Capivasertib (Breast)

Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk

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Indication

Capivasertib in combination with fulvestrant for the treatment of hormone receptor positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations following recurrence or progression on or after a CDK4/6 inhibitor with an aromatase inhibitor.

NICE TA1063

Trial Results

Phase 3 CAPItello-291 trial

- 708 women assigned to receive capivasertib plus fulvestrant (n=355) or placebo plus fulvestrant (n=353)
- Primary endpoint: Progression free survival in the overall population and the AKT pathway-altered tumours
- Overall Population: Median progression-free survival was 7.2 months in the capivasertib–fulvestrant group vs. 3.6 months in the placebo–fulvestrant group
- AKT pathway-altered population: Median progression-free survival was 7.3 months in the capivasertib–fulvestrant group vs. 3.1 months in the placebo–fulvestrant group

Regimen details

Cycle 1

Day	Drug	Dose	Route
1-4	Capivasertib	400mg BD	Oral
8-11	Capivasertib	400mg BD	Oral
15-18	Capivasertib	400mg BD	Oral
22-25	Capivasertib	400mg BD	Oral
1 & 15	Fulvestrant	500mg	Intramuscular Injection

Cycle 2 Onwards

Day	Drug	Dose	Route
1-4	Capivasertib	400mg BD	Oral
8-11	Capivasertib	400mg BD	Oral
15-18	Capivasertib	400mg BD	Oral
22-25	Capivasertib	400mg BD	Oral
1	Fulvestrant	500mg	Intramuscular Injection

Capivasertib is taken twice a day on days 1-4 of each week, followed by 3 days off. Dose reduction is required if taken concomitantly with CYP3A4 inhibitors, see details below.

Cycle frequency
28 days

Number of cycles
Until disease progression or unacceptable toxicity

Pre-medication
Prophylactic oral antihistamines can be considered for cutaneous reactions

Supportive medication
Antiemetics if required.
Loperamide if required.
Emollients should be considered

Emetogenicity
This regimen has low emetic potential – refer to local policy

Administration
Capivasertib is available as 200mg and 160mg film coated tablets. The tablets should be swallowed whole with water and not chewed, crushed, dissolved or divided. A tablet should not be taken if it is broken cracked or not otherwise intact. Doses may be taken with or without food, twice daily, approximately 12 hours apart. Capivasertib is taken for four days then followed by a three day break each week.

If a dose of capivasertib is missed, it can be taken within 4 hours after the time it is usually taken. If a dose is missed and more than 4 hours have passed, the dose should be skipped. The next dose of capivasertib should be taken at the usual time. There should be at least 8 hours between doses. If the patient vomits, an additional dose should not be taken. The next dose of capivasertib should be taken at the usual time.

Grapefruit and grapefruit juice should be **avoided** whilst taking capivasertib.

Mandatory investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&E (including creatinine)	14 days
LFTs	14 days
Fasting glucose	14 days
HbA1c*	14 days
Calcium	14 days
Magnesium	14 days

*The safety of capivasertib in patients with Type 1 and uncontrolled Type 2 diabetes (HbA1c >8% or receiving insulin) has not been established as these patients were excluded from clinical studies

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly
U&E (including creatinine)	Monthly
LFT	Monthly
Fasting glucose	Weeks 2, 4, 6 and 8 (on day 3 or 4 of the dosing week) and monthly thereafter More frequent testing is recommended in patients with diabetes, prediabetes or hyperglycaemia at baseline
HbA1c	Every 3 months
Potassium	Monthly
Calcium	Monthly
Magnesium	Monthly

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 $x10^9$/L
Platelets	≥ 100 $x10^9$/L
Creatinine clearance (CrCl)	≥ 30mL/min
Bilirubin	< 1.5 x ULN
ALT/AST	< 5 x ULN

Dose modifications

Dose level	Dose
Starting dose	400mg BD for 4 days followed by 3 days off treatment
First dose reduction	320mg BD or 4 days followed by 3 days off treatment
Second dose reduction	200mg BD or 4 days followed by 3 days off treatment

Haematological toxicity

Neutropenia and thrombocytopenia are not expected with capivasertib treatment.
If neutrophils < 1.0 x 10^9/L or platelets < 50 x 10^9/L, delay treatment until count recovery. If platelets 50-99 and neutrophils > 1.0 x 10^9/L – discuss with consultant.

Renal impairment

No dose adjustment is required for patients with mild or moderate (renal impairment (CrCl = ≥30 mL/min). Capivasertib is not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min), as safety and pharmacokinetics have not been studied in these patients.

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 - 1.5 x ULN). Limited data are available for patients with moderate hepatic impairment (bilirubin > 1.5 – 3 x ULN); only give if the benefit outweighs the risk and these patients should be monitored closely for adverse effects due to potential increase in capivasertib exposure. Capivasertib is not recommended for patients with severe hepatic impairment (bilirubin >3.0x ULN), as safety and pharmacokinetics have not been studied in these patients.

Other toxicities

Hyperglycaemia

Fasting glucose	Recommended actions
Grade 1 >ULN-8.9mmol/L or HbA1c >7%	No dose adjustment required. Initiate or intensify oral antidiabetic treatment*
Grade 2 8.9-13.9mmol/L	Initiate or intensify oral antidiabetic treatment* Withhold capivasertib until fasting glucose level decrease to ≤8.9mmol/L If recovery occurs within 28 days, resume at the same dose and maintain initiated or intensified anti-diabetic treatment If improvement is reached in more than 28 days restart at one lower dose level and maintain initiated or intensified anti-diabetic treatment
Grade 3 13.9-27.8mmol/L	Withhold capivasertib until fasting glucose ≤ 8.9 mmol/L Initiate or intensify oral anti-diabetic treatment*. Consider insulin as indicated – consult with endocrinology. Consider IV hydration & provide appropriate clinical management as per local guidelines. If fasting glucose ≤ 8.9 mmol/L within 28 days, restart capivasertib at one lower dose level and maintain initiated or intensified anti-diabetic treatment. If fasting glucose does not decrease ≤ 8.9 mmol/L within 28 days following appropriate treatment, permanently discontinue capivasertib.
Grade 4 ≥27.8mmol/L	Withhold capivasertib and consult with endocrinology. Initiate or intensify appropriate anti-diabetic treatment*. Consider insulin (dosing and duration as clinically indicated), intravenous hydration and provide appropriate clinical management as per local guidelines. If fasting glucose decreases to ≤ 27.8 mmol/l within 24 hours, then follow the guidance in the table for the relevant grade. If fasting glucose ≥ 27.8 mmol/l after 24 hours, permanently discontinue capivasertib

**Choice of antihyperglycaemic therapy* – gliclazide 40mg OD may be the preferred agent if no history of hypoglycaemia or severe renal or hepatic insufficiency. If metformin is initiated increased creatinine monitoring is recommended due to pharmacokinetic interactions. Antihyperglycaemic therapy may only be required on days of capivasertib administration (i.e. 4 days per week) to avoid episode of hypoglycaemia.

Rash

Severe cutaneous reactions have been reported with capivasertib including Stevens-Johnson syndrome, erythema multiforme and drug reaction with eosinophilia and systemic symptoms (DRESS). Patients should be advised of the signs and symptoms of severe cutaneous reactions (e.g. prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash) and capivasertib should be withheld. If severe cutaneous reaction is confirmed, capivasertib should be permanently discontinued.

Topical corticosteroids should be initiated at the first signs of rash and systemic corticosteroids should be considered for moderate to severe rashes. Consultation with a dermatologist should always be considered. Criteria for dose interruption, reduction or discontinuation are below.

Grade	Recommendation
Grade 1 (<10% body surface area (BSA) with active skin toxicity)	No dose adjustment is required Initiate topical corticosteroid treatment Consider adding oral antihistamine to manage symptoms
Grade 2 (10-30% BSA with active skin toxicity)	Withhold capivasertib until recovery to ≤ Grade 1. Initiate or intensify topical steroid treatment and consider non-sedating oral antihistamines. If recovery occurs in ≤ 28 days, resume capivasertib at the same dose level. If persistent or recurrent: restart capivasertib at next lower dose level
Grade 3 (e.g. severe rash not responsive to medical management) (>30% BSA with active skin toxicity)	Withhold capivasertib until rash improves to ≤ grade 1 Initiate or intensify topical corticosteroid (for up to 2 weeks) and oral antihistamine treatment and systemic steroids. Consult with dermatology. If recovery occurs in ≤ 28 days, resume capivasertib at next lower dose level. If symptoms do not improve to ≤ grade 1 within 28 days, discontinue capivasertib.
Recurrent Grade 3 or any Grade 4 (e.g. severe bullous, blistering or exfoliating skin conditions, any % BSA associated with extensive superinfection, with intravenous antibiotics indicated; life-threatening consequences)	Permanently discontinue capivasertib

In patients with persistent rash or previous occurrence of grade 3 rash, consider secondary prophylaxis by continuing topical steroids and/or non-sedating oral antihistamines.

Hypersensitivity reactions

Serious hypersensitivity reactions (including anaphylaxis and anaphylactic shock) manifested by symptoms including, but not limited to dyspnoea, flushing, rash, fever or tachycardia have been reported in patients treated with capivasertib. Capivasertib should be permanently discontinued in patients with serious hypersensitivity reactions.

Diarrhoea

Consider secondary prophylaxis in patients with recurrent diarrhoea

Grade	Recommendation
Grade 1 (Increase of <4 stools per day over baseline)	No dose adjustment is required Initiate appropriate medical therapy and monitor.
Grade 2 (Increase of 4-6 stools per day over baseline)	Initiate or intensify appropriate anti-diarrhoeal treatment and monitor as clinically indicated. Withhold capivasertib for up to 28 days until recovery to ≤ Grade 1 and resume capivasertib dosing at same dose or one lower dose level as clinically indicated. If Grade 2 diarrhoea is persistent or recurring, maintain appropriate medical therapy and restart capivasertib at one lower dose level, as clinically indicated.
Grade 3 (Increase of >=7 stools per day over baseline)	Withhold capivasertib until recovery to ≤ Grade 1. Initiate or intensify appropriate anti-diarrhoeal treatment and monitor as clinically indicated. If recovery occurs in ≤ 28 days, resume capivasertib at one lower dose level. If recovery to ≤ Grade 1 in > 28 days, permanently discontinue capivasertib
Grade 4 (Life threatening, urgent intervention indicated)	Permanently discontinue capivasertib

Any other toxicity (Excluding hyperglycaemia, diarrhoea and skin toxicity)

CTCAE Grade	Recommendation
Grade 1	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated
Grade 2	Withhold treatment until symptoms improve to ≤ grade 1.
Grade 3	Withhold treatment until symptoms improve to ≤ grade 1. If symptoms improve, restart at the same dose or next level dose reduction as clinically appropriate.
Grade 4	Permanently discontinue capivasertib

Side Effects

CAPItello-291 study:

Toxicity		Any grade (%)	Grade 3 or 4 (%)
Haematological	Anaemia	10.4	2
Non-haematological	Diarrhoea	72.4	9.3
	Rash	38	12.1
	Nausea	34.6	0.8
	Fatigue	20.8	0.6
	Vomiting	20.6	1.7
	Headache	16.9	0.3
	Decreased appetite	16.6	0.3
	Hyperglycaemia	16.3	2.3
	Stomatitis	14.6	2
	Asthenia	13.2	1.1
	Pruritis	12.4	0.6
	Urinary tract infection	10.1	1.4

Specific drug related side effects:

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Urinary Tract Infection	Hypersensitivity	Diabetic ketoacidosis
Anaemia	Hypokalaemia	Dermatitis
Hyperglycaemia	Dysgeusia	Exfoliative dermatitis
Decreased appetite	Acute kidney injury	Skin drug eruption
Headache	Increased HbA1c	
Diarrhoea	Abdominal Pain	
Nausea	Dyspepsia	
Vomiting	Dry skin	
Stomatitis	Erythema multiforme	
Rash	Mucosal Inflammation	
Pruritis	Pyrexia	
Fatigue	Increased blood creatinine	

Additional information:

Nil

Significant drug interactions – for full details consult product literature/ reference texts

Strong or moderate CYP3A4 inhibitors (e.g. aprepitant, clarithromycin, ciprofloxacin, conivaptan, ketoconazole, posaconazole, ritonavir, verapamil): risk of increase capivasertib exposure, the dose of capivasertib should be reduced to 320mg twice daily.

UGT2B7 inhibitors (e.g. probenecid, valproic acid): potential for increased capivasertib concentrations, monitor closely for toxicity.

Strong or moderate CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampicin, St John's Wort): co-administration with capivasertib is not recommended due to risk of reduced efficacy of capivasertib.

UGT2B7 inducers (e.g. rifampicin): potential for decreased capivasertib concentrations which may reduce efficacy.

Substrates of CYP3A or UGT1A1: concentration of substrate may increase, dose adjustment may be required for those with a narrow therapeutic window.
Substrates of CYP2B6: concentration of substrate may decrease.
OATP1B1 and OATP1B3 substrates also metabolised by CYP3A4 (e.g. simvastatin): concentration of substrate may increase, potentially increasing toxicity, consider dose reduction as indicated.
MATE1, MATE2K and OCT transporter substrates: concentration of substrate may increase.

References

- Summary of Product Characteristics: Capivasertib (Astra Zeneca) accessed 17 July 2025 via www.medicines.org.uk
- National Institute for Health and Care Excellence TA1063. Accessed 17 July 2025 via www.nice.org.uk
- Turner, NC et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2023;388:2058-2070

Version	Issue date	Review date	Revision	Written/Checked/Authorised
1	Jul 2025	Jul 2028	New protocol	Written: Dr L Pemberton (Oncology SpR, UHBW NHS Trust), Dr C Crocker (Oncology SpR, UHBW NHS Trust), Dr C Comins (Consultant Oncologist, UHBW NHS Trust), Dr T Strawson-Smith (Consultant Oncologist, UHBW NHS Trust) Checked: Kate Gregory (Lead pharmacist for SACT protocols, SWAG Cancer Alliance) Authorised: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)