Capivasertib

Indication

In combination with fulvestrant for HR-positive HER2-negative, locally advanced or metastatic breast cancer in adults with 1 or more PIK3CA, AKT1 or PTEN gene alterations and who have progressed after treatment with a CDK4 /6 inhibitor plus aromatase inhibitor.

Eligibility

- ER positive HER2 negative (IHC 0, 1+ or 2+/ISH not amplified) metastatic breast cancer or locally advanced breast cancer that is not amenable to curative treatment
- The tumour has one or more confirmed *PIK3CA*, *AKT1* or *PTEN* gene alterations
- Patient is male or is female and either post-menopausal or if pre- or peri-menopausal has undergone ovarian ablation or suppression with LHRH agonist
- Patient has previously been treated with an aromatase inhibitor
- Patient has previously undergone treatment with a CDK4/6 inhibitor
- ECOG PS 0-1
- Patient has had no prior treatment with fulvestrant
- Capivasertib will only be given in combination with fulvestrant
- Optimised blood sugar control and blood glucose monitoring throughout treatment
- No significant co-morbidities which outweigh the potential toxicities
- All Bluteq criteria are met

Cautions

- Patients with known diabetes, pre-diabetes and/or BMI >30kg/m^2. Such patents were permitted entry to the Capitello-291 trial but post-trial analysis has identified that patients with a history of diabetes or BMI >30kg/m^2 were more likely to experience hyperglycaemia. Treatment may proceed but these patients will require more intensive blood glucose monitoring.
- Patients with significant abnormalities of glucose metabolism (defined as patients with diabetes mellitus Type 1 or Type 2 requiring insulin treatment, and/or HbA1c ≥ 64 mmol/mol (8%). Whilst this is not an absolute contraindication to treatment such patients were excluded from the Capitello-291 trial and would need extremely stringent monitoring.
- Patients with a creatinine clearance <30 mL/min), as safety and pharmacokinetics have not been studied in these patients.
- Capivasertib should only be offered to patients with moderate hepatic impairment (Bil >1.5-3.0 x ULN) only 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.
- Severely symptomatic visceral disease, impending visceral crisis or any disease burden that makes the patient unsuitable for endocrine therapy

Regimen details

Capivasertib tablets 400mg BD. 4 days ON, 3 days OFF
Fulvestrant injection 500mg intramuscularly every 28 days (additional dose given on day 15 of cycle 1 only)

Cycle frequency

Every 28 days

Number of cycles

Until disease progression or unacceptable toxicity

Administration

- Fulvestrant is administered as two consecutive 5mL injections by slow intramuscular injection (1-2 minutes per injection), one into each buttock
- Capivasertib should be taken twice daily for 4 days followed by a break for 3 days. This repeats weekly (every 7 days)
- The number of tablets to take depends on the dose prescribed as below:
    - 400 mg dose: two 200 mg tablets twice a day
    - 320 mg dose: two 160 mg tablets twice a day
    - 200 mg dose: one 200 mg tablet twice a day
- Patients should take their dose of capivasertib at approximately the same time each day (with at least 8 hours between doses)
- The tablets should be swallowed whole with or without food. They should not be chewed, crushed or split prior to swallowing.
- If a dose is missed it can be taken immediately if within 4 hours of the usual administration time. After more than 4 hours the patient should be advised to miss that dose and continue regular dosing for the next scheduled dose. The patient must be informed if they vomit they must not repeat or 'double up' the next dose, and the regular dose should be taken at the next scheduled time.
- Patients should be advised to avoid grapefruit and its juices.
- Advise patient to start loperamide treatment and increase oral fluids if diarrhoea occurs while taking capivasertib and to call the helpline if > 4 stools per day or if diarrhoea does not respond to loperamide treatment within 24 hours.
- Advise the patient to take metoclopramide for nausea and/or vomiting occurs while taking capivasertib and to call the helpline if vomiting does not respond to metoclopramide treatment within 24 hours.
- Advise the patient to take cetirizine if they develop an itchy skin reaction and to call the helpline if the rash is worsening does not respond to cetirizine treatment within 2 days.
- Patients taking capivasertib should be informed of the need to interrupt treatment immediately and seek medical advice if they develop moderate or severe side effects.

Pre-medication

None

Emetogenicity

Mild

Additional supportive medication

- Emollient cream with cycle 1
- Loperamide TWO capsules to be taken initially followed by ONE capsule with each loose stool PRN (maximum daily dose 16mg) with cycle 1
- Metoclopramide 10mg TDS PRN 5 days with cycle 1
- Cetirizine 10mg OD PRN 28 days with cycle 1

Investigations – pre first cycle

Investigation	**Validity period**
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
HbA1c	14 days
Fasting blood glucose	14 days
Bone profile	14 days

- Patients at increased risk of hyperglycaemia (known diabetics, patients with pre-diabetes, those with fasting glucose (FG) > 8.9 mmol/l or BMI >30kg/m^2) must be issued with a CBG meter and taught how to use it.
- Consultation with a healthcare professional experienced in the treatment of hyperglycaemia should always take place for patients with known diabetes – inform Diabetes Nurse Specialists of intention to commence capivasertib treatment.

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST) and fasting blood glucose.

Fasting blood glucose should also be undertaken Cycle 1 day 14

Patients with known diabetes, pre-diabetes or BMI >30kg/m^2 will require more intensive monitoring of blood sugars, particularly at the start of treatment.

HbA1c to be checked prior to commencing treatment and every 3 months thereafter.

Standard limits for administration to go ahead

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

Investigation	**Limit**
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 75 x 10^9/L
Creatinine clearance	≥ 30 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 1.5 x ULN

Adverse effects

The most common adverse reactions with capivasertib are hyperglycaemia, rash, diarrhoea, UTIs, anaemia, loss of appetite altered taste, nausea and vomiting, mucositis, pruritis, fatigue, hypersensitivity, dyspepsia, dry skin, elevated creatinine.

Risk of ONJ is not known to be increased in patients concomitantly receiving capivasertib with denosumab but patients should be closely monitored for signs and symptoms of ONJ. In patients who develop osteonecrosis of the jaw, standard medical management should be initiated.

Serious adverse reactions reported in ≥ 1% of patients included cutaneous adverse drug reactions, diarrhoea, hyperglycaemia (including DKA) and vomiting.

Dose modifications

	Dose and schedule	Number and strength of tablets	
Recommended dose	400mg BD. 4 days ON, 3 days OFF	2 x 200mg tablets	
First dose reduction	320mg BD. 4 days ON, 3 days OFF	2 x 160mg tablet	
Second dose reduction	200mg BD. 4 days ON, 3 days OFF	1 x 200mg tablets	

Haematological			
Neutrophils		*Plt*	*Action*
≥1.0	*and*	≥75	Proceed with treatment
<1.0	*or*	<75	Neutropenia and thrombocytopenia are not expected with capivasertib treatment. Discuss with consultant.

Anaemia	
Hb (g/dL)	*Action*

≥90			Proceed with treatment
80-90	**and**	asymptomatic	Proceed with treatment
80-90	**and**	symptomatic	Proceed with treatment – arrange blood transfusion
<80			Proceed with treatment – arrange blood transfusion

Renal impairment

No dose adjustment in subjects with renal impairment is necessary. Capivasertib has not been studied in patients with severe renal impairment, therefore no dose recommendation can be made for patients with severe renal impairment. Capivasertib may increase creatinine through OCT2 inhibition but is not known to affect glomerular filtration rate.

Creatinine Clearance	*Action*
≥ 30ml/min	Proceed with treatment
< 30ml/min	Not studied – discuss with treating consultant

Hepatic impairment

Bilirubin		*AST +/or ALT*	*Action*
≤1.5 ULN	**and**	< 3 x ULN	Proceed with treatment
>1.5-3 x ULN	**or**	> 3 x ULN	Limited data are available for patients with moderate hepatic impairment – discuss with treating consultant
>3 x ULN	**and**	any	Treatment with capivasertib is not recommended. Consultant decision re: ongoing management.

Hyperglycaemia

Fasting plasma glucose (mmol/L)	*Initial recommendation*	*Follow up & monitoring*
>ULN-8.9 mmol/L or HBa1c > 53mmol/mol (7%) (grade 1)	Treat hyperglycaemia (see guidance below) Proceed with treatment - no dose adjustment needed	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels then continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks or as recommended by healthcare professional with expertise in the treatment of hyperglycaemia.
>8.9 to 13.9 mmol/l (grade 2)	Treat hyperglycaemia (see guidance below) Defer treatment until fasting glucose ≤8.9mmol/l If recovery ≤ 28 days resume treatment at same dose level and maintain anti-diabetic treatment. If recovery >28 days resume treatment at one lower dose level and maintain anti-diabetic treatment.	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels then continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks or as recommended by healthcare professional with expertise in the treatment of hyperglycaemia.
>13.9 to 27.8 mmol/l (grade 3)	Defer treatment until fasting glucose ≤8.9mmol/l Consider admission for hydration / appropriate interventions. Initiate or intensify oral antidiabetic treatment and consider additional	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels. If fasting glucose does not decrease to ≤8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, consultation with a physician with expertise in the treatment of hyperglycaemia is recommended.

	antidiabetic medications (such as insulin) for 1–2 days until hyperglycaemia resolves, as clinically indicated. If recovery ≤ 28 days resume treatment at one lower dose level and maintain initiated or intensified anti-diabetic treatment. If recovery >28 days permanently discontinue treatment.	If capivasertib is resumed continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks or as recommended by healthcare professional with expertise in the treatment of hyperglycaemia. All patients established on treatment for capivasertib induced hyperglycaemia will need to stop antihyperglycaemics when capivasertib is discontinued.
> 27.8 mmol/l (grade 4)	Defer treatment until fasting glucose ≤8.9mmol/l Admit patient for hydration / appropriate interventions If blood glucose remains at > 27.8 mmol/L after 24 hours permanently discontinue capivasertib.	If capivasertib is resumed continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks or as recommended by healthcare professional with expertise in the treatment of hyperglycaemia. All patients established on treatment for capivasertib induced hyperglycaemia will need to stop antihyperglycaemics when capivasertib is discontinued.

Management of hyperglycaemia:

If plasma glucose is >8.9 mmol/l, the patient should have urinary measurement of ketones and/or blood ketone measurement. If there is no suspicion of Diabetic Ketoacidosis (DKA) (clinically well patients, <2+ on standard urine sticks of <3mmol/l on blood ketone testing) then DKA and Hyperosmolar Hyperglycaemic State (HHS) should immediately be ruled out. If there is no evidence of DKA/HHS commence treatment as follows:

- In patients with no prior diagnosis of diabetes or diet controlled diabetes: commence gliclazide 40mg od (in the absence of a history of hypoglycaemia or severe renal or hepatic insufficiency) and **refer the patient urgently to the local diabetes team**. The patient's GP should also receive an urgent notification about the hyperglycaemia.
- In patients already receiving antihyperglycaemic therapy:
- For patients on oral agents (or non-insulin injectables) other than a sulfonylurea: commence gliclazide 40mg od on the days of capivasertib administration (in the absence of a history of hypoglycaemia or severe renal or hepatic insufficiency) and **refer the patient urgently to the diabetes team.** Continue other diabetes treatments. The patient's GP should also receive an urgent notification about the hyperglycaemia.
- For patients using a sulfonylurea (either alone or with other oral agents BUT not insulin): increase morning dose of gliclazide by 40 mg (unless this dose is ≥160 mg). If on maximum morning dose of gliclazide (160 mg), consider starting Humulin I or Levemir at a dose of 8 units once daily on the days of capivasertib administration. Continue other diabetes treatments. **Refer the patient urgently to the diabetes team** to titrate medication.
- For patients using insulin: **Refer the patient urgently to the diabetes team t**o titrate medication.

Insulin may be used for capivasertib induced hyperglycaemia for 1-2 days until hyperglycaemia resolves if required. However, this may not be necessary in the majority of cases of capivasertib -induced hyperglycaemia, given the short half-life of capivasertib and the expectation that glucose levels will normalise following interruption of capivasertib.

Diarrhoea	
Grade 1	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated. NB: loperamide may only be indicated on the days of loperamide administration.
Grade 2	Initiate or intensify appropriate medical therapy and monitor as clinically indicated. NB: loperamide may only be indicated on the days of loperamide administration. Defer treatment until recovery to ≤ grade 1 – resume capivasertib

	at same dose level. If grade 2 diarrhoea is persistent or recurrent reduce capivasertib by one dose level.
Grade 3	Initiate or intensify appropriate medical therapy and monitor as clinically indicated. NB: loperamide may only be indicated on the days of loperamide administration. Defer treatment until recovery to ≤ grade 1 If recovery occurs ≤28 days then resume capivasertib at the next lower dose level. If recovery to ≤ Grade 1 in > 28 days, permanently discontinue treatment.
Grade 4	Permanently discontinue treatment.

Skin Toxicity	
Grade 1: <10% BSA (body surface area) with active skin toxicity	Proceed with treatment. No dose adjustment is required. Initiate emollients and consider regular antihistamines to manage symptoms.
Grade 2: 10% to 30% BSA with active skin toxicity	Defer treatment until recovery to ≤ grade 1 Initiate or intensify topical corticosteroid treatment and oral antihistamine treatment. If recovery occurs in ≤ 28 days, resume capivasertib at the same dose level. If persistent or recurrent: restart capivasertib by one dose level.
Grade 3 (e.g. severe rash not responsive to medical management) More than 30% BSA with active skin toxicity.	Defer treatment until recovery to ≤ grade 1 Initiate or intensify treatment with moderate/higher strength topical corticosteroids and oral antihistamine treatment. Consider systemic steroids. If recovery occurs in ≤ 28 days, restart capivasertib on one lower dose level. If the symptoms do not improve to ≤ Grade 1 within 28 days discontinue capivasertib. In patients with reoccurrence of intolerable Grade 3 rash, permanently discontinue capivasertib.
Grade 4 (e.g. severe bullous, blistering or exfoliating skin conditions). Any % BSA associated extensive superinfection, with IV antibiotics indicated, life threatening	Permanently discontinue capivasertib. Consider referral to a dermatologist.

All other adverse events / toxicities	
Grade 1	Proceed with treatment Ensure adequate supportive measures in place e.g.: anti-emetics, loperamide, benzydamine as appropriate.
Grade 2	Ensure adequate supportive measures in place e.g.: anti-emetics, loperamide, benzydamine as appropriate. Consider interruption of capivasertib until recovery to Grade ≤1 or baseline. Then, resume at the same dose level.
Grade 3	**First episode:** Ensure adequate supportive measures in place e.g.: anti-emetics, loperamide, benzydamine as appropriate. Interrupt capivasertib until recovery to Grade ≤1 or baseline. If symptoms improve resume at the same dose level or one lower dose level as appropriate. **Recurrent grade 3 toxicity despite dose reduction:** If a Grade 3 or intolerable toxicity recurs, permanently

	discontinue treatment.
Grade 4	Permanently discontinue treatment.

Significant drug interactions

– for full details consult product literature/ reference texts

Medicinal products that may increase capivasertib plasma concentrations

Strong CYP3A4 inhibitors

Reduce the dose of Truqap when co-administered with strong CYP3A4 inhibitors (e.g., Boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, ensitrelvir, idelalisib, indinavir, itraconazole, josamycin, ketoconazole, lonafarnib, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir, ritonavir, telaprevir, telithromycin, troleandomycin, tucatinib, voriconazole, grapefruit or grapefruit juice) (see section SPC)

Moderate CYP3A4 inhibitors

Reduce the dose of Truqap when coadministered with moderate CYP3A4 inhibitors (e.g., aprepitant, ciprofloxacin, cyclosporine, diltiazem, erythromycin, fluconazole fluvoxamine, tofisopam, verapamil) (see section SMC)

UGTB27 inhibitors

Coadministration of Truqap with UGT2B7 inhibitors (e.g. probenecid, valproic acid) has the potential to increase capivasertib concentration, which may increase the risk of Truqap toxicity.

Medicinal products that may decrease capivasertib plasma concentrations

Strong CYP3A4 inducers

Co-administration of Truqap with strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampicin, St. John's wort) is not recommended.

Moderate CYP3A4 inducers

Co-administration of Truqap with moderate CYP3A4 inducers is not recommended (e.g., bosentan, cenobamate, dabrafenib, elagolix, etravirine, lersivirine, lesinurad, lopinavir, lorlatinib, metamizole, mitapivat, modafinil, nafcillin, pexidartinib, phenobarbital, rifabutin, semagacestat, sotorasib, talviraline, telotristat ethyl, thioridazine).

UGT2B7 inducers

Coadministration of Truqap with UGT2B7 inducers (e.g. rifampicin) has the potential to decrease capivasertib concentration. This may potentially reduce the efficacy of Truqap.

Other interactions

The exposure of drugs that are sensitive to inhibition of OATP1B1 and/or OATP1B3 if they are metabolised by CYP3A4, may increase by co-administration with capivasertib. This may lead to increased toxicity. Depending on their therapeutic window, dose adjustment may be required for drugs that are sensitive to inhibition of OATP1B1 and/or OATP1B3 (e.g., simvastatin), if they are metabolised by CYP3A4.

The exposure of drugs that are sensitive to inhibition of MATE1, MATE2K and/or OCT2 may increase by co-administration with capivasertib. This may lead to increased toxicity. Transient serum creatinine increases may be observed during treatment with capivasertib. due to inhibition of OCT2, MATE1 and MATE2K by capivasertib. Depending on their therapeutic window, dose adjustment may be needed for drugs that are sensitive to inhibition of MATE1, MATE2K, OCT2 (e.g., dofetilide, procainamide).

Patients should be instructed to avoid grapefruit and grapefruit juice as these are known to inhibit CYP3A4 enzymes and may increase exposure to capivasertib.

Concomitant administration of St John’s Wort is contraindicated

Additional comments

tablets should be swallowed whole with water and not chewed, crushed dissolved, or divided. No tablets should be ingested if it is broken, cracked, or otherwise not intact.

References

https://www.medicines.org.uk/emc/product/15839/smpc
https://www.nejm.org/doi/full/10.1056/NEJMoa2214131

THIS PROTOCOL HAS BEEN DIRECTED BY TOM KERRY AND DR DAVID EATON, DESIGNATED LEAD CLINICIAN FOR BREAST CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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