MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

TechBrief Horizon Scanning	Report No.: 002/2023

CAPIVASERTIB FOR BREAST CANCER

EXECUTIVE SUMMARY

The serine/threonine kinase AKT is frequently activated in various subtypes of breast cancer including hormone receptor-positive (HR+) disease, human epidermal growth factor receptor 2-negative (HER2-)-amplified, and triple-negative tumours. Activation of AKT isoforms promotes cell proliferation, tumour growth, and progression. Capivasertib (AZD5363) is a novel, AKT inhibitor developed by AstraZeneca as a new therapeutic approach. The combination of capivasertib with hormone therapy resulted in longer progression-free survival (PFS) and overall survival (OS) with an acceptable toxicity profile in women with HR+ HER2- metastatic breast cancer. The same results were also observed in the combination of capivasertib with chemotherapy in triple-negative metastatic breast cancer (mTNBC). More results of the ongoing phase III trials will better clarify the therapeutic role of capivasertib in breast cancer.

Keywords: Capivasertib, breast cancer, AKT inhibitor, targeted therapy, PI3K/AKT/mTOR pathway

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer worldwide and is the leading cause of cancer-related death among women.[1] The most common subtype of breast cancer is HR+, HER2-, accounting for 68% of all diagnosed breast cancer.[2]

In Malaysia, breast cancer is the most common cancer and accounted for 34.1% of all cancer among females. The new cases of breast cancer had increased from 32.1% (2007 to 2011) to 34.1% (2012 to 2016) of overall cancer among women. The incidence was highest among Chinese (40.7 per 100,000) followed by Indian (38.1 per 100,000) and Malay (31.5 per 100.000).[3]

Although there are many available treatments for breast cancer, the treatment process is often accompanied by the development of drug resistance, which eventually leads to treatment failure. Activating phosphoinositide 3-kinase, catalytic, alpha polypeptide (PI3KCA) mutation is the most common genetic alteration in HR+ breast cancer. The tumours may initially respond to breast cancer, however, 15 to 20% are intrinsically resistant to treatment, and another 30 to 40% acquire resistance to treatment over a period of many years.[4]

THE TECHNOLOGY

The serine/threonine kinase AKT is a key component of the phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR signaling pathway as it exerts an important role in cell growth, proliferation, survival, and metabolism.[5] The three members of AKT family are encoded by three genes (AKT1, AKT2, and AKT3). The serine/threonine kinase AKT is frequently activated in various subtypes of breast cancer including hormone receptor-positive (HR+) disease, human epidermal growth factor receptor 2-negative (HER2-)-amplified, and triple-negative tumours.[5,6] Activation of AKT isoforms (AKT1, AKT2, and AKT3) promotes cell proliferation, tumour growth, and progression. The activation is also associated with resistance to conventional treatment such as anti-HER2 regimen, endocrine treatment, and chemotherapy.[7]

Capivasertib (AZD5363) is a novel, AKT inhibitor developed by AstraZeneca. It competes with adenosine triphosphate (ATP) to associate with AKT kinase at the ATP binding sites, and inhibit all AKT isoforms activity (Figure 1).[5] Capivasertib has shown preclinical efficacy both in-vivo and in-vitro and is currently being evaluated as a monotherapy and in combination with existing treatment in tumours harbouring alterations in the AKT pathway. Capivasertib 400 mg is administered orally twice daily according to an intermittent dosing schedule of four days on and three days off.[7,8]

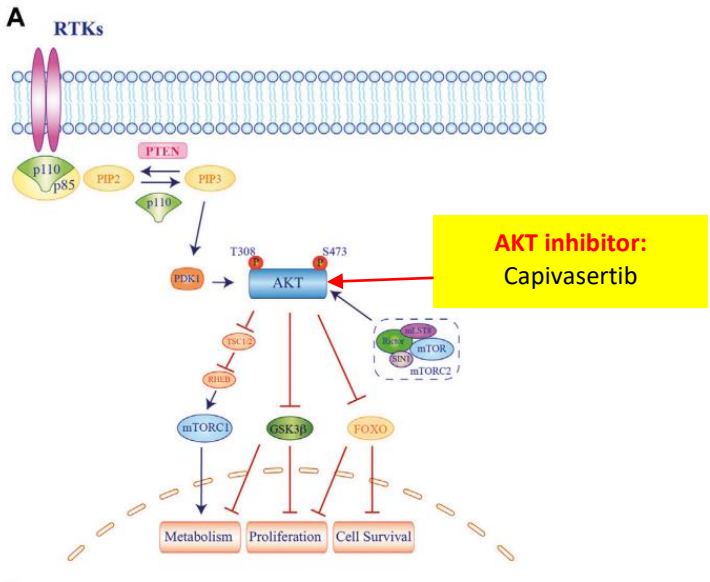

Figure 1. Mechanism of Action of Capivasertib

PATIENT GROUP AND INDICATION

Capivasetib is indicated for patients with breast cancer. It is currently tested in patients with HER+, HER2-, metastatic breast cancer and triple-negative metastatic breast cancer (mTNBC) as a combination with hormone therapy or chemotherapy.

CURRENT PRACTICE

Based on the Malaysian Clinical Practice Guideline (CPG) on Management of Breast Cancer, the systemic treatments available for breast cancer are as below:

Table 1. Systemic Treatment for Breast Cancer[9]

Type of Treatment	Mechanism of Action	Drugs
Chemotherapy	Chemotherapy drugs kill fast-growing cells in the body. It can be given before surgery (neoadjuvant) to downstage the tumour and improve surgery outcome; or after surgery (adjuvant) to reduce the rate of cancer recurrence.	• Anthracyclines: Doxorubicin Epirubicin • Taxanes: Paclitaxel, Docetaxel • 5-fluorouracil (5-FU) • Antimetabolites: Capecitabine, Gemcitabine • Vinorelbin • Cyclophosphamide • Carboplatin • Eribulin
Hormonal Therapy	Hormone therapy slows or stops the growth of hormone-sensitive tumours by blocking the body's ability to produce hormones or interfering with hormones' effects on breast cancer cells.	• Aromatase inhibitors (AI): Anastrozole, Letrozole, Exemestane • Selective oestrogen receptor modulators (SERM): Tamoxifen, • Selective oestrogen receptor down-regulator (SERD): Fulvestrant
Targeted Therapy	Targeted drug therapy is directed at (target) proteins on breast cancer cells that help them grow, spread, and live longer. Targeted drugs work to destroy cancer cells or slow down their growth.	• Cyclin dependant kinases 4 and 6 (CDK 4/6) Inhibitors: Palbociclib, Ribociclib, Abemaciclib • Mammalian target of rapamycin (mTOR) inhibitors: Everolimus • Phosphatidylinositol-3-kinases (PI3K) inhibitors: Alpelisib • Monoclonal antibodies: Transtuzumab, Pertuzumab • Kinase Inhibitor: Lapatinib • Poly ADP ribose polymerase (PARP) inhibitor: Olaparib, Talazaparib

SAFETY AND EFFICACY

A systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed, and general search engines such as Google Scholar and US Food and Drug Administration (US FDA). Based on retrievable evidence, four randomised controlled trials were included in this review.

A. Efficacy

i. HR+ HER2- Metastatic Breast Cancer

Three trials reported the effectiveness of capivasertib in combination with hormone therapy or chemotherapy in women with HR+, HER2- metastatic breast cancer.

Combination of Capivasertib with Hormone Therapy

In the randomised, double-blind, placebo-controlled phase II FAKTION trial, capivasertib in combination with fulvestrant was evaluated in post-menopausal women with aromatase inhibitor (AI)-resistant, HR+, HER2- metastatic breast cancer. A total of 140 patients were randomised (1:1) to receive fulvestrant 500mg (day-1) every 28 days (plus a 500mg loading dose on day 15 of cycle-1), with either capivasertib 400mg (n=69) or matching placebo (n=71), orally twice daily on an intermittent weekly scheduled of four days on, and three days off, starting on cycle-1 day 15.[10]

Median follow-up for the data cut-off was 58.5 months for the capivasertib group, and 62.3 months for the placebo group. The progression-free survival (PFS) in the intention-to-treat population was 10.3 months (95% CI 5.0 to 13.4) in the capivasertib group compared with 4.8 months (95% CI 3.1 to 7.9) for the placebo group (adjusted hazard ratio [HR] 0.56 [95% CI 0.38 to 0.81]; two-sided p=0.0023). The median overall survival (OS) in the capivasertib versus placebo group was 29.3 months (95% CI 23.7 to 39.0) versus 23.4 months (95% CI 18.7 to 32.7, adjusted HR 0.66 [95% CI 0.45 to 0.97]; two-sided p=0.035).[10]

In a subgroup of patients who had PI3KCA pathway alteration (n=74), the median PFS was 12.8 months (95% CI 6.6 to 18.8) in the capivasertib group compared with 4.6 months (95% CI 2.8 to 7.9) in the placebo group (p=0.014). The median OS for the capivasertib group was 38.9 months (95% CI 23.3 to 5.7) compared with 20.0 months (95% CI 14.8 to 31.4) in the placebo group (p=0.0047). No significant differences in PFS and OS were observed in the non-altered subgroup treated with capivasertib versus placebo.[10]

The ongoing phase III CAPItello-291 trial further evaluated the combination of capivasertib plus fulvestrant in post-menopausal women with HR+, HER2- metastatic breast cancer following recurrence or progressing on or after an AI (with or without CDK4/6 inhibitor). A total of 708 patients were randomised (1:1) to either capivasertib group (n = 355) or the placebo group (n = 353). The objective response rate (ORR) was 22.9% among patients in the capivasertib group compared with 12.2% in the placebo group. The median PFS was 7.2 months (95% CI 7.2 to 7.4) among those who received capivasertib plus fulvestrant versus 3.6 months in the placebo plus fulvestrant group (95% CI 2.8 to 3.7; HR, 0.60; 95% CI 0.51 to 0.71; two-sided p<0.001).[11]

In a subgroup of patients who had PI3KCA alterations, the median PFS was 7.3 months (95% CI 5.5 to 9.0) in the capivasertib group versus 3.1 months

(95% CI 2.0 to 3.7) in the placebo group (HR, 0.50; 95% CI 0.38 to 0.65; two-sided p<0.001). In the non-altered population, the PFS was 7.2 months (95% CI 4.5 to 7.4) in the capivasertib group versus 3.7 months (95% CI 3.0 to 5.0) in the placebo group (HR, 0.70; 95% CI 0.56 to 0.88).[11]

Combination of Capivasertib with Chemotherapy

The BEECH trial is a randomised, double-blind, placebo-controlled phase II study that evaluated the combination of capivarsertib with paclitaxel patients with HR+, HER2- metastatic breast cancer with or without a PIK3CA mutation. A total of 110 patients were randomised to receive capivasertib 400mg twice daily with paclitaxel 90mg/m^2 (day-1, 8, and 15 of a 28-day cycle) (n=54) or placebo plus paclitaxel (n=56). In the overall population, median PFS was 10.9 months (95% CI 8.3 to 12.4) in the capivasertib group and 8.4 months (95% CI 8.2 to 10.8) in the placebo group (HR 0.80; 80% CI 0.60 to 1.06, p=0.308). In the PIK3CA mutation subpopulation, median PFS was 10.9 months (95% CI 8.7 to 11.5) in the capivasertib group and 10.8 months (95% CI 8.3 to 14.3) in the placebo group (HR 1.11; 80% CI 0.73 to 1.68, p=0.760).[12]

Combination of Capivasertib with CDK 4/6 Inhibitor and Hormone Therapy

The ongoing CAPItello-292 phase III trial will further evaluate the effectiveness of capivasertib in combination with Palbociclib and fulvestrant in patients with HR+, HER2- metastatic breast cancer. This trial is expected to complete by 2026.[13]

ii. Metastatic Triple-Negative Breast Cancer

One trial reported the effectiveness of capivasertib in combination with chemotherapy in women with metastatic triple-negative breast cancer (mTNBC).

Combination of Capivasertib with Chemotherapy

In the randomised, double-blind, placebo-controlled phase II PAKT trial, 140 patients with mTNBC (with or without a PIK3CA mutation) were randomised to receive capivasertib 400mg twice daily with paclitaxel 90mg/m2 (day-1, 8, and 15 of a 28-day cycle) (n=70) or placebo plus paclitaxel (n=70). After a median follow-up of 18.2 months (95% CI, 13.5 to 24.0), 112 progression events were reported. The ORR was 34.8% in the capivasertib group and 19.0% in the placebo group.[14] The median PFS and OS for the overall population and PIK3CA mutation subpopulation were described in Table 2:

Table 2. Median PFS and OS[14]

End Point	Overall Population		PIK3CA Mutation Subpopulation	
	Capivasertib + Paclitaxel	Placebo + Paclitaxel	Capivasertib + Paclitaxel	Placebo + Paclitaxel
PFS				

Median (95% CI)	5.9 months (3.8 to 7.5)	4.2 months (3.5 to 5.2)	9.3 months (3.7 to 17.7)	3.7 months (1.9 to 5.9)
HR (95% CI)	0.74 (0.50 to 1.08)		0.30 (0.11 to 0.79)	
2-sided p	0.11		0.01	
OS				
Median (95% CI)	19.1 months (10.9 to 20.9)	12.6 months (10.4 to 16.9)	NR (10.2 to NR)	10.4 months (4.0 to NR)
HR (95% CI)	0.61 (0.37 to 0.99)		0.37 (0.12 to 1.12)	
2-sided p	0.04		0.07	

Abbreviations: PFS – Progression-free survival, OS – overall response rate, NR – not reached

B. Safety

Combination of Capivasertib with Hormone Therapy

In the FAKTION study, the most common grade III or IV adverse events reported in capivasertib group were hypertension (32%), diarrhoea (14%), and rash (14%). One death due to atypical pulmonary infection was assessed as possibly related to capivasertib treatment.[10]

In the CAPItello-291 trial, rash (12.1%), diarrhoea (9.3%), and hyperglycaemia (2.3%) were the most common grade III or IV adverse events reported in capivasertib group. The rate of discontinuation due to adverse events was 13% among patients who received capivasertib plus fulvestrant versus 2.3% among patients who received placebo plus fulvestrant. The safety profile was similar for the AKT-altered group.[11]

Combination of Capivasertib with Chemotherapy

The most commonly reported adverse events in capivasertib group (patients with HR+, HER2- metastatic breast cancer) of BEECH trial were diarrhoea (76%), alopecia (52%), and nausea (39%).[12]

In the PAKT trial, the most common grade III or IV adverse events reported in the capivasertib group versus the placebo were diarrhoea (13% versus 1%), infection (4% versus 1%), neutropaenia (3% versus 3%), rash (4% versus 0%), and fatigue (4% versus 0%), respectively.[14]

ESTIMATED COST

The cost of 200mg capivasertib for research use is USD1350 (RM5900).[15]

OTHER ISSUES

A. Organisational

There was no organisational issue identified on capivasertib.

B. Societal/ethical

The combination of capivasertib with fulvestrant and palbociclib as a new strategy to boost capivasertib efficacy in upcoming CAPItello-292 phase III trial has raised some concern about the additional or cumulative toxicities.

POTENTIAL IMPACT

The combination of capivasertib with hormone therapy resulted in longer PFS and OS with an acceptable toxicity profile in women with HR+ HER2- metastatic breast cancer. The same results were also observed in the combination of capivasertib with chemotherapy in mTNBC. More results of the ongoing phase III trials will better clarify the therapeutic role of capivasertib in breast cancer.

REFERENCES

1. WHO International Agency for Research on Cancer. Global Cancer Observatory (GLOBOCAN) 2018. Available at: https://gco.iarc.fr/ Accessed on 2 February 2023.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results Program: Female Breast Cancer Subtype. Available at: https://seer.cancer.gov/statfacts/html/breast-subtypes.html Accessed on 2 February 2023.
3. National Cancer Institute, Ministry of Health Malaysia. Malaysia National Cancer Registry Report (MNCR) 2012-2016. Putrajaya: Ministry of Health Malaysia; 2019.
4. Lei JT, Anurag M, Haricharan S, et. al. Endocrine therapy resistance: new insights. Breast. 2019;48 Suppl 1(Suppl 1):S26-S30.
5. Martorana F, Motta G, Pavone G, et al. AKT Inhibitors: New Weapons in the Fight Against Breast Cancer? Front Pharmacol. 2021;12:662232.
6. Hua H, Zhang H, Chen J, et. al. Targeting Akt in cancer for precision therapy. J Hematol Oncol. 2021;14(1):128.
7. Andrikopoulou A, Chatzinikolaou S, Panourgias E, et al. The emerging role of capivasertib in breast cancer. Breast. 2022;63:157-167.
8. AstraZeneca. Capivasertib. Available at: https://www.astrazeneca.com/media-centre/press-releases/2022/capivasertib-pfs-in-hr-positive-breast-cancer.html (Accessed on 31 January 2023)
9. Malaysian Health Technology Assessment Section. Clinical Practice Guideline Management of Breast Cancer. 3rd ed. Putrajaya: Ministry of Health Malaysia; 2020.
10. Howell SJ, Casbard A, Carucci M, et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. Lancet Oncol. 2022;23(7):851-864.

11. CancerNetwork. Capivasertib Plus Fulvestrant Yields PFS Improvement in HR+/HER2- Breast Cancer. Available at: https://www.cancernetwork.com/view/capivasertib-plus-fulvestrant-yields-pfs-improvement-in-hr-her2-breast-cancer (Accessed on 2 February 2023).
12. Turner NC, Alarcón E, Armstrong AC, 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(5):774-780.
13. ClinicalTrials.gov. Capivasertib + Palbociclib + Fulvestrant for HR+/HER2- Advanced Breast Cancer (CAPItello-292). Available at: https://clinicaltrials.gov/ct2/show/NCT04862663 (Accessed on 2 February 2023).
14. Schmid P, Abraham J, Chan S, 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. 2020;38(5):423-433.
15. MedKoo Biosiences, Inc. Capivasertib. Available at: https://www.medkoo.com/products/4993 (Accessed on 14 February 2023).

Prepared by:
Balqis binti Abdul Ghani
Senior Principal Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Reviewed by:
Dr Syaqirah Akmal
Public Health Physician
Senior Principal Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Izzuna Mudla Binti Mohamed Ghazali
Public Health Physician
Deputy Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Disclosure: The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

Horizon Scanning Unit, MaHTAS,
Medical Development Division,
Ministry of Health, Malaysia

Email: horizonscanningunit.cptk@moh.gov.my
Web: http://www.moh.gov.my