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Review On Breast Cancer And It's Treatment : Capivasertib and combination with fulvestrant

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Abstract : This study has been undertak A Bosom disease, or breast cancer, is a malignant tumor that develops from breast cells. It can originate in different parts of the breast, including the ducts that carry milk to the nipple or the glands that produce milk. Over time, these cancerous cells can invade nearby tissues and spread to other parts of the body. More than half of bosom growths harbor modifications in at least one qualities of the phosphatidylinositol 3-kinase (PI3K) pathway including PIK3CA changes (31%), PTEN misfortune (34%), PTEN transformations (5%) and AKT1 transformations (3%). While PI3K and mTOR inhibitors are as of now endorsed in cutting edge bosom disease, AKT inhibitors have been as of late evolved as another restorative methodology. Capivasertib (AZD5363) is a novel, specific ATP-cutthroat skillet AKT kinase inhibitor that applies comparable action against the three AKT isoforms, AKT1, AKT2, and AKT3

Keywords **– Breast cancer, Capivasertib, fulvestrant, biomarkers ,immunomodulation .**

INTRODUCTION

The Capivasertib is a strong dish AKT inhibitor with Outstanding enemy of proliferative action in preclinical models.The PI3K/AKT/mTOR pivot explicitly has a focal Situation in a few pathways with key capabilities in Advancing cell endurance, development, and multiplication.(1 Significant cross-talk between these pathways and Middle people of estrogen receptor flagging are very much Appreciated, and hence these middle people are coherent focuses In chemical delicate disease.Previous endeavors at Hindrance of these downstream kinases are featured By the BOLERO-2 preliminary, Which assessed the expansion of Everolimus, a specific mTOR inhibitor, to the aromatase Inhibitor exemestane, and detailed an improvement In movement free endurance yet not in generally speaking endurance. Hindrance of PI3K, albeit especially viable in Patients with growths with PIK3CA changes, has Demonstrated testing attributable to the poisonousness profile of PI3K Inhibitors.The extent of purpose for capivasertib may be more extensive Than at first gathered(2,3). AKT lies downstream of A few outstanding targets, including ERBB2 (HER2) and ERBB3 (HER3). Systems with mixes of HER2-Coordinated treatment could uncover a job for AKT hindrance In the administration of HER2-positive sickness and Triple-negative bosom disease, where transformations in The PIK3CA/AKT/PTEN pathway happen in 10-23% of Cancers.(4,5,6)

In a multipart Stage I review (ClinicalTrials.gov, NCT01226316), capivasertib monotherapy and, consequently, mix treatment with fulvestrant was tried in various genomically chose extension partners with anticipated PI3K/AKT/PTEN pathway enactment.(7) Here we report the Stage I development companion assessing capivasertib and fulvestrant in PTEN-freak, ER+ MBC patients. Concentrate on goals were to affirm security and decency and evaluate fundamental antitumor action of the mix treatment in this understanding populace, and to depict exploratory genomic biomarker examinations of gathered coursing growth DNA (ctDNA) and cancer tests.(8)

Bosom Disease

Normally, disease is named after the body part in which it started; in this manner, bosom malignant growth alludes to the whimsical development and expansion of cells that begin in the bosom tissue.The bosom is made out of two primary sorts of tissues i.e., glandular tissues and stromal (supporting) tissues(9,10). Glandular tissues house the milk-delivering organs (lobules) and the pipes (the milk sections) while stromal tissues incorporate greasy and sinewy connective tissues of the bosom. The bosom is likewise comprised of lymphatic tissue-insusceptible framework tissue that eliminates cell liquids and waste(11). There are a few sorts of growths that might foster inside various region of the bosom. Most growths are the consequence of harmless (non-dangerous) changes inside the bosom. For instance, fibrocystic change is a non-malignant condition wherein ladies foster growths (gathered bundles of liquid), fibrosis (development of scar-like connective tissue), knottiness, and areas of thickening, delicacy, or bosom pain.Most bosom diseases start in the cells that line the pipes (ductal tumors)(12). Some start in the cells that line the lobules (lobular malignant growths), while a modest number beginning in different tissues .Bosom disease, a term often used colloquially for breast

cancer, is a significant health concern affecting individuals worldwide, predominantly women but also impacting men. This article aims to provide a comprehensive overview of bosom disease, covering its definition, risk factors, symptoms, diagnosis, treatment, and preventive measures.(13,14)

Risk Factors:

- Gender: Women are at a much higher risk than men.
- Age: The risk increases with age, with most cases occurring in women over 50.
- Family history: Having close relatives with breast cancer can elevate the risk.
- Genetic mutations: Inherited mutations in genes such as BRCA1 and BRCA2 can significantly increase susceptibility.
- Hormonal factors: Early menstruation, late menopause, hormone replacement therapy, and never giving birth or having the first child after the age of 30 can influence risk.
- Lifestyle factors: Factors such as alcohol consumption, obesity, and lack of physical activity may contribute to the risk.(15,16)

Symptoms:

- A lump or mass in the breast or underarm area.
- Changes in breast size or shape.
- Skin changes on the breast, such as dimpling, puckering, or redness.
- Nipple changes, such as inversion, discharge, or scaling.
- Breast pain or tenderness.(17)

Diagnosis:

- Early detection plays a crucial role in the successful treatment of bosom disease. Diagnostic methods may include:
- Breast self-examination: Regular self-checks can help individuals detect any unusual changes in their breasts.
- Clinical breast examination: Healthcare providers perform a physical examination to check for lumps or other abnormalities.
- Mammography: X-ray imaging of the breast can detect tumors at an early stage.
- Biopsy: Tissue samples are taken from suspicious areas for laboratory analysis to confirm the presence of cancerous cells.(18,19)

Treatment:

- Treatment for bosom disease depends on various factors, including the stage of cancer, its type, and individual health considerations. Common treatment options may include:
- Surgery: Removing the tumor or the entire breast (mastectomy) may be necessary.
- Radiation therapy: High-energy rays are used to kill cancer cells or shrink tumors.
- Chemotherapy: Drugs are administered to destroy cancer cells throughout the body.

- Hormone therapy: Medications are used to block the effects of hormones that promote the growth of certain types of breast cancer.
- Targeted therapy: Drugs target specific molecules involved in cancer growth and progression.(20)

Prevention:

- While some risk factors for bosom disease are beyond control, individuals can take steps to reduce their risk, such as:
- Maintaining a healthy weight.
- Being physically active.
- Limiting alcohol consumption.
- Breastfeeding, if possible.
- Regularly screening for breast cancer, especially for those with a family history or other risk factors.(21)

Types

Painless Bosom Disease cells that are bound to the pipes and don't attack encompassing greasy and connective tissues of the bosom. Ductal carcinoma in situ (DCIS) is the most well-known type of painless bosom malignant growth (90%). Lobular carcinoma in situ (LCIS) is more uncommon and considered a marker for expanded bosom disease risk.

Obtrusive Bosom Disease cells that advanced the pipe and lobular wall and attack the encompassing greasy and connective tissues of the bosom. Oancer can be intrusive without being metastatic (spreading) to the lymph hubs or different organs.Painless Bosom Disease cells that are bound to the pipes and don't attack encompassing greasy and connective tissues of the bosom. Ductal carcinoma in situ (DCIS) is the most well-known type of painless bosom malignant growth (90%). Lobular carcinoma in situ (LCIS) is more uncommon and considered a marker for expanded bosom disease risk.

Regularly happening Chest Illness

Lobular carcinoma in situ (LCIS, lobular neoplasia): The expression, "in situ," alludes to malignant growth that has not spread past the area where it at first created. LCIS is a sharp expansion in the quantity of cells inside the milk organs (lobules) of the bosom.

Ductal carcinoma in situ (DCIS): DCIS, the most widely recognized kind of harmless bosom disease, is bound to the conduits of the bosom. For instance, ductal comedocarcinoma.

Invading lobular carcinoma (ILC)

ILC is otherwise called obtrusive lobular carcinoma. ILC starts in the milk organs (lobules) of the bosom, however frequently spreads (metastatizes) to different locales of the body. ILC represents 10% to 15% of bosom diseases.

Invading ductal carcinoma (IDC): IDC is otherwise called obtrusive ductal carcinoma. IDC starts in the milk channels of the bosom and enters the mass of the pipe, attacking the greasy tissue of the bosom and conceivably different districts of the body. IDC is the most widely recognized kind of bosom disease, representing 80% of bosom malignant growth analyze.(22,23)

Less commonly occurring Bosom Disease

Medullary carcinoma: Medullary carcinoma is an obtrusive bosom malignant growth that frames an unmistakable limit between cancer tissue and typical tissue. Just 5% of bosom tumors are medullary carcinoma.

Mutinous carcinoma: Likewise called colloid carcinoma, mutinous carcinoma is an intriguing bosom malignant growth framed by the bodily fluid delivering disease cells. Ladies with mutinous carcinoma for the most part have a preferred guess over ladies with more normal kinds of intrusive carcinoma.

Rounded carcinoma: Cylindrical carcinomas are an extraordinary sort of invading (intrusive) bosom carcinoma. Ladies with rounded carcinoma by and large have a preferable visualization over ladies with more normal sorts of obtrusive carcinoma. Cylindrical carcinomas represent around 2% of bosom malignant growth analyze.

Incendiary bosom malignant growth

Fiery bosom malignant growth is the presence of aroused bosoms (red and warm) with dimples and additionally thick edges brought about by disease cells obstructing lymph vessels or diverts in the skin over the bosom. However incendiary bosom malignant growth is uncommon (representing just 1% of bosom tumors), it is very quickly developing.

Paget's infection of the areola

An uncommon type of bosom malignant growth that starts in the milk pipes and spreads to the skin of the areola and areola, Paget's illness of the areola just records for around 1% of bosom diseases.

Phylloides growth

Phylloides growths (likewise spelled "phyllodes") are can be either harmless (non-dangerous) or threatening (carcinogenic). Phylloides growths foster in the connective tissues of the bosom and might be treated by careful evacuation. Phylloides growths are exceptionally uncommon; under 10 ladies pass on from this kind of bosom disease every year in the US .(24,25)

Capivasertib in Chemical Receptor-Positive High level Bosom Disease

Roughly 70% of cutting edge bosom tumors express the chemical receptor estrogen or progesterone (or both) and don't have human epidermal development factor receptor 2 (HER2) overexpression.1 In these patients, endocrine treatment, frequently an aromatase inhibitor, joined with a cyclin-subordinate kinase 4 and 6 (CDK4/6) inhibitor is the pillar of first-line treatment for cutting edge sickness. Such treatment has been displayed to further develop movement free and in general endurance considerably as contrasted and aromatase inhibitor treatment alone. In any case, most patients have illness movement and treatment of these patients stays a clinical test.(26) Proper endocrine-based treatment after illness movement during aromatase inhibitor treatment, regardless of a CDK4/6 inhibitor, is muddled. In any case, choices incorporate the specific estrogen-receptor degrader fulvestrant as monotherapy or as a component of blend treatment.(27)

AKT is the vital hub of the phosphatidylinositol 3-kinase (PI3K)- AKT-PTEN flagging pathway. Overactivation of the pathway happens in around half of chemical receptor-positive, HER2-negative bosom diseases through enacting transformations in PIK3CA and AKT1 and inactivating adjustments in PTEN.Alterations might be available at the hour of malignant growth repeat and can likewise be gained through past treatment, incorporating with CDK4/6 inhibitors. AKT flagging may likewise be enacted without even a trace of hereditary modifications in patients with endocrine obstruction. (28)Hindrance of this pathway has been effective in pretreated chemical receptor-positive high level bosom malignant growth — results that prompted administrative endorsement. (29)The PI3K α-particular inhibitor alpelisib, joined with fulvestrant, in PIK3CA-freak growths in the Sunlight based 1 (Clinical Investigations of Alpelisib in Bosom Disease 1) preliminary and the mammalian objective of rapamycin (mTOR) inhibitor everolimus, joined with exemestane, in the BOLERO-2 (Bosom Malignant growth Preliminaries of Oral Everolimus-2) preliminary had more noteworthy viability than endocrine treatment alone.Both randomized preliminaries were directed before the accessibility of CDK4/6 inhibitors, however in a follow-on stage 2, single-bunch preliminary (BYLieve), specialists endeavored to address the requirement for information in this setting with alpelisib in addition to fulvestrant.(30)

Capivasertib is an orally bioavailable, little atom inhibitor of each of the three AKT isoforms. Capivasertib restrained AKT in preclinical models, bringing about dephosphorylation of key downstream focuses on; the medication additionally showed antiproliferative action in bosom malignant growth cell lines and had synergistic antitumor movement in mix with endocrine treatment in preclinical models.(31) In the stage 2 FAKTION preliminary, therapy with capivasertib in mix with fulvestrant essentially further developed movement free and generally speaking endurance as contrasted and fulvestrant alone among postmenopausal ladies with chemical receptor-positive high level bosom malignant growth who had recently gotten endocrine therapy.Here, we present the essential examination of CAPItello-291, a stage 3 preliminary that evaluated the viability and security of capivasertib-fulvestrant treatment in patients with chemical receptor-positive, HER2-negative high level bosom malignant growth whose sickness had advanced during or after aromatase inhibitor treatment, regardless of a CDK4/6 inhibitor.(32,33)

The PI3K/AKT/PTEN pathway Is regularly unusually enacted in bosom malignant growth (BC) and engaged with protection from hormonal treatment. Various medications focusing on this pathway are endorsed or being developed, including the dish AKT inhibitor capivasertib (AZD5363). (34)Beginning stage investigations of capivasertib as monotherapy for strong diseases (for example NCT01226316, NCT01625286) have utilized hereditary testing to choose patients considered probably going to answer in light of AKT1, PIK3CA or PTEN changes. Be that as it may, not all chosen patients answered.(35) Randomized stage 2 examinations on Capivasertib as blend treatment showed the significance of setting; a more articulated reaction in mix with paclitaxel was seen in TNBC patients whose cancers held onto a change on AKT1, PIK3CA or PTEN (Schmid et al. ASCO 2018), though a similar mix in ER+ HER2-progressed/metastatic BC patients didn't show a clinical advantage in the general populace nor in the PIK3CA-change subgroup (Turner et al. Ann Oncol 2019).(36)

Biomarkers of Reaction to AKT Inhibitors

The ID of biomarkers of reaction to AKT inhibitors is of crucial significance to boost the expected viability of these designated specialists, seeking after a "customized medication" approach for bosom disease patients. To this end, correlatives and translational examinations have been widely directed with regards to clinical preliminaries, however results are as yet inconclusive.Determining the phosphorylation level of downstream effectors is valuable to lay out whether AKT restraint actually downregulates PI3K

hyperactivation. In the STAKT preliminary, patients with recently analyzed HR-positive early BC gotten capivasertib for 4.5 days preceding a medical procedure. Contrasted and pattern levels, posttreatment phosphorylation of the downstream effectors GSK3β, PRAS40, and S6 was essentially diminished, demonstrating that capivasertib successfully obstructed its objective (Robertson et al., 2020)(37). A significant lessening of phospho-GSK3β was likewise seen among metastatic BC patients treated with capivasertib in stage I/II preliminaries (Banerji et al., 2018; Turner et al., 2019). On the other hand, just a humble decrease of pS6, PTEN, and stathmin phosphorylation arose in an open door (Charm) preliminary assessing MK-2206 in early BC patients, independently of their characteristic subtype (Kalinsky et al., 2018). A more thorough phospho-proteomic examination was done on the early HR-negative/HER2-positive BC and TNBC populace of the I-SPY2 preliminary, with high pAKT, pSGK, pmTOR, and pTSC2 levels preceding neoadjuvant treatment with MK-2206 and standard treatment emphatically relating with pCR rates (Wolf et al., 2020).(38)

The Ki-67 multiplication file has additionally been assessed in neoadjuvant preliminaries to evaluate AKT inhibitors' adequacy. In accordance with the detailed information referenced over, a reduction in Ki-67 was seen after treatment with capivasertib in the STAKT preliminary, while no tremendous contrasts in pre-and posttreatment Ki-67 arose in the MK-2206 Charm preliminary (Kalinsky et al., 2018; Robertson et al., 2020).(39)

Restricted proof is accessible on the job of immunomodulation as a biomarker of reaction to AKT inhibitors. In the FAIRLANE preliminary, a resistant score was determined among early TNBC patients getting ipatasertib or fake treatment in addition to paclitaxel in the neoadjuvant setting. While an increment of this score during treatment essentially connected with cancer reaction in the control arm, a similar affiliation was not tracked down in the exploratory gathering (Oliveira et al., 2019).provided(40) Reliably, in the I-SPY2 preliminary, entire transcriptome examination and broad protein clusters neglected to show a relationship between's the safe mark and reaction to preoperative MK-2206 among TNBC patients. Notwithstanding, this mark was essentially connected with cancer reaction in the HER2-advanced populace, recommending that — in this BC subtype — the safe climate might assume a significant part in intervening reaction to AKT restraint (Wolf et al., 2020).(41)

Mix with fulvestrant in PTEN-freak trama center positive metastatic bosom disease

This Stage I extension concentrate on provided details regarding the wellbeing and viability of the skillet AKT inhibitor, capivasertib, in blend with the emergency room bad guy, fulvestrant, in a genomically chose progressed ER+ BC populace holding onto a qualified malicious PTEN quality change in the growth. PTEN transformations select for a forceful genomic subtype of ER+ BC, with related protection from standard-of-care treatments.(42) Capivasertib in addition to fulvestrant had an OK wellbeing profile that was predictable with earlier data16 and shown antitumor action in this vigorously pretreated patient associate (middle 7 earlier treatments), remembering for those recently treated with fulvestrant. (43,44)Despite the fact that viability showed up barely preferable in fulvestrantpretreated over in fulvestrant-gullible patients, there were remarkable phenotypic and genomic contrasts between these patient associates. In particular, at enlistment, fulvestrant-gullible patients had more instinctive illness, got less earlier endocrine and more chemotherapy, and, possible intelligent of this earlier treatment receipt, had a lower ESR1-and higher TP53-change rate, which without a doubt could likewise be demonstrative of a more forceful sickness science at baseline.(45)Overall, be that as it may, and given the unfortunate prognostic genomic subgroup chose for this review, sensible viability (ORR 21%; CBR24 42%) was found in the fulvestrant-pretreated partner. Overall, this clinical dataset upholds earlier observations proposing PTEN as a negative prognostic biomarker in BC, given the somewhat short middle PFS (2.7 [95% CI 2-4]) length saw across the review populace. In this multicenter global review, nearby testing was dependable, with focal review affirmation of non-utilitarian PTEN status accomplished in all patients.(46) Critically, PTEN seemed, by all accounts, to be the predominant driver growth change in this study populace. Moreover, the preliminary adds support for enlistment in genomically chose review to be founded principally on neighborhood testing, in this manner staying away from postponements to concentrate on gatherings from the effect of focal testing, especially in beginning stage signal-chasing concentrates, for example, these. The joining of mTOR and CDK4/6 inhibitors into endocrine treatment has prompted significant enhancements in persistent outcomes. Close to half of our PTEN-freak concentrate on populace had gotten earlier CDK4/6 inhibitor treatment. This is specifically compelling given late information proposing PTEN inactivation as a component of protection from this restorative class as well as PI3Kαselective inhibitors, loaning backing to coordinate AKT inhibitors in this setting(47).
Prominently, in the Stage I/II randomized FAKTION study, which exhibited a PFS benefit with the expansion of capivasertib to fulvestrant in a microscopically unselected, aromatase-inhibitor-safe yet fulvestrant-gullible ER+ MBC populace, a subgroup of patients with PIK3CA change (by computerized bead polymerase chain response) or potentially PTEN misfortune (by IHC) didn't seem to have any more noteworthy aversion to the blend than those without the predefined modifications. Critically, in any case, no FAKTION members had gotten past CDK4/6 inhibitor treatment, and the pace of AKT1 and PTEN transformations in that study has not yet been reported. Our review had a few significant impediments, including the preliminary not being officially fueled to look at viability across fulvestrant-credulous and-pretreated partners, as well as the little understanding numbers. It is likewise critical that the fulvestrant-gullible patients selected may have had a more forceful illness aggregate and a less fortunate visualization than the fulvestrant-pretreated partner, albeit the example size restricted any proper examinations.(48) At the arranged break examination, the fulvestrant-gullible partner didn't meet its objective incentive for CBR24, so enlistment was stopped, bringing about a companion of just 12 patients. Besides, the uncommonness of this biomarker prompted sluggish gathering in the fulvestrant-pretreated associate (around 29 months), with the outcome that this accomplice was shut prior to arriving at the objective of 24 patients. (49)All in all, this study shows that capivasertib in blend with fulvestrant has clinical movement in vigorously pretreated PTENmutant ER+ MBCpatients, an unfortunate prognostic BC subtype. PTEN was the prevailing driver cancer change in these patients. Further examinations of patients pretreated with a CDK4/6 inhibitor in the continuous Stage III review CAPItello-291 (NCT04305496), which is assessing mix capivasertib with fulvestrant, will conclusively illuminate PTEN's job as a restorative objective in BC. In the Stage I concentrate on detailed here, this forceful sickness Element seemed to show extraordinary science

with basically a subset reliant upon AKT and emergency room for multiplication, a perception that might benefit remedially from utilizing an AKT inhibitor blend .(50)

Conclusion

- Breast cancer is a complex disease with various subtypes and genetic mutations, highlighting the importance of personalized treatment approaches.
- The phosphatidylinositol 3-kinase (PI3K) pathway plays a central role in breast cancer development and progression, making it a target for therapeutic interventions.
- Capivasertib, a novel pan-AKT kinase inhibitor, shows promising anti-proliferative activity in preclinical models and has been investigated in clinical trials for its efficacy in breast cancer treatment.
- Combination therapies, such as capivasertib with fulvestrant, have demonstrated safety and efficacy in genomically selected patient populations, particularly those with PTEN mutations.
- Biomarker analysis, including genomic profiling and assessment of downstream signaling pathways, is crucial for patient selection and predicting response to targeted therapies like capivasertib.
- Further research, including larger clinical trials like CAPItello-291, is needed to validate the therapeutic potential of capivasertib and its role in improving outcomes for patients with breast cancer, especially those with specific genetic alterations.

References

[1] 2022 Jun; 63: 157–167. Published online 2022 Apr 1. Doi: 10.1016/j.breast.2022.03.018 PMCID: PMC9011110PMID: 35398754"The emerging role of capivasertib in breast cancer"Angeliki Andrikopoulou,a Spyridoula Chatzinikolaou,a Evangelia Panourgias,b Maria Kaparelou,a Michalis Liontos,a Meletios-Athanasios Dimopoulos,a and Flora Zagouria,∗

2. Millis S.Z., Ikeda S., Reddy S., Gatalica Z., Kurzrock R. Landscape of phosphatidylinositol-3-kinase pathway alterations across 19 784 diverse solid tumors. JAMA Oncol. 2016;2:1565–1573. doi: 10.1001/JAMAONCOL.2016.0891. [PubMed] [CrossRef] [Google Scholar]

3. Nitulescu G.M., Van De Venter M., Nitulescu G., Ungurianu A., Juzenas P., Peng Q., et al. The Akt pathway in oncology therapy and beyond (Review) Int J Oncol. 2018;53:2319–2331. doi: 10.3892/IJO.2018.4597. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

4. . Turner N.C., Alarcón E., Armstrong A.C., Philco M., López Chuken Y.A., Sablin M.P., et al. BEECH: a dose-finding run-in followed by a randomised phase II study assessing the efficacy of AKT inhibitor capivasertib (AZD5363) combined with paclitaxel in patients with estrogen receptor-positive advanced or metastatic breast cancer, and in a PIK3CA mutant sub-population. Ann Oncol. 2019;30:774. Doi: 10.1093/ANNONC/MDZ086. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Choi A.R., Kim J.H., Woo Y.H., Cheon J.H., Kim H.S., Yoon S. Co-treatment of LY294002 or MK-2206 with AZD5363 attenuates azd5363-induced increase in the level of phosphorylated AKT. Anticancer Res. 2016;36:5849–5858. Doi: 10.21873/ANTICANRES.11170. [PubMed] [CrossRef] [Google Scholar]

6. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Goncalves A, Lee KH, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 2018;379:753–63. [PMC free article] [PubMed] [Google Scholar]

7. Bertucci F, Ng CKY, Patsouris A, Droin N, Piscuoglio S, Carbuccia N, et al. Genomic characterization of metastatic breast cancers. Nature 2019;569:560–4. [PubMed] [Google Scholar]
Published online 2020 Apr 20. Doi: 10.1158/1078-0432.CCR-19-3953

8. Baselga J, Dent SF, Cortés J, Im Y-H, Diéras V, Harbeck N, et al. Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): primary analysis from SANDPIPER. J Clin Oncol 2018;36(18 Suppl):abst LBA1006. [Google Scholar]

9. McCormack VA. Dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15(6):1159–1169. [PubMed] [Google Scholar]

10. Chen J, Pee D, Ayyagari R, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. J Natl Cancer Inst. 2006;98(17):1215–1226. [PubMed] [Google Scholar]

11. Gail MH. Discriminatory accuracy from single-nucleotide polymorphisms in models to predict breast cancer risk. J Natl Cancer Inst. 2008;100(14):1037–1041. [PMC free article] [PubMed] [Google Scholar]

12. Spicer DV, Ursin G, Parisky YR, et al. Changes in mammographic densities induced by a hormonal contraceptive designed to reduce breast cancer risk. J Natl Cancer Inst. 1994;86(6):431–436. [PubMed] [Google Scholar]

13. Cuzick J, Warwick J, Pinney E, Warren RML, Duffy SW. Tamoxifen and breast density in women at increased risk of breast cancer. J Natl Cancer Inst. 2004;96(8):621–628. [PubMed] [Google Scholar]

14. Johns PC, Yaffe MJ. X-ray characterisation of normal and neoplastic breast tissues. Phys Med Biol. 1987;32(6):675–695. [PubMed] [Google Scholar]

15. Rojas K, Stuckey A. Breast Cancer Epidemiology and Risk Factors. Clinical obstetrics and gynecology. 2016;59:651–672. [PubMed] [Google Scholar]

16. Kispert S, McHowat J. Recent insights into cigarette smoking as a lifestyle risk factor for breast cancer. Breast Cancer: Targets and Therapy. 2017;9:127–132. [PMC free article] [PubMed] [Google Scholar]

17. Morrow M, Waters J, Morris E. MRI for breast cancer screening, diagnosis, and treatment. Lancet. 2011;378:1804–1811. [PubMed] [Google Scholar]

18. Self-detection remains a key method of breast cancer detection for U.S. women. Roth MY, Elmore JG, Yi-Frazier JP, Reisch LM, Oster NV, Miglioretti DL. J Womens Health (Larchmt) 2011;20:1135–1139. [PMC free article] [PubMed] [Google Scholar]

19. American Cancer Society recommendations for the early detection of breast cancer. [Dec; 2020];https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html American Cancer

20. What happens at each stage of breast cancer? Medically reviewed by Faith Selchick, DNP, AOCNP, Nursing, Oncology — By Bethany Cadman — Updated on October 8, 2021

21. Alvin J. Siteman Cancer Center Hospital,The Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine is a cancer treatment, research and education institution with six locations in the St. Louis area.

22. Azzopardi et al., 1982 J.G. Azzopardi, O.F. Chepick, W.H. Hartmann, N.A. Jafarey, A. Llombart-Bosch, L. Ozzello, F. Rilke, N. Sasano, L.H. Sobin, S.C. Sommers, H. Stalsberg, J. Sugar, A.O. WilliamsThe world health organization histological typing of breast tumors – second edition. The World Organization Am. J. Clin. Pathol., 78 (1982), pp. 806-816

23. Behbod and Rosen, 2005,F. Behbod, J.M. Rosen,Will cancer stem cells provide new therapeutic targets? Carcinogenesis, 26 (2005), pp. 703-711

24. Bertucci et al., 2006,F. Bertucci, P. Finetti, N. Cervera, E. Charafe-Jauffret, E. Mamessier, J. Adelaide, S. Debono, G. Houvenaeghel, D. Maraninchi, P. Viens, C. Charpin, J. Jacquemier, D. Birnbaum,Gene expression profiling shows medullary breast cancer is a subgroup of basal breast cancers Cancer Res., 66 (2006), pp. 4636-4644

25. Bertucci et al., 2008,F. Bertucci, B. Orsetti, V. Negre, P. Finetti, C. Rouge, J.C. Ahomadegbe, F. Bibeau, M.C. Mathieu, I. Treilleux, J. Jacquemier, L. Ursule, A. Martinec, Q. Wang, J. Benard, A. Puisieux, D. Birnbaum, C. Theillet,Lobular and ductal carcinomas of the breast have distinct genomic and expression profiles Oncogene, 27 (2008), pp. 5359-5372

26. Razavi P, Chang MT, Xu G, Bandlamudi C, Ross DS, Vasan N, et al The genomic landscape of endocrine-resistant advanced breast cancers. Cancer Cell 2018;34:427–38.

27. Lux MP, Fasching PA, Schrauder MG, Hein A, Jud SM, Rauh C, et al The PI3K pathway: background and treatment approaches. Breast Care 2016;11:398–404.

28. Andre 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 2019;380:1929–40.

29. 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;448:439–44.

30. 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 2008;98:1533–5.

31. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70.

32. Smyth LM, Zhou Q, Nguyen B, Yu C, Lepisto EM, Arnedos M, et al Characteristics and outcome of AKT1 E17K-mutant breast cancer defined through AACR GENIE, a clinicogenomic registry. Cancer Discov 2020;10:526–35.

33. Brown JS, Banerji U. Maximising the potential of AKT inhibitors as anti-cancer treatments. Pharmacol Ther 2017;172:101–15.

34. Chang MT, Asthana S, Gao SP, Lee BH, Chapman JS, Kandoth C, et al Identifying recurrent mutations in cancer reveals widespread lineage diversity and mutational specificity. Nat Biotechnol 2016;34:155–63.

35. Hassan B, Akcakanat A, Holder AM, Meric-Bernstam F. Targeting the PI3-kinase/Akt/mTOR signaling pathway. Surg Oncol Clin N Am 2013;22:641–64.

36. Rudolph M, Anzeneder T, Schulz A, Beckmann G, Byrne AT, Jeffers M, et al AKT1 (E17K) mutation profiling in breast cancer: prevalence, concurrent oncogenic alterations, and blood-based detection. BMC Cancer 2016;16:622.

37. M.J. Duffy et al.,Validated biomarkers: the key to precision treatment in patients with breast cancer Breast(2016)

38. M.J. Duffy et al.,Clinical use of biomarkers in breast cancer: updated guidelines from the European group on tumor markers (EGTM) Eur. J. Cancer (2017)

39. E. Senkus et al.,Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up ESMO guidelines committee,Ann. Oncol.(2015)

40. J.M. Bueno-de-Mesquita et al. Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: a prospective community-based feasibility study (RASTER)
Lancet Oncol (2007)

41. Y. Kataoka et al.Association between gain-of-function mutations in PIK3CA and resistance to HER2-targeted agents in HER2-amplified breast cancer cell lines
Ann. Oncol. (2010)

42. Curtis, C. et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 486, 346–352 (2012).

43. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 490, 61–70 (2012).

44. Meric-Bernstam, F. et al. Survival outcomes by TP53 mutation status in metastatic breast cancer. JCO Precis. Oncol. 2018, PO.17.00245 (2018).

45. Lebok, P. et al. Partial PTEN deletion is linked to poor prognosis in breast cancer. BMC Cancer 15, 963 (2015).

46. Goetz, M. P. et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J. Clin. Oncol. 35, 3638–3646 (2017).

47. Jones, R. H. et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, Phase 2 trial. Lancet Oncol. 21, 345–357 (2020).

48. Banerji, U. et al. A Phase I open-label study to identify a dosing regimen of the pan-AKT inhibitor AZD5363 for evaluation in solid tumors and in PIK3CA-mutated breast and gynecologic cancers. Clin. Cancer Res. 24, 2050–2059 (2018).

49. Schmid, P. et al. Capivasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer: the PAKT trial. J. Clin. Oncol. 38, 423–433 (2020).

50. Carr, T. H. et al. Defining actionable mutations for oncology therapeutic development. Nat. Rev. Cancer 16, 319–329 (2016).