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Indirect treatment comparison of efficacy and safety of capivasertib-fulvestrant versus alpelisib-fulvestrant for *PIK3CA*-altered, HR-positive, advanced breast cancer after disease progression following endocrine-based therapy

Evelien de Wilt[1], Robert Hettle[2], Bengt Liljas[3*]

[1]Health Economics and Payer Evidence, AstraZeneca, Cambridge, UK; [2]Health Technology Assessment and Modelling Science, AstraZeneca, Cambridge, UK; [3]Health Economics and Payer Evidence, AstraZeneca, Gaithersburg, MD, USA.

Objective

- To assess the relative efficacy and safety of capivasertib-fulvestrant versus alpelisib-fulvestrant for patients with HR-positive, HER2-negative, *PIK3CA*-altered ABC, via an anchored indirect treatment comparison

Conclusions

- Results from the efficacy indirect treatment comparison indicate that capivasertib-fulvestrant has numerically improved PFS and a high probability of being more efficacious (based on PFS) than alpelisib-fulvestrant
- Results of the safety indirect treatment comparison suggest that capivasertib-fulvestrant has an overall more favorable safety profile versus alpelisib-fulvestrant with a lower risk of treatment discontinuation due to AEs, a significant reduction in the risk of any grade 4 AEs, and any grade of hyperglycemia, rash, weight decreased, alopecia, and stomatitis. Capivasertib-fulvestrant has an increased risk of any grade diarrhea when compared with alpelisib-fulvestrant
- Results are exploratory and subject to limitations

Plain language summary

Why did we perform this research?

- Following the recent approval of capivasertib-fulvestrant in the US, Japan and several other countries, people with HR-positive/HER2-negative ABC who have specific genetic alterations in their tumors called *PIK3CA* mutations now have two treatment options:
  - Capivasertib (a drug that blocks the activity of a protein called AKT, reducing the growth of cancer cells) plus fulvestrant (a standard treatment for breast cancer) for people with genetic alterations in *PIK3CA, AKT1*, and/or *PTEN* genes
  - Alpelisib (a drug that blocks the activity of a protein called PI3K, reducing the growth of cancer cells) plus fulvestrant for people with genetic alterations in the *PIK3CA* gene
- However, as these two treatment options have not been compared directly in clinical research, there is a lack of evidence to support healthcare decision-making in choosing one treatment versus the other

How did we perform this research?

- An indirect treatment comparison is a well-established statistical method used by healthcare decision-makers to compare treatments when clinical trials directly comparing the treatments are unavailable
- In this analysis, researchers used the established indirect treatment comparison approach to compare the efficacy and side effects of capivasertib-fulvestrant and alpelisib-fulvestrant

What were the findings of this research, and what are the implications?

- This research found that people with HR-positive/HER2-negative, *PIK3CA*-altered ABC treated with capivasertib-fulvestrant are likely to live longer with their disease without it getting worse (progressing) compared with those treated with alpelisib-fulvestrant. This is called progression-free survival.
- The findings also suggest that the side effects of treatment with capivasertib-fulvestrant are generally more favorable than with alpelisib-fulvestrant
- These findings can be used to guide evidence-based healthcare decision-making for people with this type of breast cancer

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*Corresponding author email address: Bengt.Liljas@astrazeneca.com

Introduction

- For patients with HR-positive/HER2-negative, *PIK3CA*-altered ABC with disease progression following endocrine-based therapy, there are now two FDA-approved treatment options:
  - **Alpelisib-fulvestrant:** Alpelisib, a PI3K alpha-selective inhibitor, in combination with fulvestrant, is available for patients with *PIK3CA*-mutated HR-positive/HER2-negative ABC based on results from the Phase 3 SOLAR-1 study[1]
  - **Capivasertib-fulvestrant:** Capivasertib, a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3), in combination with fulvestrant, is available for patients with HR-positive/HER2-negative ABC with one or more *PIK3CA/AKT1/PTEN*-alterations based on results from the Phase 3 CAPItello-291 study.[2] Capivasertib-fulvestrant is therefore an option both for patients with *PIK3CA* alterations, as well as those who are *PIK3CA*-unaltered but have an *AKT1* or *PTEN* alteration
- At present, there are no head-to-head studies evaluating the efficacy and safety of capivasertib-fulvestrant versus alpelisib-fulvestrant in patients with *PIK3CA*-altered ABC
- In this analysis, we conduct an anchored indirect treatment comparison of capivasertib-fulvestrant versus alpelisib-fulvestrant in *PIK3CA*-altered ABC using evidence from their respective phase 3 clinical trials

Methods

Literature identification

- A systematic literature review was conducted to identify relevant studies for inclusion in the indirect treatment comparison
- Identified studies were initially screened according to the following inclusion criteria: (1) patient population: HR-positive, HER2-negative or HER2-mixed/not reported/unknown unresectable and/or metastatic breast cancer previously treated with endocrine therapy in the (neo) adjuvant or advanced setting; (2) intervention: any pharmacological treatment for ABC; (3) comparator: no restriction; (4) outcomes: PFS, OS, safety; and (5) study type: randomized controlled trials, single-arm clinical studies, systematic literature reviews, and meta-analyses

Selection of trials for indirect treatment comparison

- Interventions of interest: capivasertib-fulvestrant and alpelisib-fulvestrant
- Outcomes of interest: efficacy (PFS) and safety (discontinuations due to AEs, any grade AEs [individual or grouped])
- Population of interest: patients with *PIK3CA*-altered, HR-positive, HER2-negative ABC after prior endocrine therapy

Trials included in indirect treatment comparison

- Two studies were identified for inclusion in the indirect treatment comparison: CAPItello-291 and SOLAR-1. Key details of these studies are shown in Table 1. The review identified two phase 2 studies that were excluded from the indirect treatment comparison (1) the phase 2 FAKTION study for capivasertib which reported results in patients with *PIK3CA*, *AKT* or *PTEN* alterations, but no subgroup results for *PIK3CA* only were available, and (2) the BYLieve study for alpelisib which did not have a control arm from which to perform an anchored indirect treatment comparison
- Key baseline characteristics for the population of patients with *PIK3CA/AKT1/PTEN*-alterations for CAPItello-291 and the *PIK3CA*-mutated population of SOLAR-1, and sources of heterogeneity, are shown in Table 2. Sources of heterogeneity included menopausal status, previous use of CDK4/6 inhibitors and previous treatment for advanced disease, presence of visceral metastases and endocrine status

Statistical analyses

- Comparative efficacy and safety were assessed using an anchored indirect treatment comparison performed in a Bayesian framework,[3] with the two studies connected via a common comparator arm of placebo-fulvestrant. This anchored indirect treatment comparison approach was selected as the most appropriate methodology for comparing capivasertib-fulvestrant to alpelisib-fulvestrant based on the available evidence
  - The treatment effects for PFS were modeled as the log-hazard ratio and its standard error using data from the subgroup of patients with *PIK3CA* alterations from either study
  - The treatment effects for safety were conducted on a risk difference scale using aggregate data from the overall safety analysis set of each study,[4] based on the tolerability profiles being similar regardless of alteration status. For individual AEs, analysis was conducted using any grade data to minimize the effects of any changes to grade boundaries between CTCAE versions
  - Results were summarized as the posterior hazard ratio/risk difference and its associated 95% credible interval. For the efficacy analysis, the posterior distribution of the hazard ratio and the Bayesian probability of a hazard ratio of <1.0 (i.e., improved PFS) for capivasertib-fulvestrant versus alpelisib-fulvestrant was also calculated

Methods

Table 1. Overview of characteristics of studies included in the indirect treatment comparison

Characteristics	CAPItello-291	SOLAR-1
Design	Phase 3 double-blind, randomized, placebo-controlled	Phase 3 double-blind, randomized, placebo-controlled
Total number of patients randomized	708 overall/289 *PIK3CA/AKT1/PTEN*-altered	572 overall/341 *PIK3CA*-altered
Date of analysis	Efficacy and safety: August 15, 2022	Efficacy in *PIK3CA*-mutated cohort: June 12, 2018; Safety: April 23, 2020
Study drugs	400 mg capivasertib (two 200 mg tablets taken twice a day = total daily dose 800 mg) given on an intermittent weekly dosing schedule until progression or tolerability. Patients were dosed on days 1 to 4 in each week of a 28-day treatment cycle	300 mg alpelisib (one 200 mg tablet and two 50 mg tablets) once a day with continuous dosing until progression or tolerability
	500 mg fulvestrant intramuscularly on day 1 of each 28-day cycle and additionally on day 15 of cycle 1	
CTCAE version	CTCAE v5.0	CTCAE v4.03
Key inclusion/exclusion criteria		
Menopausal status	Pre-, peri-, or post-menopausal	Post-menopausal
Disease stage	Locally advanced or metastatic breast cancer not amenable to curative therapy	
Disease type	Histologically confirmed HR-positive/HER2-negative breast cancer determined from most recent tumor sample	
Prior treatment history	Patients with endocrine therapy resistance based on recurrence or progression on or after treatment with an aromatase inhibitor. Up to 2 prior lines of endocrine therapy and up to 1 prior line of chemotherapy in the metastatic setting	
– CDK4/6 inhibitor use	Prior CDK4/6 inhibitors allowed (at least 51% required)	No protocol-defined requirement
ECOG performance status status	0/1	
Diabetes/HbA1c	Patients with diabetes mellitus type 1, and diabetes mellitus type 2 requiring insulin treatment, or HbA1c ≥8.0% (63.9 mmol/mol) were excluded	Patients with an established diagnosis of diabetes mellitus type 1 or uncontrolled type 2 diabetes (fasting plasma glucose level, >7.7 mmol per liter), or HbA1c >6.4%), were excluded
Biomarker testing	Patients were enrolled irrespective of their tumor alteration status *PIK3CA*, *AKT1*, and *PTEN*-altered status was determined retrospectively, post-randomization, using central tumor tissue testing by Foundation Medicine Inc.'s FoundationOne®CDx (F1CDx) in all countries except China (OncoScreen Plus, Burning Rock Biotech; n=8)	Patients were required to have adequate tumor tissue for the analysis of *PIK3CA*-mutation testing, conducted by a Novartis-designated laboratory, and were split into two cohorts (*PIK3CA*-mutated vs. not *PIK3CA*-mutated)

Table 2. Overview of key baseline characteristics of patients in studies included in the indirect treatment comparison

Key demographic characteristics	CAPItello-291 (*PIK3CA/AKT1/PTEN*-altered)*		SOLAR-1 (*PIK3CA*-altered)	
	Capivasertib-fulvestrant (n=155)	Placebo-fulvestrant (n=134)	Alpelisib-fulvestrant (n=169)	Placebo-fulvestrant (n=172)
Alteration; n (%) – Any *PIK3CA (alone or in combination with AKT/PTEN)* – *AKT* only – *PTEN* only	 116 (75) 18 (12) 21 (14)	 103 (77) 15 (11) 16 (12)	 169 (100) – –	 172 (100) – –
Median age (years)	58	60	63	64
ECOG PS 0/1; (%)	60/40	72/27	66/33	66/34
Post-menopausal; (%)	84	78	100	100
Prior CDK4/6 inhibitor use; (%)	73	69	5	6
Visceral metastases; (%)	67	73	55	58
Previous treatments for advanced disease; (%) – 0 – ≥1	 8 92	 15 85	 52 47	 52 48
Endocrine status; (%) – Primary resistance – Secondary resistance	 39 61	 41 59	 14 71	 13 74

*Key baseline characteristics for *PIK3CA*-altered only population have not been reported. Percentage values may not sum to 100% due to rounding.

Results

Efficacy

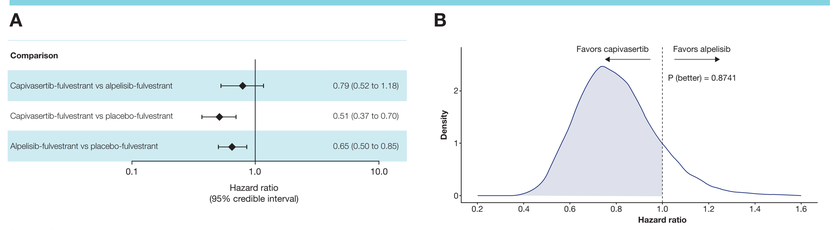
- The anchored efficacy indirect treatment comparison used data from the subgroup of patients with any *PIK3CA* alterations for CAPItello-291[5] and the *PIK3CA*-mutated population of SOLAR-1[1] (Table 3)

Table 3. PFS results in patients with *PIK3CA* alterations used in the indirect treatment comparison

	CAPItello-291		SOLAR-1	
	Capivasertib-fulvestrant (n=116)	Placebo-fulvestrant (n=103)	Alpelisib-fulvestrant (n=169)	Placebo-fulvestrant (n=172)
Treatment effect; hazard ratio (95% CI)	0.51 (0.37 to 0.69)		0.65 (0.50 to 0.85)	

- Estimated hazard ratios for PFS from the anchored indirect treatment comparison are shown in Figure 1A
  - Capivasertib-fulvestrant was associated with a numerically improved hazard ratio (0.79; 95% CI 0.52 to 1.18) compared to alpelisib-fulvestrant
- The Bayesian probability of capivasertib-fulvestrant being more efficacious (hazard ratio <1.0) than alpelisib-fulvestrant was 87% (Figure 1B)

Figure 1. A) Forest plot of PFS outcomes from the anchored indirect treatment comparison. B) Probability distribution of the hazard ratio for PFS of capivasertib-fulvestrant versus alpelisib-fulvestrant

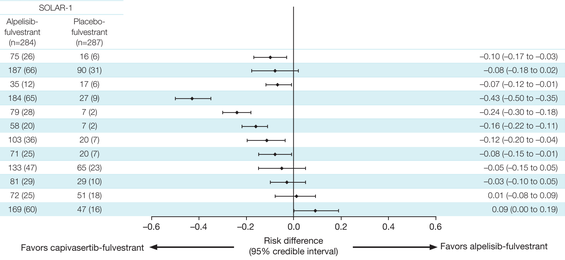


Safety

- The anchored safety indirect treatment comparison used data from the safety analysis set of both studies; all patients regardless of alteration status from CAPItello-291 safety analysis set (n=705; reported at the time of the primary analysis)[2] and SOLAR-1 (n=571; reported at the final analysis)[6] were included
  - Safety outcomes were included where comparable data for both trials were available
- The safety-anchored indirect treatment comparison results (Figure 2) suggest:
  - The risk of treatment discontinuation due to AEs is significantly lower for capivasertib-fulvestrant when compared with alpelisib-fulvestrant
  - Capivasertib-fulvestrant is associated with a significant reduction in the risk of any grade 4 AE, and any grade of hyperglycemia, weight decreased, alopecia, rash, and stomatitis when compared with alpelisib-fulvestrant
  - There is no significant difference in the risk of any grade 3 AE, and any grade of nausea, vomiting, or fatigue when comparing capivasertib-fulvestrant with alpelisib-fulvestrant
  - Capivasertib-fulvestrant has an increased risk of any grade diarrhea when compared with alpelisib-fulvestrant

Figure 2. Forest plot of absolute risk difference for AEs*

	Number of events (%)				
	CAPItello-291		SOLAR-1		
	Capivasertib-fulvestrant (n=355)	Placebo-fulvestrant (n=350)	Alpelisib-fulvestrant (n=284)	Placebo-fulvestrant (n=287)	
Any AE leading to discontinuation	46 (13)	8 (2)	75 (26)	16 (6)	–0.10 (–0.17 to –0.03)
Any grade 3 AE	139 (39)	44 (13)	187 (66)	90 (31)	–0.08 (–0.18 to 0.02)
Any grade 4 AE	9 (3)	10 (3)	35 (12)	17 (6)	–0.07 (–0.12 to –0.01)
Any grade of hyperglycemia	58 (16)	13 (4)	184 (65)	27 (9)	–0.43 (–0.50 to –0.35)
Any grade weight decreased	12 (3)	8 (2)	79 (28)	7 (2)	–0.24 (–0.30 to –0.18)
Any grade alopecia	12 (3)	5 (1)	58 (20)	7 (2)	–0.16 (–0.22 to –0.11)
Any grade rash	78 (22.0)	15 (4.3)	103 (36)	20 (7)	–0.12 (–0.20 to –0.04)
Any grade stomatitis	52 (15)	17 (5)	71 (25)	20 (7)	–0.08 (–0.15 to –0.01)
Any grade nausea	123 (35)	54 (15)	133 (47)	65 (23)	–0.05 (–0.15 to 0.05)
Any grade vomiting	73 (21)	17 (5)	81 (29)	29 (10)	–0.03 (–0.10 to 0.05)
Any grade fatigue	74 (21)	45 (13)	72 (25)	51 (18)	0.01 (–0.08 to 0.09)
Any grade diarrhea	257 (72)	70 (20)	169 (60)	47 (16)	0.09 (0.00 to 0.19)



*Reported using CTCAE v5.0 in CAPItello-291 and using CTCAE v4.03 in SOLAR-1.
A risk difference of less than zero indicates a lower risk of an event with capivasertib-fulvestrant versus alpelisib-fulvestrant, and vice versa for values that are greater than zero.

Study strength and limitations

Strengths

- The analysis was conducted on trial data obtained from a large and comprehensive systematic review of clinical trials in ABC, although only two trials were identified. No studies were excluded based on region or timeframe, providing a comprehensive evidence base
- Following guideline recommendations, an anchored indirect treatment comparison was selected as the most appropriate method based on available evidence from the Phase 3 CAPItello-291 and SOLAR-1 trials
- The efficacy analysis was conducted using the *PIK3CA*-altered subgroup data of CAPItello-291 and SOLAR-1 to maximise the comparability of populations across studies
- The safety analyses were conducted using the safety analysis sets of each study, including a broader population than the *PIK3CA*-altered subgroup to maximize the sample size for detecting differences

Limitations

- As with all treatment comparisons, there is a risk of bias from differences in treatment effect modifiers (i.e., characteristics that change the relative effect of treatment versus placebo) across the two studies, and it is unclear which of the study and patient characteristics are solely prognostic (e.g., endocrine status) or are associated with treatment effects. Notably, there were differences in prior CDK4/6 inhibitor treatment across studies. In CAPItello-291, the treatment effect was consistent across subgroups, mitigating the need to adjust the effect of capivasertib for prior CDK4/6 inhibitor use in the treatment comparison.[2] The extent to which the effect of alpelisib is also consistent across prior CDK4/6 inhibitor subgroups is uncertain due to the small size of the post-CDK4/6 inhibitor subgroup in SOLAR-1
- The efficacy analysis relied on data from a post-hoc non-stratified subgroup of CAPItello-291 (*PIK3CA* alterations) overall
- Safety results may be subject to bias due to between-study differences in the CTCAE versions used to monitor AEs

Abbreviations

ABC, advanced breast cancer; AE, adverse event; AKT, AKT serine/threonine kinase; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, US Food and Drug Administration; HbA1c, hemoglobin A1c; HER2, human epidermal growth factor receptor 2; HR-positive, hormone receptor-positive; OS, overall survival; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; *PTEN*, phosphatase and tensin homolog; US, United States.

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