6) 159 (76.4)	 0.75 (0.49-1.15)	 0.008		

PS<3 and prior exposure to fulvestrant were significantly associated with a longer PFS by multivariate analysis.

Fulvestrant pretreatment impact

Figure 2. Progression free survival according to fulvestrant pretreatment

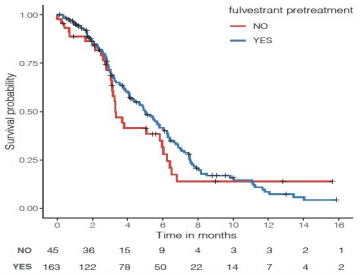


Table 2. Comparison of clinical features

	Fulvestrant-naïve (N=46)	Fulvestrant-pretreated (N=163)	p value
Prior chemotherapy	35 (76%)	125 (76.7%)	1
Prior everolimus	15 (32.6%)	101 (61.9%)	0.004
Age<60	23 (50%)	69 (42.3%)	0.35
Mean number of previous systemic treatments	2.9	5.2	<0.0001
PS<3	44 (95.6%)	158 (96.9%)	0.13

Fulvestrant pretreated population was enriched in patients who had a long disease control by everolimus with mPFS= 8.3 months (7.1-11.0) vs 4.3 (3.9-8.4) in the fulvestrant-naïve population

Safety profile

Table 3. Adverse events according to NCI CTCAE v 5.0

	All grades	Grade 3 or 4
Hyperglycemia	53.1%	13.4%
Skin rash	34.4%	8.1%
Fatigue	57.4%	4.8%
Diarrhea	23.4%	1.9%

Dose reduction: 90 patients (43.1%)
Temporary discontinuation: 81 patients (38.8%)

Conclusion

Despite heavy pre-treatments, alpelisib+fulvestrant had a clinically relevant efficacy in the French EAP population.
Prior treatment with either everolimus or fulvestrant did not overtly impair alpelisib/fulvestrant efficacy.

Acknowledgements

Patients and families, clinical research team.

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Figure 7. Poster ASCO 2021 "Alpelisib and fulvestrant efficacy in HR-positive HER2-negative PIK3CA-mutant advanced breast cancer: data from the French early access program"

SERMENT D'HIPPOCRATE

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

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

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

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

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

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

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les moeurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

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

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

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

ORDRE NATIONAL DES MÉDECINS
Conseil National de l'Ordre

Résumé :

Chez l'Homme, la voie de la phosphoinositide 3-kinase (PI3K) joue un rôle central dans le cancer et en particulier dans le cancer du sein (CS). PI3K est mutée dans environ 25 à 40 % des CS selon les sous-types et atteint 40 % dans les CS avec récepteurs hormonaux (RH)-positifs. Le gène PIK3CA, qui code pour p110α de la sous-unité catalytique de PI3K, est le deuxième gène le plus muté dans le cancer en général. Trois mutations "hotspot", deux sur l'exons 9 (E545K et E542K du domaine helical) et une sur l'exon 20 (H1047R du domaine kinase) de PIK3CA, représentent 80 % de toutes les mutations.

Le développement des thérapeutiques ciblant ces mutations a commencé avec les pan-inhibiteurs (principalement le buparlisib et le pictilisib). Les pan-inhibiteurs n'ont pas montré l'efficacité attendue mais ont néanmoins ouvert la voie aux inhibiteurs spécifiques de PI3Kα (principalement l'alpelisib et le taselisib). Malgré le rôle central de PI3K dans l'oncogenèse, seule une activité anti-tumorale modeste a été observée avec les inhibiteurs. De plus, ceux-ci présentent un profil de toxicité non négligeable.

Tous les sous-types de CS possèdent leur propre voie métabolique et la compréhension des mécanismes de résistance aux inhibiteurs de PI3K reste à parfaire. Nous devons également apprendre à mieux manager ces thérapeutiques afin d'optimiser leur utilisation.

Le but de cette revue est d'examiner le développement de chacun des inhibiteurs de PI3K évalués dans le CS. Notre propos concernera les pan-inhibiteurs, les inhibiteurs sélectifs de p110α et leur développement dans tous les sous-types de CS. Nous passerons en revue les échecs, les succès et les possibilités futurs de cette classe thérapeutique dans la prise en charge du CS.

Nous explorerons également une cohorte de cancers du sein métastatiques RH+/HER2- hormonorésistants traités par ALPELISIB et FULVESTRANT dans notre institution.

Mots-clés : Cancer du sein ; inhibiteur sélectif de PI3K ; pan-inhibiteur de PI3K ; revue de la littérature.