Chemotherapy Protocol

PROSTATE

APALUTAMIDE

Regimen

- Prostate cancer

Indication

- Apalutamide is recommended for non-metastatic prostate cancer as defined by recent imaging with conventional imaging with both a whole body isotope bone scan and a CT/MR scan of the chest, abdomen and pelvis.Patients with the sole abnormality of pelvic lymph nodes measuring less than 2cm in short axis diameter and which are below the aortic bifurcation are eligible for apalutamide in this indication.

    - has a proven histological or cytological diagnosis of adenocarcinoma of the prostate without neuroendocrine differentiation or features of a small cell carcinoma.
    - hormone-resistant (castrate-resistant) disease as defined by 3 rising PSA levels (after the nadir PSA level) and taken at least 1 week apart during androgen deprivation therapy.
    - serum testosterone level is <1.7nmol/L on gonadotrophin releasing hormone agonist/antagonist therapy or after bilateral orchidectomy.
    - the current PSA level is >=2ng/ml
    - is at high risk of developing metastatic disease as defined by a PSA doubling time of <= 10 months during continuous ADT.
    - has not received any previous 2nd generation androgen receptor inhibitors (such as enzalutamide, darolutamide, apalutamide) or CYP17 enzyme inhibitors (such as abiraterone) unless apalutamide has been accessed via a company early access scheme for this specific indication
    - that apalutamide is being given only in combination with androgen deprivation therapy
    - that apalutamide is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment.
    - a formal medical review as to how apalutamide is being tolerated and whether treatment with apalutamide should continue or not will be scheduled to occur at least by the start of the third 4-weekly cycle of treatment.
    - that the patient has an WHO performance status of either 0 or 1 or 2.

- Apalutamide is recommended as an option for patients who have a proven histological or cytological diagnosis of adenocarcinoma of the prostate or has presented with a clinical picture consistent with metastatic prostate cancer with both widespread bone metastases radiologically typical of prostate cancer and a serum PSA of greater than or equal to 50 ng/mL.

    - has newly diagnosed metastatic prostate cancer that is hormone sensitive and has currently received androgen deprivation therapy (ADT) for no longer than 3 months.

- has not received any upfront docetaxel chemotherapy for metastatic hormone sensitive prostate cancer and has been assessed as being ineligible for docetaxel on the grounds of either having significant comorbidities (i.e. the patient should not be treated with docetaxel) or the patient is fit for upfront docetaxel but after fully informed consent has chosen not to receive upfront docetaxel.
- apalutamide is being given only in combination with ADT.
- has not previously received any apalutamide or any other androgen receptor targeted agent unless the patient has received apalutamide via a company early access scheme and the patient meets all the other criteria listed here
- apalutamide is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment.
- a formal medical review as to how apalutamide is being tolerated and whether treatment with apalutamide should continue or not will be scheduled to occur at least by the start of the third 4-weekly cycle of treatment.

Toxicity

Drug	Adverse Effect
Apalutamide	**Very common**: Arthralgia, decreased appetite, diarrhoea, hot flushes, hypertension, fatigue, fractures, falls, skin rash, **Common**: Alopecia, pruritis, muscle spasms, ischaemic heart disease, hypothyroidism, hypercholesterolaemia, hypertriglyceridaemia **Uncommon**: Seizure

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, U&Es, LFTs, PSA, thyroid function tests and blood pressure at baseline.
- FBC, U&Es, LFTs, PSA and blood pressure every four weeks for the first 12 weeks then every 8-12 weeks thereafter and thyroid function tests if clinically indicated.

Dose Modifications

The dose modifications listed are for liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

Hepatic Impairment

- No dose adjustment is necessary for patients with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively).
- Apalutamide is not recommended in patients with severe hepatic impairment as there are no data in this patient population and apalutamide is primarily hepatically eliminated.

Renal impairment

- No dose adjustment is necessary for patients with mild to moderate renal impairment.

- Caution is required in patients with severe renal impairment as apalutamide has not been studied in this patient population. If treatment is started, patients should be monitored for the adverse reactions listed above and dose reduced accordingly.

Skin rash

Rash is reported in 25% of patients on apalutamide. It is commonly described as macular or maculopapular in presentation and has a median onset within 3 months. It typically resolves after 2 months. Corticosteroids and antihistamines have been used to treat the rash (see rash management table)

Grade	Management
1	Continue apalutamide at current dose Initiate topical steroid cream AND oral antihistamine Monitor for change in severity
2 or symptomatic grade 1	Hold apalutamide for up to 28 days Initiate topical steroid cream AND oral antihistamine Monitor for change in severity When rash or related symptoms improve to Grade ≤ 1, reinitiate apalutamide. Consider dose reduction at -1 dose level (ie 180mg daily)
≥ 3	Hold apalutamide for up to 28 days Initiate topical steroid cream AND oral antihistamine Consider short course of oral steroid Reassess after 2 weeks, if the rash is unchanged or worse, initiate oral steroids (if not done already) and refer to dermatology Reinitiate apalutamide at -1 dose level when rash resolved to Grade ≤ 1 If dose reduction will lead to a dose of less than 120mg – discontinue apalutamide

Dose reduction

Dose level -1: Apalutamide 180mg daily
Dose level -2: Apalutamide 120mg daily

Hypothyroidism

Grade 1-2 hypothyroidism was reported in 30% of patients who were already receiving thyroid replacement therapy and in 7% of patients who were not receiving thyroid replacement. Median onset for hypothyroidism was 4 months. Monitor thyroid function regularly throughout treatment with apalutamide and initiate or dose adjust thyroid replacement therapy as indicated

Other

If a patient experiences a NCI-CTCAE Grade 3 or greater toxicity or an intolerable adverse reaction, dosing should be withheld until symptoms improve to Grade 1 or below or original grade, then should be resumed at the same dose or a reduced dose (180 mg or 120 mg), if warranted.

Regimen

28 day cycle until disease progression (12 cycles will be set in Aria)

Drug	Dose	Days	Administration
Apalutamide	240mg	1-28	Oral

Dose Information

- Apalutamide is available as 60mg film-coated tablets

Administration Information

- If a dose is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra tablets should not be taken to make up the missed dose.

- Apalutamide film-coated tablets should be swallowed whole and can be taken with or without food.

Additional Therapy

- Consider starting Calcium+Vitamin D supplements (ie Adcal D3 2 tablets daily) for long term bone health in all patients. For those with a moderate or high risk FRAX score request a DEXA scan and adjust treatment accordingly.

Additional Information

- Apalutamide treatment should be supervised by a consultant oncologist.

- Apalutamide is a strong inducer of CYP3A4 and CYP2C19 and a weak inducer of CYP2C9, co-administration of apalutamide with substrates of these CYP enzymes has resulted in substantial reductions in plasma concentrations of these substrates leading to a lost or reduced clinical effect.

- Concomitant use of apalutamide with medicinal products that are primarily metabolised by CYP3A4 (e.g., darunavir, felodipine, midazolam, simvastatin), CYP2C19 (e.g., diazepam, omeprazole), or CYP2C9 (e.g., warfarin, phenytoin) can result in lower exposure to these medicinal products. Substitution for these medicinal products is recommended when possible or evaluation for loss of efficacy should be performed if the medicinal product is continued.

- Co-administration of apalutamide with warfarin and coumarin-like anticoagulants should be avoided. If co-administration with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol) is unavoidable, additional International Normalised Ratio (INR) monitoring should be conducted.

References

1. Kim N Chi., N Agarwal., A Bjartell., *et a* l(2019). Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *New England Journal of Medicine.* 381; 12-24
2. M Smith., F Saad., S Chowdhury., *et al*. (2018). Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *New England Journal of Medicine*. 378;1409-1418.
3. Janssen-Cilag Ltd (2021). Erleada 60mgfilm-coated tablets Summary of Product Characteristics. Online at https://www.medicines.org.uk/emc/product/9832. Last accessed 15/02/2022
4. BC Cancer Protocol Summary for Treatment of Non-Metastatic Castration Resistant Prostate Cancer using Apalutamide. Online at http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Genitourinary/UGUPAPA_Protocol.pdf Last accessed 15/02/2022

REGIMEN SUMMARY

Apalutamide

Day 1

Take Home Medicines

1. Apalutamide 240mg once a day oral
   Administration Instructions
   Oral SACT.
   Swallow whole, either with or without food.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.0	February 2022		Eleanor Taylor Oncology Pharmacist	Dr Simon Crabb Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.