Discoveries Journals
publishing the future

DISCOVERIES 2019, Oct-Dec, 7(4): e103
DOI: 10.15190/d.2019.16

Focused REVIEW

PI3K Inhibitors for Breast Cancer: First FDA Approved Regimen

Andreea Lucia Stancu *

Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

*Corresponding author: Andreea Lucia Stancu, MD, Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Harvard Institute of Medicine, 4 Blackfan Circle, Boston, MA, 02215, USA. E-mail: astancu@bwh.harvard.edu

Citation: Stancu AL. PI3K Inhibitors for Breast Cancer: First FDA Approved Regimen. *Discoveries* 2019, 7(4); e103. DOI:10.15190/d.2019.16

ABSTRACT

PI3K pathway is the most common aberrantly activated pathway in breast cancer, making it an attractive therapeutic target. Despite initial disappointment with several randomized trials of pan-PI3K inhibitors in HR-positive breast cancer, there has been continued effort to more precisely target PI3K isoforms, which has led to clinical benefit for patients with advanced breast cancer

Alpelisib (Piqray) is the first PI3K inhibitor approved by the FDA in 2019, to be used in combination with the FDA-approved endocrine therapy fulvestrant, to treat 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.

Keywords: PI3K inhibitors, breast cancer, FDA approval, alpelisib.

Abbreviations:
Food and Drug Administration (FDA); European Medicines Agency (EMA)

1. Introduction

The phosphatidylinositol 3-kinase (PI3K)-protein kinase B (PKB/AKT)-mammalian target of rapamycin (mTOR) axis regulates critical physiological functions and cellular processes, including cell proliferation, growth, survival, motility and metabolism[1]. The phosphatidylinositol 3-kinase (PI3K) pathway is the most common aberrantly activated pathway in breast cancer, making it an attractive therapeutic target. This pathway has been extensively reviewed elsewhere[2].

Phosphatidylinositol 3-kinases (PI3Ks) are a family of lipid kinases that are divided into three classes based on their structures and substrate specificitie.

In breast cancer, the PI3K/AKT/mTOR pathway can be deregulated by a number of different mechanisms. First, PIK3CA activating mutations located either at the helical or the kinase domain are present in more than one-third of early breast cancer tumors (45% in luminal A, 29% in luminal B, 39% in HER2-enriched and 9% in basal-like tumors)[3-19]. A recent report has identified similar mutation rates in metastatic breast cancer (MBC) biopsies, confirming the clonal character of this mutation [20]. Second, inactivating events might occur in tumor suppressor genes, mostly PTEN, but also PIK3R1, INPP4B, TSC1, TSC2 and LKB1, leading to the activation of this pathway[18-22]. In addition, PIK3CA amplification and mutations in the AKT gene have been also described[20,23-25].

Recent molecular profiling data from MBC patients seem to indicate that in advanced HR+/HER2- breast cancer, a PIK3CA mutation would lead to a certain resistance to chemotherapy and a poor outcome[26-28]. In the case of HER2-positive breast cancer, PIK3CA mutations seem to

be associated with worse prognosis, either in the advanced and in the early setting[29,30]. Moreover, the PI3K/Akt/mTOR pathway has been described as potentially intervening in secondary endocrine resistance in HR-positive breast cancer[31]. In preclinical models, long-term estrogen-deprived breast cancer cells and long-term exposure to tamoxifen are associated to an up-regulation of the PI3K pathway, leading to a ligand-independent activation of ER by its phosphorylation through the mTOR complex 1 (mTORC1)/S6K1 axis[31,32]. Hence, there is a strong rationale to therapeutically target the PI3K/AKT/mTOR axis, especially in HR-positive breast cancer.

Piqray (alpelisib) was recently approved by the FDA, to be used in combination with the FDA-approved endocrine therapy fulvestrant, to treat 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.

The FDA also approved the companion diagnostic test, therascreen PIK3CA RGQ PCR Kit, to detect the PIK3CA mutation in a tissue and/or a liquid biopsy. Patients who are negative by the therascreen test using the liquid biopsy should undergo tumor biopsy for PIK3CA mutation testing.

This focused review describes the first FDA approved regimen based on PI3K inhibition that can be used in breast cancer treatment.

2. PI3K inhibitors in clinical trials

Initially, a number of pan-PI3K inhibitors were developed and used. This include buparlisib and pictilisib. Early PI3K inhibitors (PI3Ki) targeted each of the four catalytic isoforms of class I PI3Ks, potentially for a broader activity in a number of tumor types with a range of molecular alterations. However, this broad inhibition may lead to potentially a higher risk of adverse events (AEs), which could limit the use of such agents at therapeutic doses.

Despite initial disappointment with several randomized trials of pan-PI3K inhibitors in HR-positive breast cancer, there has been continued effort to more precisely target PI3K isoforms, which has led to clinical benefit for patients with advanced breast cancer.

Selective inhibition of specific PI3K isoforms may allow the administration of therapeutic doses of drugs without the off-target toxicity, although they require a narrower patient selection[42]. In breast cancer, the most common molecular alterations in the PI3K pathway are activating mutations in the PIK3CA gene, inducing hyperactivation of p110α. Hence, development in breast cancer patients has been focused on inhibitors with higher selection for this isoform. Examples of selective inhibitors are alpelisib and taselisib,

3. First FDA approved PI3K inhibitor for breast cancer: alpelisib (Piqray)

Piqray is the first PI3K inhibitor to demonstrate a clinically meaningful benefit in treating patients with this type of breast cancer. The ability to target treatment to a patient's specific genetic mutation or biomarker is becoming increasingly common in cancer treatment, and companion diagnostic tests assist oncologists in selecting patients who may benefit from these targeted treatments.

Alpelisib (BYL719; Novartis Pharmaceuticals, Basel, Switzerland) is the first oral PI3Ki to selectively target the class I p110α-isoform (IC50=4.6 nM)[43]. A phase I trial (NCT01219699) included patients with PIK3CA-altered advanced solid tumors and showed sensitivity to alpelisib monotherapy[44]. The combination of alpelisib with fulvestrant demonstrated synergism when combined in xenografts models[31]. In a phase Ib dose expansion trial (NCT01219699), alpelisib plus fulvestrant led to a complete or partial response in 29% of heavily pretreated MBC patients with PIK3CA-mutated tumors[45] and a favorable safety profile in these patients with mainly on-target effects, notably hyperglycemia, nausea or diarrhea.

Common side effects of Piqray are high blood sugar levels, increase in creatinine, diarrhea, rash, decrease in lymphocyte count in the blood, elevated liver enzymes, nausea, fatigue, low red blood cell count, increase in lipase (enzymes released by the pancreas), decreased appetite, stomatitis, vomiting, weight loss, low calcium levels, aPTT prolonged (blood clotting taking longer to occur than it should), and hair loss. Health care professionals are advised to monitor patients taking Piqray for severe hypersensitivity reactions (intolerance).

In light of these results, the phase III SOLAR-1 clinical trial (NCT02437318) was conducted to

evaluate the efficacy and safety of alpelisib plus fulvestrant in HR+/HER2- MBC patients previously treated with endocrine therapy. The study was enriched with tumors harboring a PIK3CA mutation but included also a cohort of PIK3CA wild-type (wt) as a proof-of-concept of activity in this subgroup[46]. The primary end point was PFS in the PIK3CA-mutated cohort, whereas secondary end points included, among others, overall survival (OS) in the PIK3CA-mutated cohort and safety and efficacy in the PIK3CAwt group (determined by OS and PFS). PIK3CA status was centrally determined before entry using tumor tissue. In the PIK3CA-mutant cohort (n = 341), the median PFS was 11 months (95% CI, 7.5–14.5) in the alpelisib arm versus 5.7 months (95% CI, 3.7–7.4) in the fulvestrant-placebo group (HR, 0.65; 95% CI, 0.50–0.85; P < 0001). In contrast, in the PIK3CAwt cohort (n = 231), alpelisib administration was not associated with a significant effect in PFS (7.4 versus 5.6 months; HR 0.85; 95% CI, 0.58–1.25).

As observed with the initial phase I clinical trials, alpelisib toxicity was associated with specific p110α inhibition and included hyperglycemia (all-grade, 63.7% versus 9.8% for the alpelisib and placebo arms, respectively), diarrhea (57.7% 15.7%) and rash (35.6% versus 5.9%). Permanent discontinuation of alpelisib or placebo due to AEs occurred in 25% of patients in the alpelisib group versus 4.2% in the placebo arm; hyperglycemia and rash were the two main AEs leading to discontinuation of alpelisib. These toxicities were observed despite the exclusion of patients with diagnosed type 1 diabetes or uncontrolled type 2 diabetes. Moreover, the clinical trial was amended during its course to restrict the inclusion of patients with pre-diabetes and to provide guidelines for early management of hyperglycemia.

Results from the SOLAR-1 trial led to the approval by the Food and Drug Administration (FDA) of alpelisib in combination with fulvestrant for postmenopausal women, and men, with HR+/HER2-, PIK3CA-mutated, advanced or MBC as detected by an FDA-approved test following progression on or after an endocrine-based regimen. The currently approved companion diagnostic test is therascreen®PIK3CA RGQ PCR Kit (QIAGEN Manchester, Ltd., Germany), to select patients who have PIK3CA mutations in tumor tissue specimens and/or ctDNA isolated from plasma specimens. The recommendation by the FDA is to initially carry out the test in ctDNA and if the test is negative for PIK3CA mutations in plasma, patients should undergo testing for PIK3CA mutations in tumor tissue. Outside the United States, there is no mandatory companion diagnostic test to determine PIK3CA mutation status. A question remains as to whether to use tumor tissue or ctDNA for its determination. A subgroup analysis from the SOLAR-1 phase III trial evaluating PFS by PIK3CA-mutational status measured in ctDNA observed that assessing mutational status via liquid biopsy resulted in even larger clinical benefit compared with tissue biopsy, with improvement of median PFS from 3.7 months to 10.9 months. Indeed, while patients with PIK3CA mutations evaluated in tissue samples had a 35% reduction in risk for disease progression, the risk reduction was 45% for patients with PIK3CA mutations identified in ctDNA. Moreover, in the combined analyses from the BELLE-2 and BELLE-3 clinical trials, PIK3CAmut tumors derived more benefit from buparlisib treatment as compared with PIK3CAwt, although this benefit seemed to be numerically higher when the PIK3CA mutation was identified by BEAMing in ctDNA as compared with those identified by PCR in tumor tissue. Based on these results, the easy accessibility of ctDNA and the good correlation of PIK3CA mutation status determined by ctDNA and tumor tissue makes it plausible to initially use ctDNA and to carry out research for a PIK3CA mutation in the tumor tissue in the case of ctDNA negativity.

4. Conclusion

The high frequency of genetic alterations in the PI3K pathway has provided the rationale for development of inhibitors targeting PI3K/AKT PMID: 31828441.

Piqray is the first PI3K inhibitor to demonstrate a clinically meaningful benefit in treating patients with breast cancer harboring specific mutatinos. The ability to target treatment to a patient's specific genetic mutation or biomarker is becoming increasingly common in cancer treatment, and companion diagnostic tests assist oncologists in selecting patients who may benefit from these targeted treatments.

This is a promising result, but only a small but important step in our fight against breast cancer.

Acknowledgments

The author is funded by a US NIH T32 grant.

Conflict of interests

There are no conflicts of interest.

References

1 Levy, S. B. & Bonnie, M. Antibacterial resistance worldwide: Causes, challenges and responses. Nat. Med. 2004, 10: S122–S129.
2 Bretonnière, C. et al. Strategies to reduce curative antibiotic therapy in intensive care units (adult and paediatric). Intensive Care Med. 2015. 41: 1181–1196.
3 Hornsey, M. & Wareham, D. W. In vivo efficacy of glycopeptide-colistin combination therapies in a Galleria mellonella model of Acinetobacter baumannii infection. Antimicrob. Agents Chemother. 2011, 55: 3534–3537.
4 Bush, K. A resurgence of β-lactamase inhibitor combinations effective against multidrug-resistant Gram-negative pathogens. Int. J. Antimicrob. Agents 2015, 46: 483–493.
5 Martinez, J. L. General principles of antibiotic resistance in bacteria. Drug Discov. Today Technol. 2014, 11: 33–39.
6 Bassetti, M. et al. Preventive and therapeutic strategies in critically ill patients with highly resistant bacteria. Intensive Care Med. 2015, 41: 776–795.
7 Delory, T. et al. Impact of a program combining pre-authorization requirement and post-prescription review of carbapenems: An interrupted time-series analysis. Eur. J. Clin. Microbiol. Infect. Dis. 2013, 32: 1599–1604.
8 Álvarez-Lerma, F. et al. Prevention of Ventilator-Associated Pneumonia: The Multimodal Approach of the Spanish ICU "Pneumonia Zero" Program. Crit. Care Med. 2018; 46(2):181-188.
9 Derde, L. P. G et al. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. Lancet Inf. Dis. 2014, 14: 31–39.
10 Jacobs, M. et al. Population pharmacokinetics of colistin methanesulfonate and colistin in critically ill patients with acute renal failure requiring intermittent hemodialysis. Antimicrob. Agents Chemother. 2016, 60: 1788–1793.
11 Ruppé, É., Woerther, P.-L. & Barbier, F. Mechanisms of antimicrobial resistance in Gram-negative bacilli. Ann. Intensive Care 2015, 5: 21.
12 Hussar DA. New Drugs 2019, part 4. Nursing. 2019 Nov;49(11):34-43.
13 Eljaaly K, Alharbi A, Alshehri S, Ortwine JK, Pogue JM. Plazomicin: A Novel Aminoglycoside for the Treatment of Resistant Gram-Negative Bacterial Infections. Drugs. 2019 Feb;79(3):243-269.
14 Scott LJ. Eravacycline: A Review in Complicated Intra-Abdominal Infections. Drugs. 2019 Feb;79(3):315-324.
15 European Medicines Agency. Xerava (Eravacycline): summary of product characteristics. 2018. http://www.ema.europa.eu/. Accessed in December 2019.
16 Kaul G, Saxena D, Dasgupta A, Chopra S. Sarecycline hydrochloride for the treatment of acne vulgaris. Drugs Today (Barc). 2019 Oct;55(10):615-625.
17 Moore A, Green LJ, Bruce S, Sadick N, Tschen E, Werschler P et al. Once-Daily Oral Sarecycline 1.5 mg/kg/day Is Effective for Moderate to Severe Acne Vulgaris: Results from Two Identically Designed, Phase 3, Randomized, Double-Blind Clinical Trials. J Drugs Dermatol. 2018 Sep 1;17(9):987-996.
18 Moore AY, Charles JEM, Moore S. Sarecycline: a narrow spectrum tetracycline for the treatment of moderate-to-severe acne vulgaris. Future Microbiol. 2019 Sep;14:1235-1242.
19 Rodvold KA, Burgos RM, Tan X, Pai MP. Omadacycline: A Review of the Clinical Pharmacokinetics and Pharmacodynamics. Clin Pharmacokinet. 2019 Nov 27.
20 Opal S, File TM, van der Poll T, Tzanis E, Chitra S, McGovern PC An Integrated Safety Summary of Omadacycline, a Novel Aminomethylcycline Antibiotic. Clin Infect Dis. 2019 Aug 1;69(Supplement_1):S40-S47.
21 Lan SH, Chang SP, Lai CC, Lu LC, Chao CM. The efficacy and safety of omadacycline in treatment of acute bacterial infection: A systemic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2019 Dec;98(51):e18426.
22 Abrahamian FM, Sakoulas G, Tzanis E, Manley A, Steenbergen J, Das AF. Omadacycline for Acute Bacterial Skin and Skin Structure Infections. Clin Infect Dis. 2019 Aug 1;69(Supplement_1):S23-S32.
23 O'Riordan W, Cardenas C, Shin E, Sirbu A, Garrity-Ryan L, Das AF et al. Once-daily oral omadacycline versus twice-daily oral linezolid for acute bacterial skin and skin structure infections (OASIS-2): a phase 3, double-blind, multicentre, randomised, controlled, non-inferiority trial. Lancet Infect Dis. 2019 Oct;19(10):1080-1090.
24 https://www.cosmopharma.com/news-and-media/press-releases-and-company-news/2018/181119 ; Accessed in December 2019
25 Steffen R, Jiang ZD, Gracias Garcia ML, Araujo P, Stiess M, Nacak T. Rifamycin SV-MMX® for treatment of travellers' diarrhea: equally effective as ciprofloxacin and not associated with the acquisition of multi-drug resistant bacteria. J Travel Med. 2018 Jan 1;25(1)

26 https://www.centerwatch.com/directories/1067-fda-approved-drugs/listing/4098-recarbrio-imipenem-cilastatin-and-relebactam Accessed in December 2019.

27 https://www.mrknewsroom.com/news-release/prescription-medicine-news/fda-approves-mercks-recarbrio-imipenem-cilastatin-and-releba Accessed in December 2019.

28 https://www.rxlist.com/pretomanid-side-effects-drug-center.htm Accessed in December 2019

29 Tweed CD, Dawson R, Burger DA, Conradie A, Crook AM, Mendel CM et al. Bedaquiline, moxifloxacin, pretomanid, and pyrazinamide during the first 8 weeks of treatment of patients with drug-susceptible or drug-resistant pulmonary tuberculosis: a multicentre, open-label, partially randomised, phase 2b trial. Lancet Respir Med. 2019 Dec;7(12):1048-1058.

30 McKenna L, Furin J.. Are pretomanid-containing regimens for tuberculosis a victory or a victory narrative? Lancet Respir Med. 2019 Dec;7(12):999-1000.

31 [No authors listed]. Lefamulin (Xenleta) for community-acquired bacterial pneumonia. Med Lett Drugs Ther. 2019 Sep 23;61(1581):145-148.

32 Choi JJ, McCarthy MW. Cefiderocol: a novel siderophore cephalosporin. Expert Opin Investig Drugs. 2018 Feb;27(2):193-197.

33 Sato T, Yamawaki K. Cefiderocol: Discovery, Chemistry, and In Vivo Profiles of a Novel Siderophore Cephalosporin. Clin Infect Dis. 2019 Nov 13;69(Supplement_7):S538-S543.

34 Ito A, Sato T, Ota M, Takemura M, Nishikawa T, Toba S et al. In Vitro Antibacterial Properties of Cefiderocol, a Novel Siderophore Cephalosporin, against Gram-Negative Bacteria. Antimicrob Agents Chemother. 2017 Dec 21;62(1). pii: e01454-17.

35 Zhanel GG, Golden AR, Zelenitsky S, Wiebe K, Lawrence CK, Adam HJ,. Cefiderocol: A Siderophore Cephalosporin with Activity Against Carbapenem-Resistant and Multidrug-Resistant Gram-Negative Bacilli. Drugs. 2019 Feb;79(3):271-289

36 Bassetti M. et al., New antibiotics for ventilator-associated pneumonia, Curr Opin Infect Dis. 2018, 31(2): 177-186.

37 WHO, Antibacterial agents in clinical development, May 2017. Available at http://www.who.int/medicines/news/2017/IAU_AntibacterialAgentsClinicalDevelopment_webfinal_2017_09_19.pdf Accessed on 29 March 2018.

38 Choi J.J.and McCarthy M.W. Cefiderocol: A novel siderophore cephalosporin, Expert Opinion on Investigational Drugs, 2018, 27(2): 193-197.

39 Wyckoff E.E. et al. Catechol Siderophore Transport by Vibrio cholerae. J Bacteriol. 2015, 197(17): 2840-9.

40 Hackel M.A. et al. In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, against a Recent Collection of Clinically Relevant Gram-Negative Bacilli from North America and Europe, Including Carbapenem-Nonsusceptible Isolates (SIDERO-WT-2014 Study). Antimicrob Agents Chemother. 2017, 61(9): 2017.

41 Nichols D . et al. Use of ichip for high-throughput in situ cultivation of "uncultivable" microbial species. Appl Environ Microbiol. 2010, 76: 2445–50.

42 Lewis, K. Platforms for antibiotic discovery. Nature Rev. Drug Discov. 2013, 12: 371–387.

43 Ling L.L., et al. A new antibiotic kills pathogens without detectable resistance. Nature. 2015, 517: 455–9.

44 Homma T., et al. Dual targeting of cell wall precursors by teixobactin leads to cell lysis. Antimicrob Agents Chemother. 2016, 60(11): 6510–6517.

45 Arias C. A and Murray B. E. A New Antibiotic and the Evolution of Resistance. N Engl J Med. 2015, 372(12): 1168–1170.

46 Hover B.M. et al. Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-positive pathogens. Nature Microbiology. 2018, 3(4): 415-422.