Oncological Treatments for Metastatic Prostate Cancer Jan 2020

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Aims/Objectives of Session

- To increase general understanding about treatments for metastatic prostate cancer – good news story!
- To increase the understanding about the choices men face when first diagnosed with advanced prostate cancer
- To inform you about our services and how they can support men (and health professionals) in their decision making.

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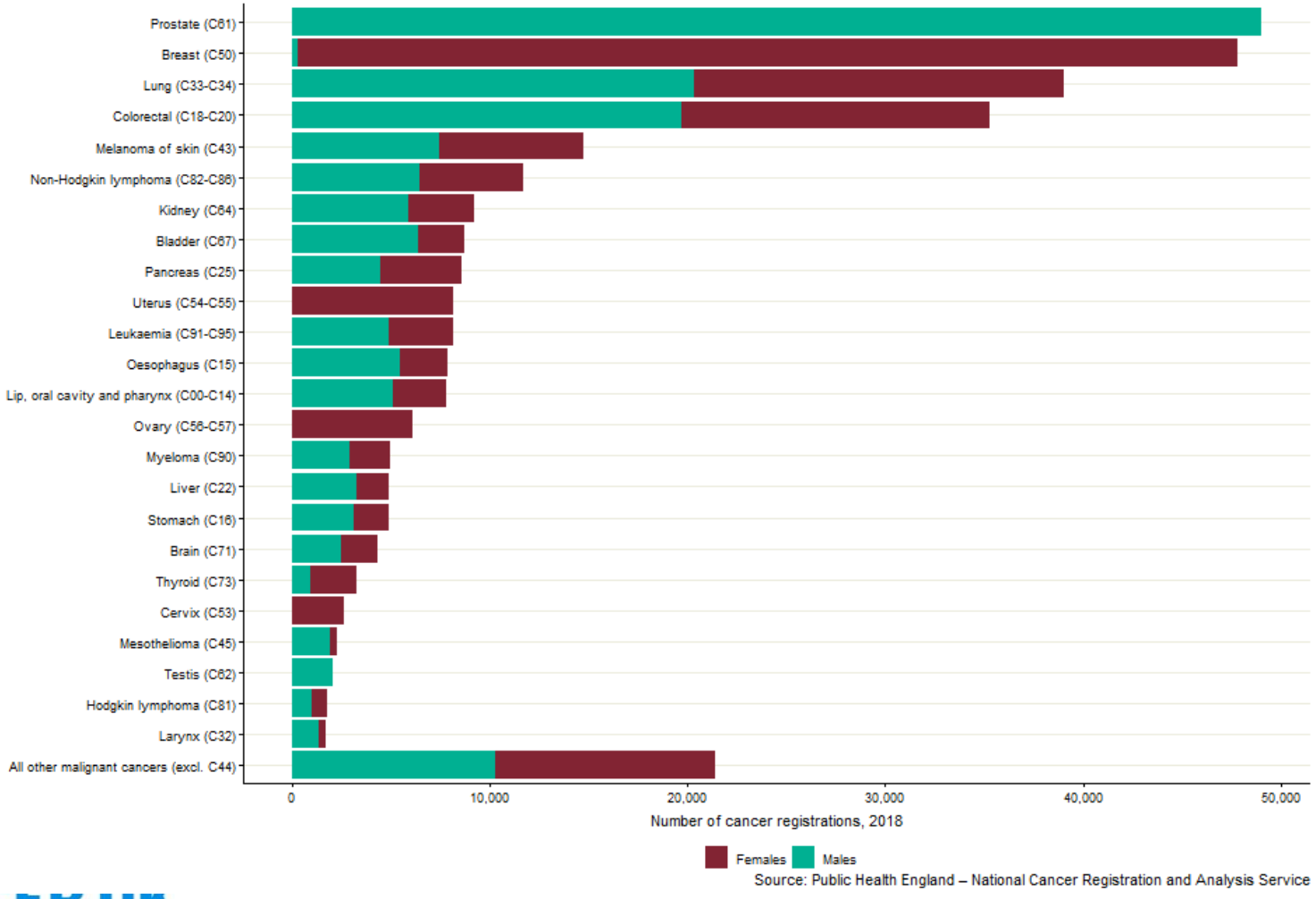
Public Health England – Cancer cases diagnosed in 2018 (interim report – full report spring 2020)



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What is the scale of metastatic prostate cancer?

- 16% were diagnosed with metastatic prostate cancer (stable on previous year) (NCPA 2019)
- Mortality rates from prostate cancer decreased by 12% in the decade up to 2016 (Public Health England 2017)

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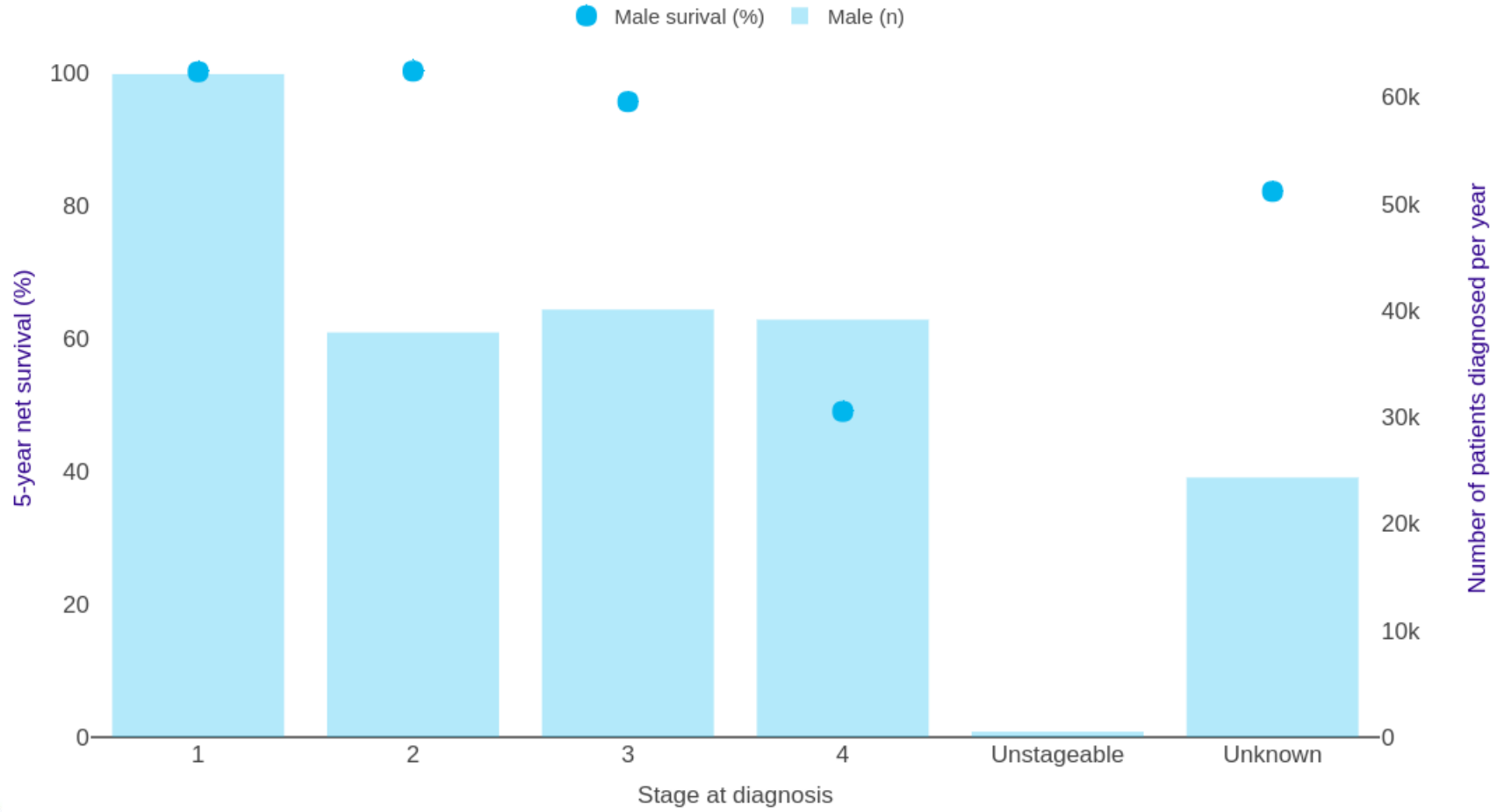
Survival data by stage: adults diagnosed 2013-2017, followed up to 2018 – Cancer Research UK



Five-year net survival decreases from Stage 3 (96%) to Stage 4 (49%), a difference of 47 percentage points.

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Metastasis in Stampede trial in ZA/docetaxel arms

- Standard of care (n=1184) Standard of care plus zoledronic acid (n=593) Standard of care plus docetaxel (n=592) Standard of care plus zoledronic acid and docetaxel (n=593)

- Bone metastases (54%) (51%) (52%) (52%)
- Nodal metastases(19%) (20%) (17%) (20%)
- Lung metastases (3%) (3%) (2%) (2%)
- Liver metastases (1%) (2%) (1%) (2%)
- Other metastases (4%) (6%) (4%) (4%)

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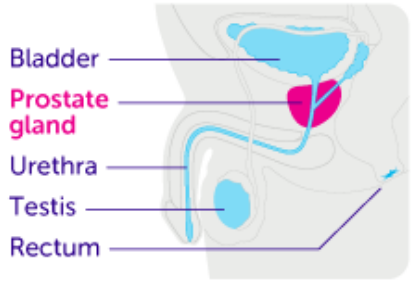
James, N et al (2016), *Addition of docetaxel, zoledronic acid, or both to fi rst-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial* [Online],Lancet 2016; 387: 1163–77

HOW DO PROSTATE CANCERS SPREAD?



WHAT WAS PREVIOUSLY THOUGHT...

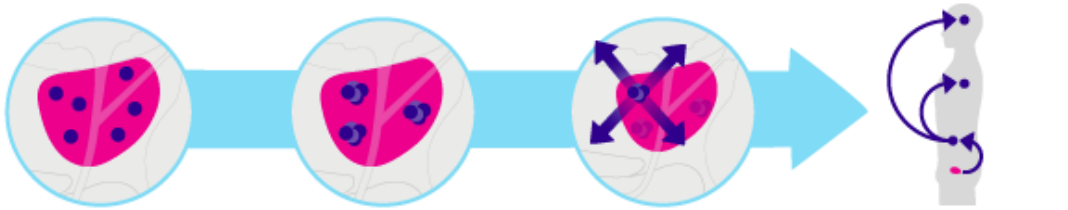
1 Single DNA copying error: cells start rapidly dividing

2 Tumour forms

3 More errors accumulate: tumour becomes able to spread

4 Cancer cells break away from the prostate to form secondary tumours

WHAT RECENT FINDINGS SUGGEST HAPPENS...



1 Many normal-looking cells have DNA errors

2 Multiple genetically different tumours can form

3 One (or more) of these becomes able to spread

4 Cancer cells from the rogue tumour break away, then keep spreading around the body

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WE WILL BEAT CANCER SOONER
cruk.org

CANCER RESEARCH UK

Routes to Metastasis:

- Local Spread
- Blood Stream
- Lymph nodes

Chemotherapy !!!!

Hormone Therapy!

Abiraterone?

‘Incurable but treatable’ Cancer Diagnosis

Have a think about a clinical trial…

Often no clinical nurse specialists in oncology!

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Newly diagnosed metastatic misunderstandings…

- “I’m terminal” (newly diagnosed man)
- “There’s not much that can be done”
- “I’ve got bone cancer”
- “The treatment will only treat the cancer that’s in the prostate”
- “The hormone therapy will turn me into a woman/they’re giving me women’s hormones”

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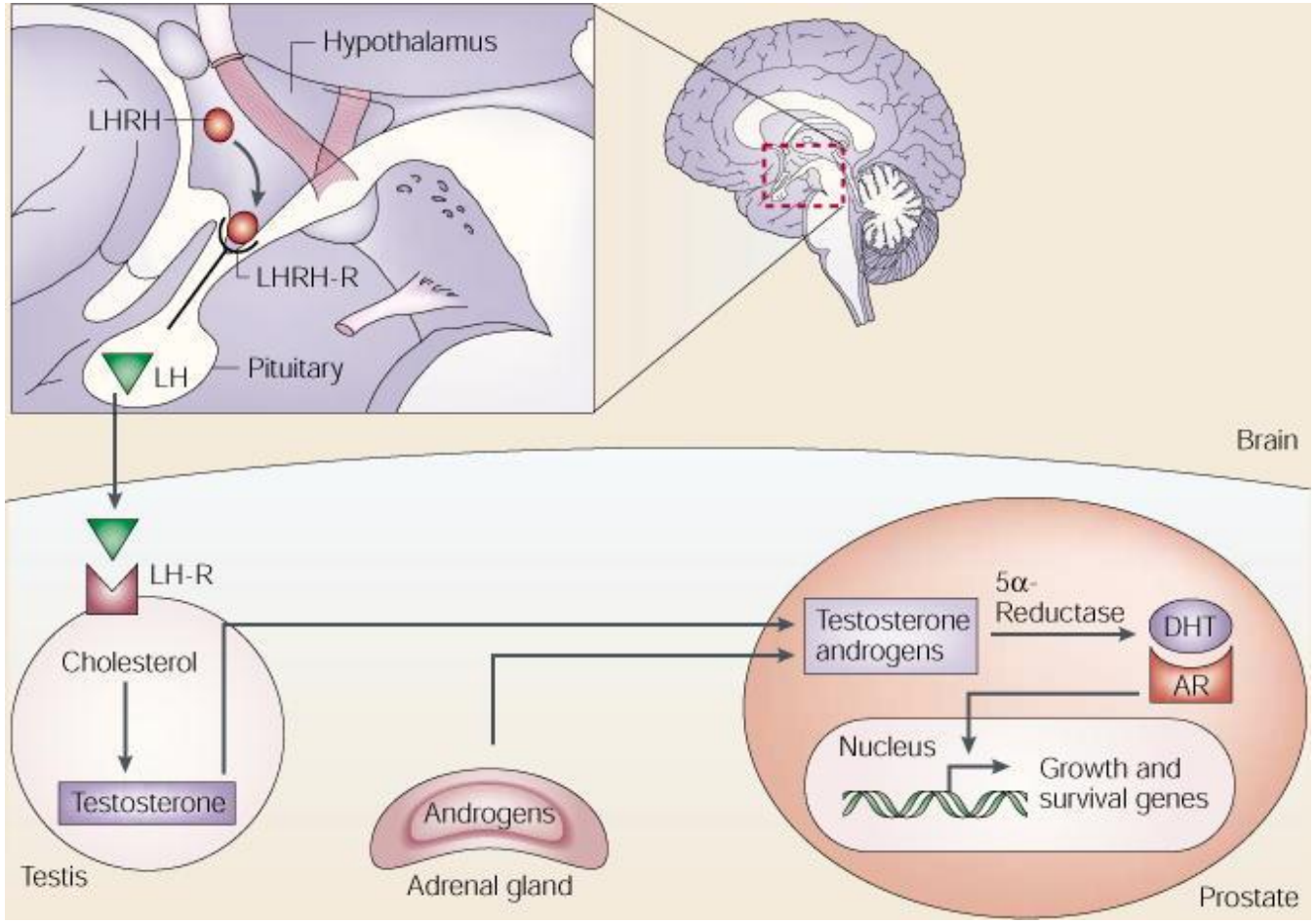
Testosterone Production



Androgen receptors also in:

- Bone
- Muscles
- Brain

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A history of prostate cancer treatment Denmeade, S and ,Isaacs, JT
Nat Rev Cancer. 2002 May; 2(5): 389–396.

Hormone Therapy

Standard of care since 1940s

- Not all men will want treatment
- Surgical castration – cost effective and can achieve castrate levels (<15ng/dl) in 12 hours. (Standard is < 50 ng/dl - ?should be 20 ng/dl) (Ramani, 2017)
- LHRH agonist
- LHRH antagonist
- MAB
- Anti-androgen monotherapy

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LHRH Agonists

Flare

LH peaks at 24 hours

Testosterone levels peak at 3 days

Pain begins at 12 hours, peaking at 36 hours

Increase risk of SCC

Both Bicalutamide and cyproterone are licensed:

Mahler, C et al (1998) found:

Bicalutamide+Zoladex – resulted in testosterone levels remaining the same or slightly elevated for 10 days

Cyproterone+Zoladex – resulted in a drop of testosterone from the start

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Long term LHRH Agonists

- LHRH down regulates the LHRH receptors
- 2-17% of patients on LHRH agonists fail to achieve castrate levels of < 50 ng/dl
- 2-25% of patients may experience ‘mini-flares’ of > 50ng/dl with each subsequent treatment – Higher PSA relapse rate in men who experience these break-through flares. (Ramani, 2017 https://youtu.be/MKsgVjO8mx8)

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Antagonist: Degaralix

- Don’t get flare response
- Significant drop in testosterone by day 1 – castrate levels by day 3

NICE Guidance 24/8/16: “ Degaralix is recommended as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastasis, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016”

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MAB

- Combination of an anti-androgen with androgen deprivation therapy (ADT)

Adrenal glands continue to produce 5-10% of testosterone

Only slight advantage (few months) over some years to having MAB from the start – but increase in side effects. Overall literature unclear as to benefit

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Bicalutamide Monotherapy

- In the metastatic setting there is an overall survival advantage to LHRH of some months

- NICE Guidelines: “For men with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia in the hope of retaining sexual function, offer anti-androgen monotherapy with bicalutamide”

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Intermittent Hormone Therapy

A trial looking at intermittent versus continuous hormone therapy in advanced prostate cancer (EORTC 30985)

- Men who had a PSA of 4 ng/ml or less (and wasn't rising) in months 6 and 7 could be put into 1 of 2 treatment groups
- In the intermittent treatment (IT) group started hormone therapy drugs again if their PSA level >15-20ng/ml, or back to its original level if <20ng/ml or if they developed symptoms.
- After 7 months of treatment, they could stop the treatment again if their PSA level had gone back down. Can be repeated.

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Intermittent Hormone Therapy

- The average length of time men lived after randomisation was
- 5.8 years in the continuous therapy group
- 5.1 years in the intermittent group
- Three months after being randomised, the intermittent therapy group reported fewer ED problems and improved mental health. But after 15 months, there was not any real difference in reported quality of life between the 2 groups.
- PSA Nadir was a strong predictor of outcome
- PSA>4ng/ml – more risk of progression

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Side Effects of hormone therapy

- Loss of libido/ED
- Fatigue
- Hot flushes
- Osteoporosis
- Decline in intellectual capacity, emotional lability, depression
- Hot flushes
- Decreases in muscular strength
- Weight gain – Increase in abdominal fat
- Anaemia
- Metabolic Syndrome

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What can men on HT do to help themselves?

- Stay active – and increase physical activity where possible
- Stop smoking
- Reduce alcohol consumption
- Try to reduce weight where this is already a problem
- Eat a healthy diet
- Calcium and vitamin D supplements.

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Stampede – Radiotherapy to the prostate in metastatic disease

- (55 Gy in 20 fractions over 4 weeks) or weekly (36 Gy in six fractions over 6 weeks) schedule that was nominated before randomisation.
- metastatic burden was classified according to the definition used in the CHAARTED trial: high metastatic burden: four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both; all other assessable patients were considered to have low metastatic burden.
- Significant survival benefit to men with low-volume metastatic disease having prostate radiotherapy – no benefit in high-volume disease

	High	**Low**
CHAARTED (volume)	≥ 4 Bone metastasis including ≥ 1 outside vertebral column or spine **OR** Visceral metastasis https://uroweb.org/guideline/prostate-cancer/#6_4	Not high

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Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial, Parker, Christopher C et al.The Lancet, Volume 392, Issue 10162, 2353 - 2366

Docetaxel vs Abiraterone

+ currently…Scotland vs rest of UK

Both demonstrate improvement in

- overall survival
- time to failure free survival
- skeletal related events

<u>Docetaxel</u>

- Given 6 cycles, 3 weekly
- If good response some clinicians would re-challenge with docetaxel
- Tolerated best when fit

<u>Abiraterone</u>

- Taken every day until progression
- No point in using once it has failed
- Requires long term steroids!

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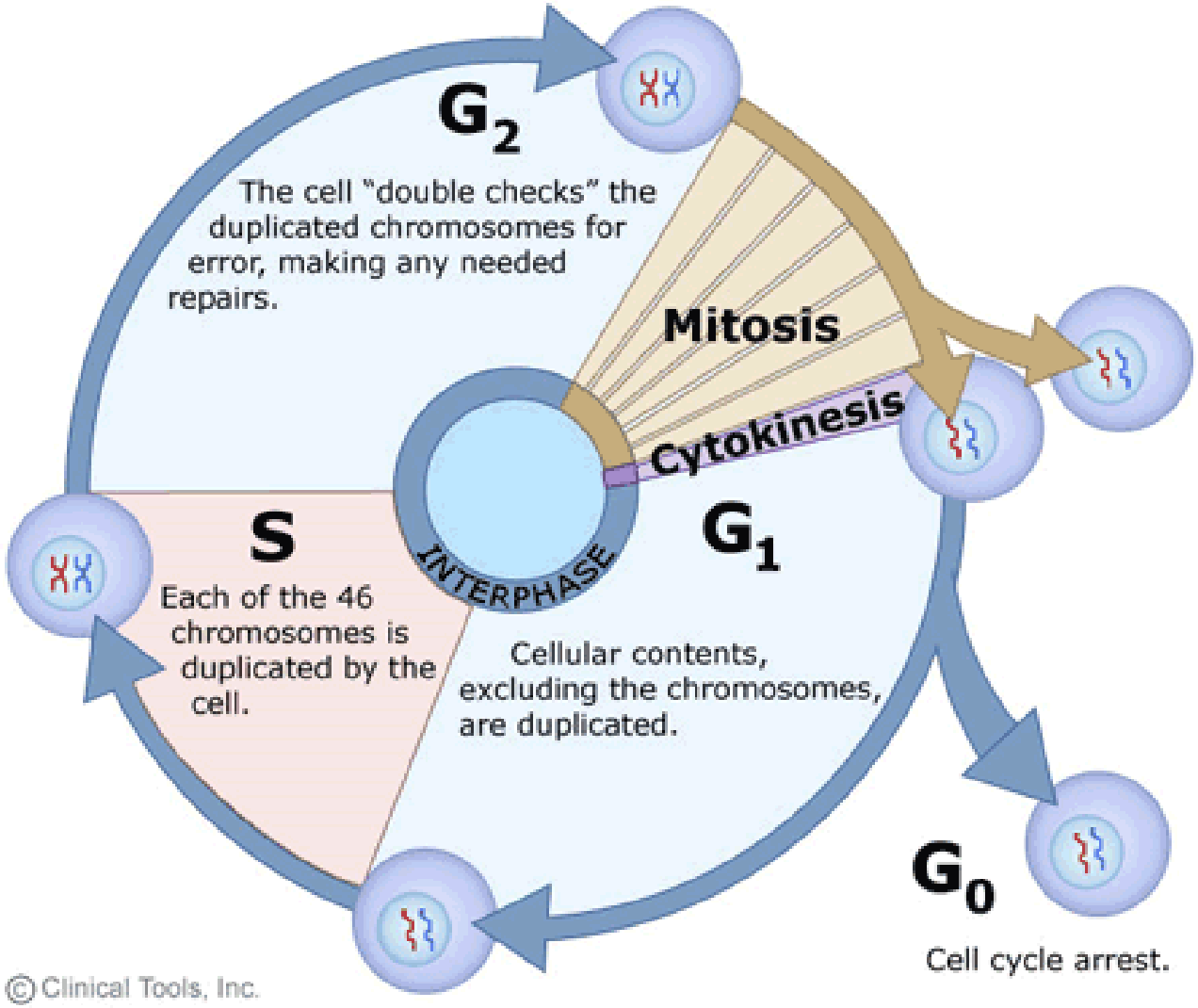
The Cell Cycle



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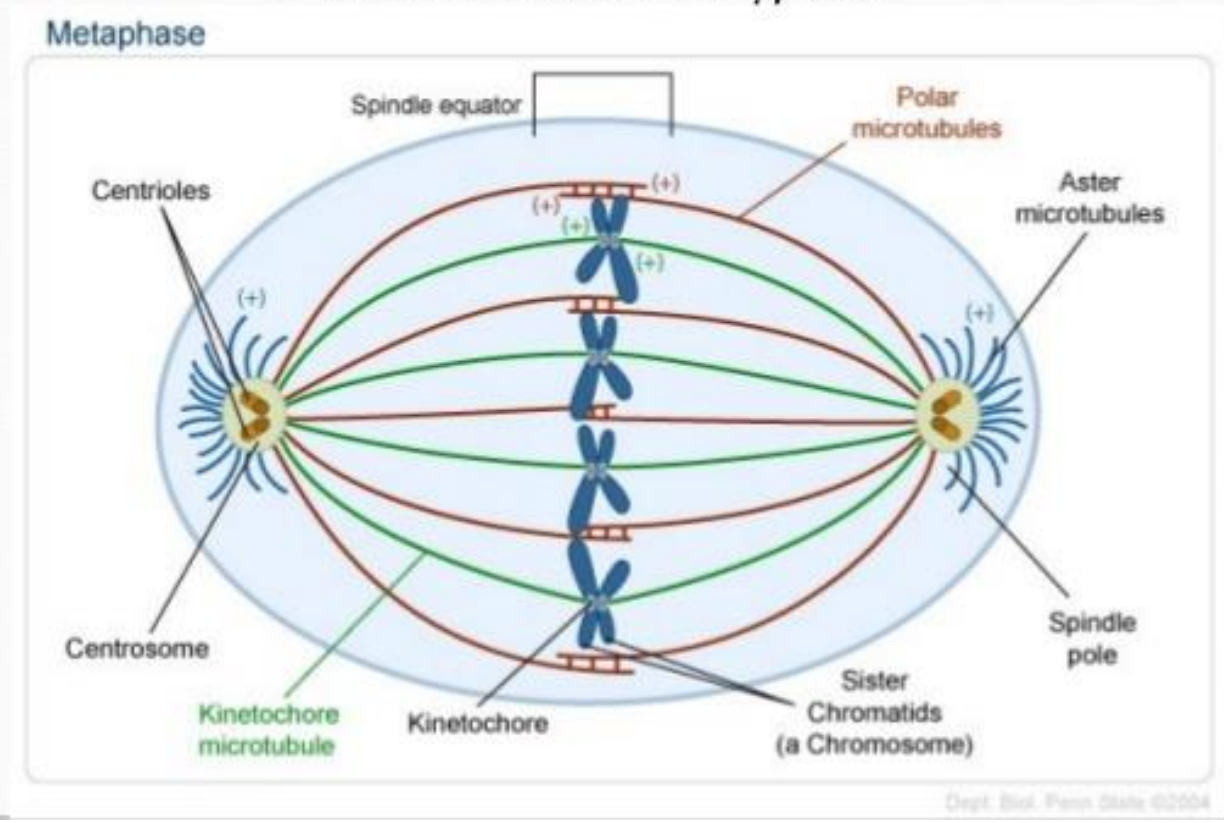
Microtubules

- Microtubules are major components of spindle fibre used to pull apart chromosomes during cell



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Pre treatment with chemotherapy

- Dental check
- Careful with vaccinations – always check with the hospital team
- Advise careful use of birth control (often suggested that couple use 2, rather than 1 method)

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How is it given?

- In early situation – 6 cycles, 3 weeks apart
- In hormone resistant/rechallenge setting up to 10 cycles
- Given with prednisolone ?
- Pre-dosed with dexamethasone – to prevent hypersensitivity reactions and fluid retention. E.g. 8mg Dex 12 hours, 3 hours and 1 hour before docetaxel infusion
- Before each treatment: Bloods and clinical review

  - dose reductions, treatment delays, medication review
- Must be given 24 hour number to ring in emergency

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Side Effects

- Allergic reaction
- Extravasation
- Vein pain
- Bone marrow suppression
  - -Anaemia
  - -Thrombocytopenia
  - - Neutropenia
- Nausea/vomiting
- Fatigue
- Loss of appetite/taste changes
- Sore mouth
- Constipation
- Diarrhoea
- Hair Loss
- Skin changes
- Nail changes
- Eye problems
- Muscle/joint pain
- Peripheral Neuropathy
- Pneumonitis
- Planta- palmer syndrome
- Ankle and leg w

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Information for patients about docetaxel

- Chemotherapy for prostate cancer isn't as intensive as for many other types of cancer
- Generally well tolerated – most men have some side effects but these are usually manageable. A few men have minimal side effects and some men will have more serious side effects (77% of men allocated to Doc in Stampede received 6 cycles, 81% received 5 – 8% didn't start)
- Assessment happens before each cycle of treatment – treatment may be adjusted
- The list of potential side effects is for reference – it doesn't mean that they will experience them all
- Men should not be feeling sick with appropriate medication – but they might need the hospital to adjust their antiemetics
- They will lose their hair – it will grow back (but visible sign they're having chemotherapy)
- They will have a 24hour chemotherapy phone number for problems.

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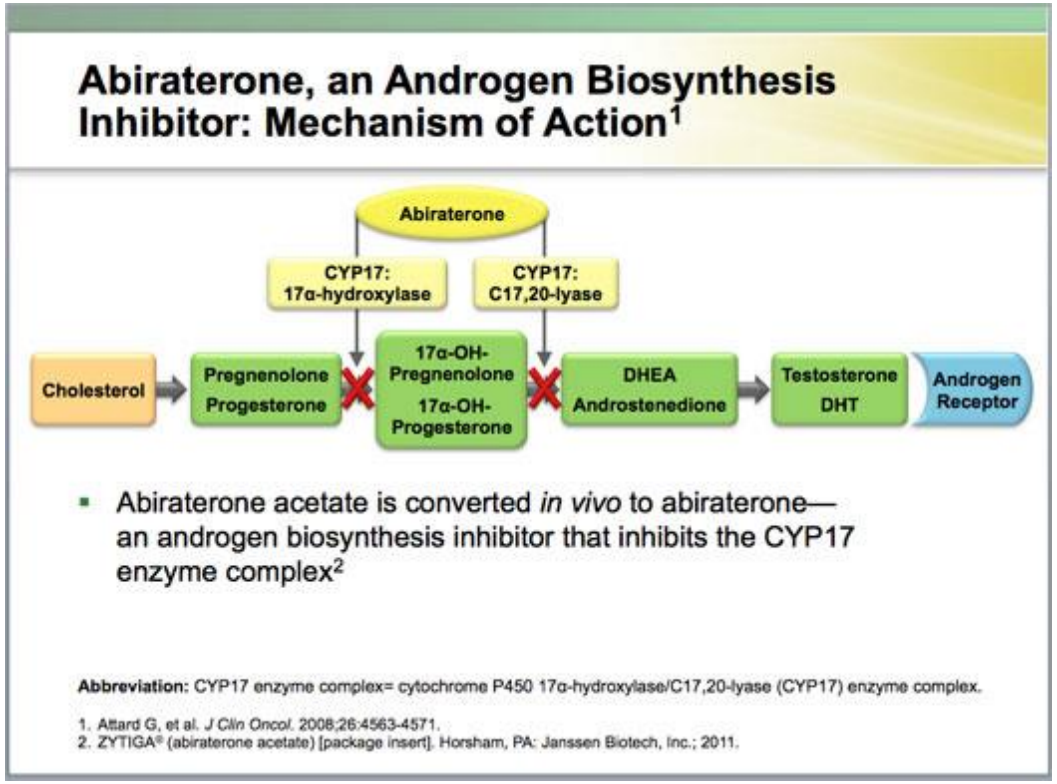
Abiraterone

- To make testosterone the body makes an enzyme, cytochrome p17 (CYP17)
- Abiraterone blocks CYP17 in testicles, adrenals and tumour tissue and stops testosterone production. Irreversible change.



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Abiraterone

- From current data from Stampede, abiraterone offers the same early advantage as docetaxel BUT not NICE approved – but is approved in Scotland.
- Currently available for mCRPC under NICE guidelines COU-AA-301Trial demonstrated 5.2 average survival benefit in this setting over placebo.
- Taken 1x/day with Prednisolone
- Needs to be taken on an empty stomach: At least 1 hour before food or 2 hours after a meal
- Taken same time each day
- Dose adjusted for hepatic impairment, or if this occurs during treatment, withhold until recovery and restart at a reduced dose.
- Have to be seen in clinic monthly: Bloods monthly – potassium
- Monitoring of BP
- Watching for symptoms of water retention

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Abiraterone side effects (CRUK)

- On Stampede Trial 20% of men came off treatment because of side effects

- Hepatotoxicity can be severe and fatal
- More than 10%
- Swelling to feet and legs in 30% of men
- UTI
- Hypertension
- Diarrhoea
- Low levels of potassium

More than 1%

Blood in urine

Bone fractures

Neutropenia

Raised cholesterol

Changes to the way the heart works

Liver changes

Indigestion and heart burn

Skin rash

Less than 1%

Muscle weakness

Pain in muscles and joints

Changes in salt level

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PCUK Best Practice Pathway

- There is little evidence available for treatment sequencing.
- • Docetaxel (rechallenged if patient has responded well) – Up to 10 cycles if
- treatment is effective and side effects tolerated
- • Dexamethansone (low-dose dexamethasone therapy is thought to be effective in
- addition to second- or third-line anti-androgens, or anti-androgen withdrawal)
- • Prednisolone (often in combination with docetaxel and cabazitaxel to lower
- prostate-specific antigen and quality-of-life benefits, including appetite stimulation)
- • Abiraterone or Enzalutamide
- • Radium 223 (if the patient has symptomatic bone metastases and no known
- visceral metastases, have had docetaxel and/or is contra-indicated to docetaxel
- • Cabazitaxel (in combination with prednisolone if the patient has had docetaxel).

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Stampede

- http://www.stampedetrial.org/participants/about-stampede/

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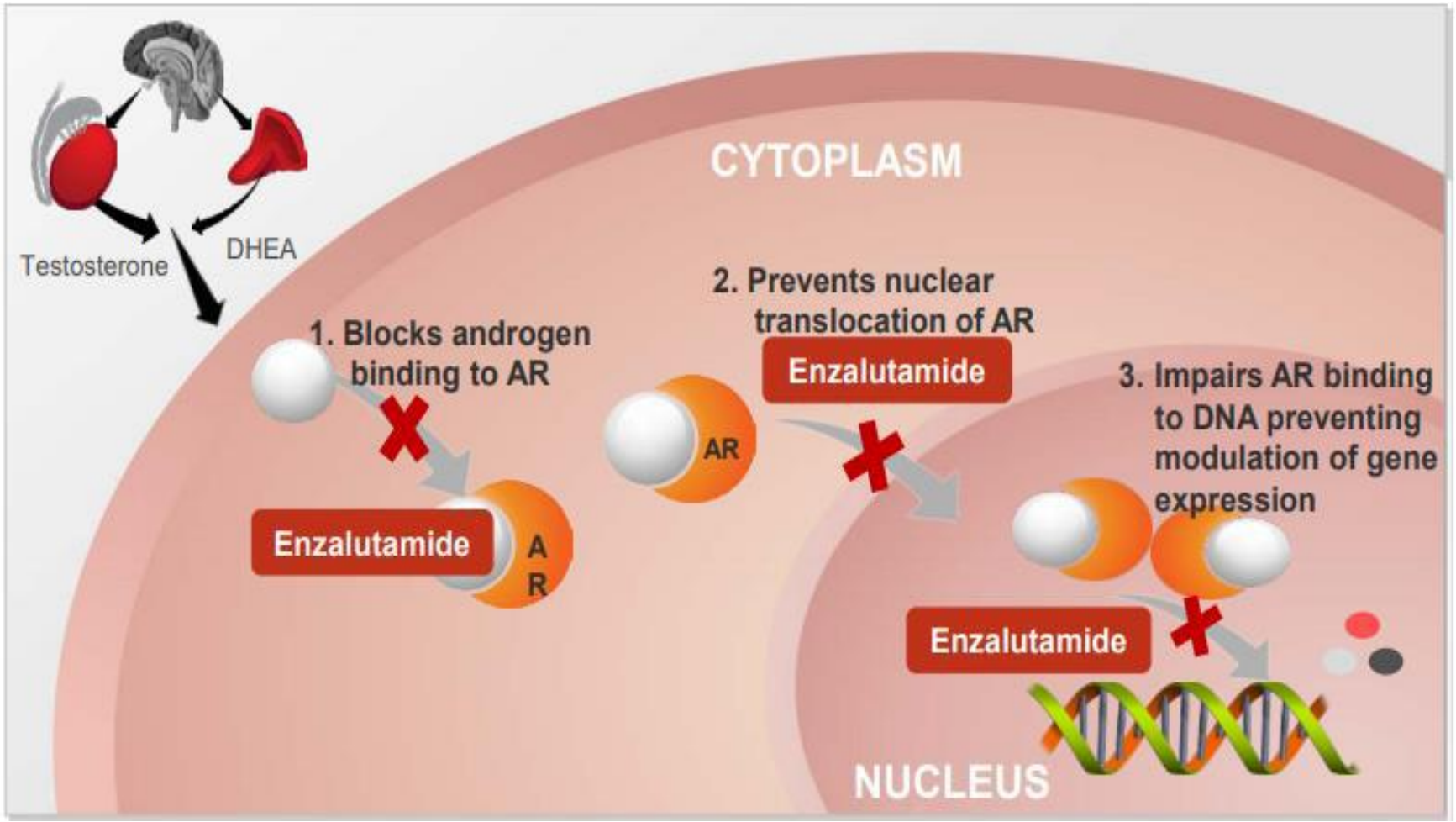
Enzalutamide

Competitively inhibits androgen binding to receptors and inhibits androgen receptor nuclear translocation and interaction with DNA



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Enzalutamide

- The results showed that patients taking enzalutamide lived an average of 18.4 months, compared with 13.6 months for the placebo group.
- The men's quality of life was also assessed, including measures of their energy levels, ability to cope with their illness and levels of pain. 43 per cent of men in the enzalutamide group had an improved quality of life, compared with 18 per cent of men taking a placebo. CRUK
- Taken 1x/day with or without food 160 mg (4×40 mg soft capsules) daily.
- Siezures occurred in 0.4% of patients receiving Xtandi but in 2.2% of me with predisposing factors

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Enzalutamide side effects

- More than 1 in 10 people (10%). Tiredness and weakness (fatigue) during and after treatment
- Tiredness and weakness occurs in about 1 in 3 men (33%).
- Hot flushes and sweats. Hot flushes happen in about 2 in 10 men (20%).
- Headaches Headaches affect about 1 in 10 men (10%).
- High blood pressure

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Enzalutamide side effects

1 in 100 people (1%)

- Memory problems
- Breast swelling
- Dry skin
- Falls
- Bone thinning
- Anxiety
- Restless legs syndrome

Rare side effects

- Each of these effects happens in fewer than 1 in 100 people (1%). :
- Risk of seizures
- Bruising, bleeding gums or nosebleeds

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Radium-223

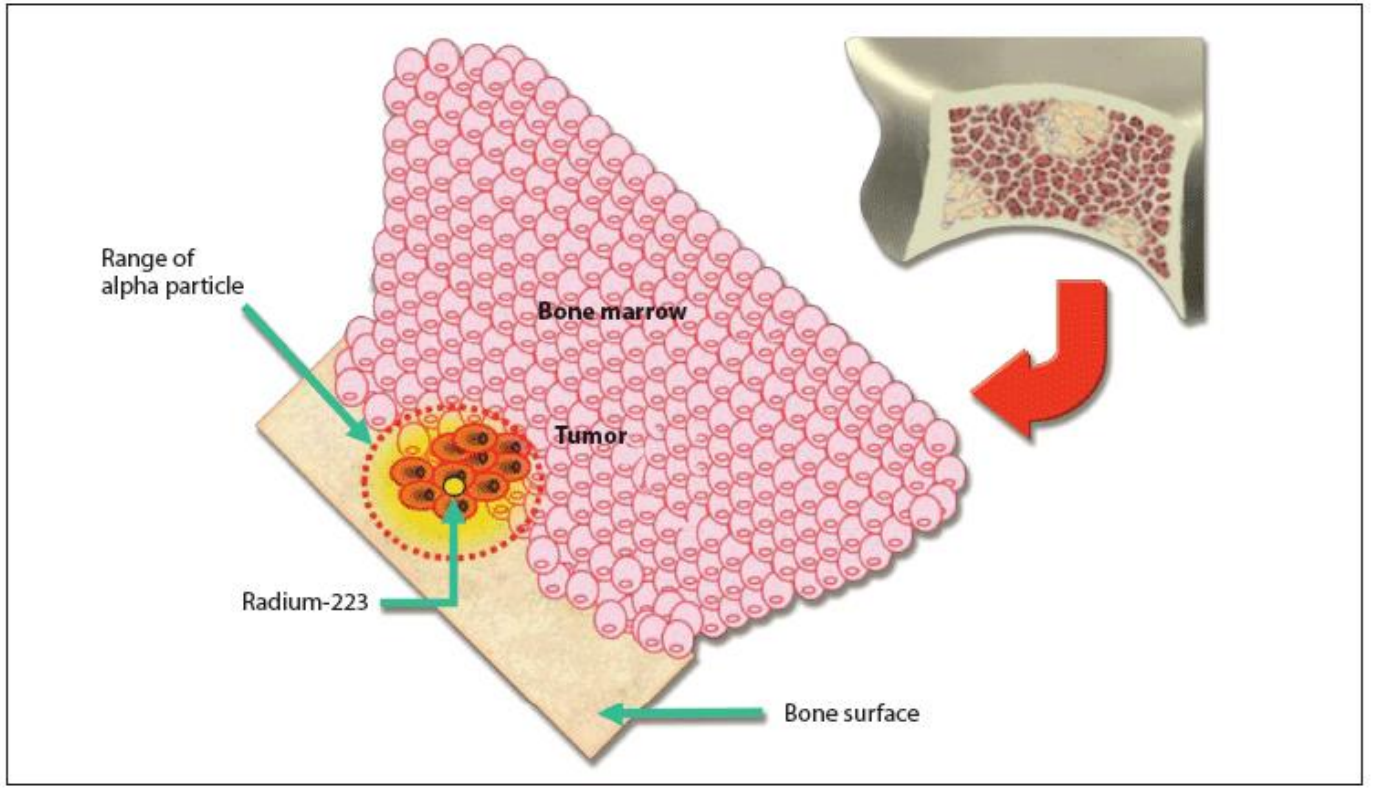

Figure 3: Bone-Targeted Localized Mechanism of Action of α-Pharmaceuticals—This diagram demonstrates that alpha particles have a much shorter range than beta particles; thus alpha particles have a much more localized effect within bone. Figure from Henriksen G et al. Cancer Res. 2002,[39] with permission from the American Association for Cancer Research.

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Radium-223

- Radium-223 dichloride is recommended as an option for treating hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases in adults, only if:
- they have already had docetaxel or docetaxel is contraindicated or is not suitable for them.
- The drug is only recommended if the company provides radium-223 dichloride with the discount agreed in the patient access scheme.
-

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Cabazitaxel

- Cabazitaxel in combination with prednisone or prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer in people whose disease has progressed during or after docetaxel chemotherapy, only if:
- the person has an ECOG performance status of 0 or 1
- the person has had 225 mg/m^2 or more of docetaxel
- treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first).

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The Future?

- Olaparib
- Stampede: Enzalutamide + Abiraterone results awaited
- Ongoing Metformin and oestrogen patches
- what impact is PSMA scanning likely to have?
- https://www.ukctg.nihr.ac.uk/
- https://www.ukctg.nihr.ac.uk/trials?query=%257B%2522query%2522%253A%2522METASTATIC%2520PROSTATE%2520CANCER%2522%257D

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How can Prostate Cancer UK Support Men (and their health professionals)

- Information online (prostatecanceruk.org)
- Literature
- Specialist Nurses – for anyone affected by prostate cancer but also health professionals (0800 074 8383)
- Fatigue Service
- Sexual Support Service
- Possible 1-2-1
- Support Groups
- Best Practice Pathway

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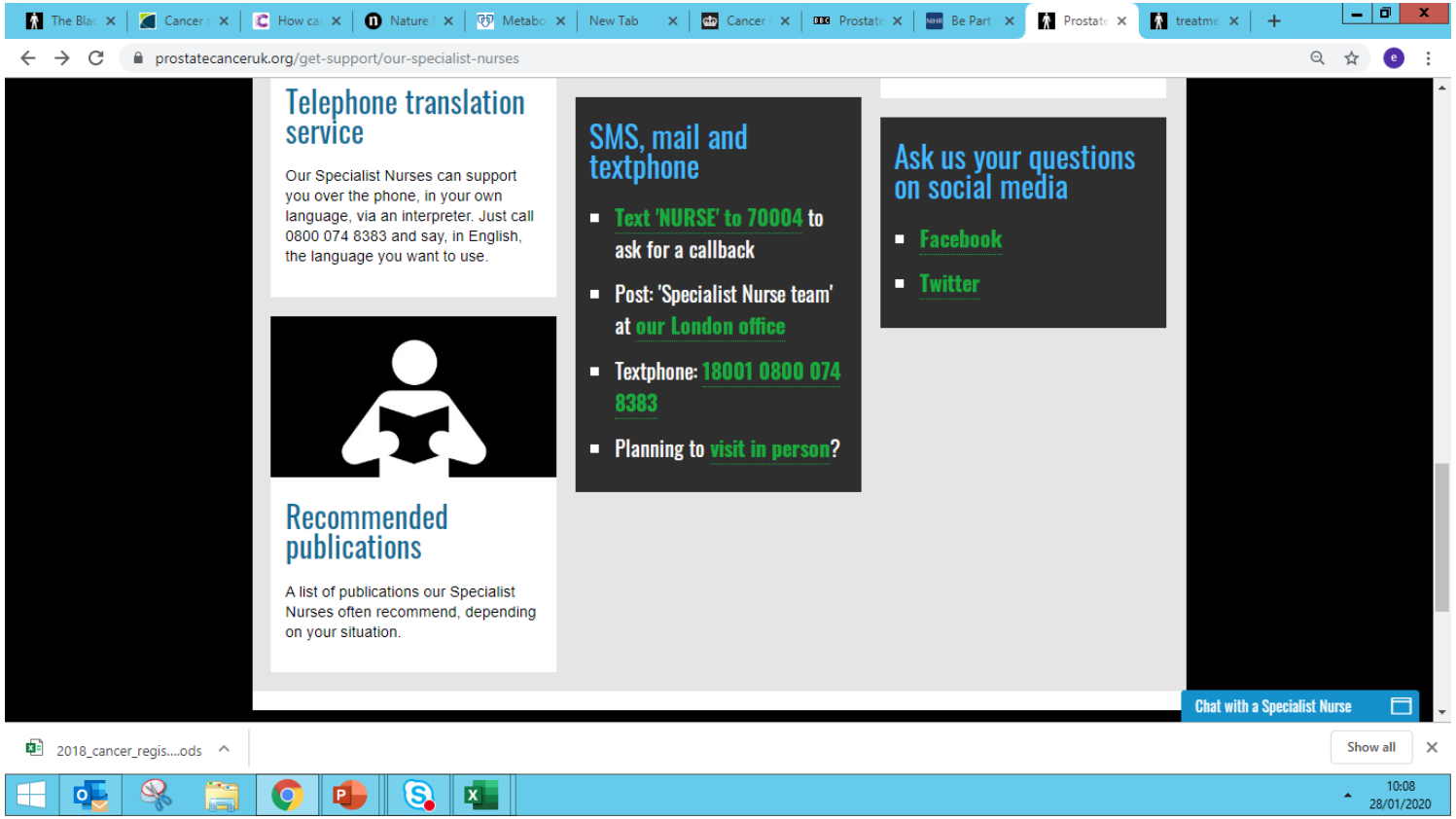
Not sure which publications might help?
Get support -> Our Specialist Nurses



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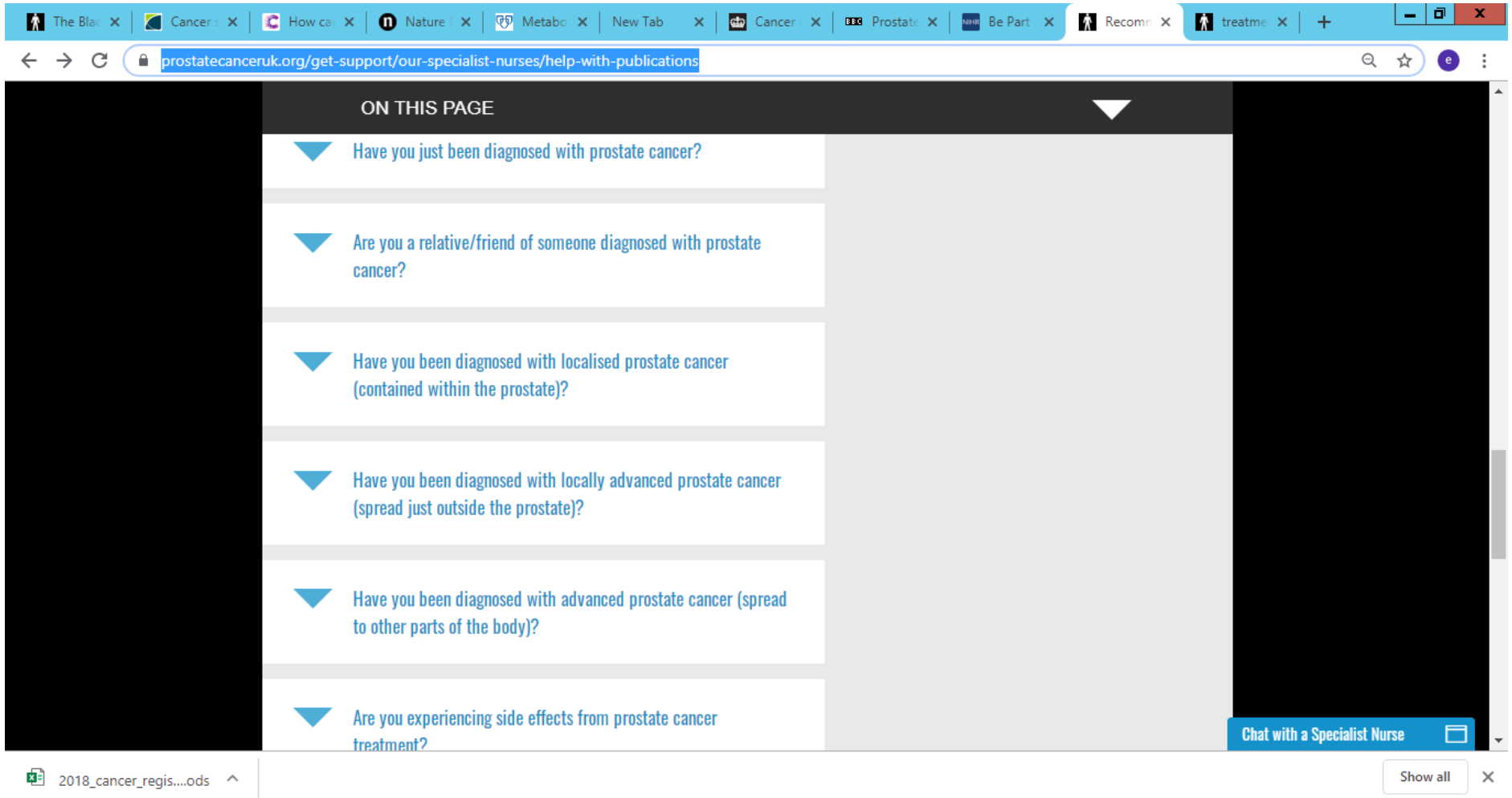

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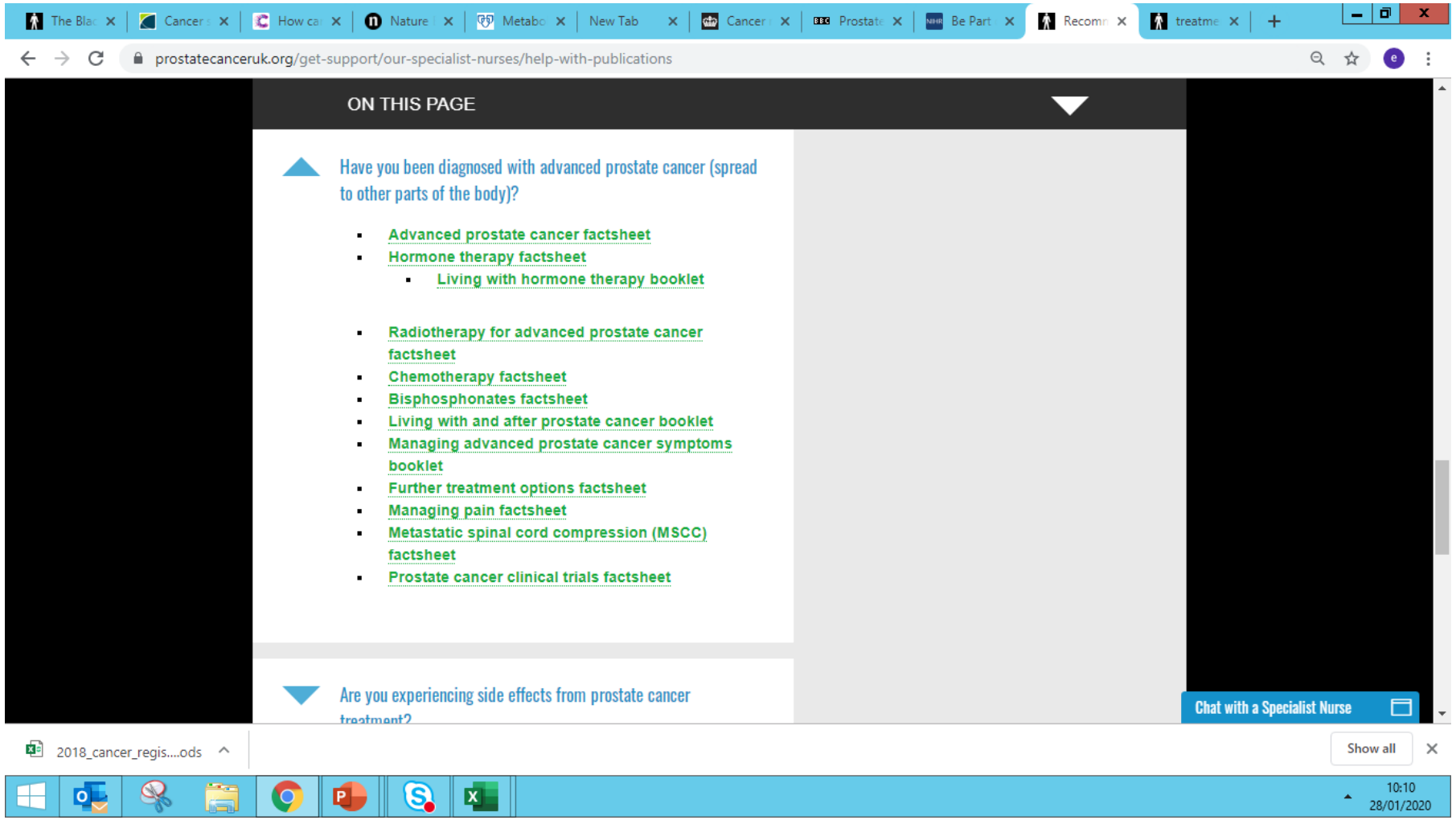

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In Conclusion

- Things are changing fast in metastatic prostate cancer!
- In the future treatment will hopefully better tailored to the individual.

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References and Useful Links

- James, N.D. et al (2016) ‘Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE); survival results from an adaptive, multiarm, multistage, platform randomised controlled trial’ *The Lancet,* 387: 1163-77
- James, N.D. et al (2017) ‘Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy’ *The New England Journal of Medicine,* 377:338-351
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- NICE Prostate Cancer Guidelines: https://www.nice.org.uk/guidance/ng131
- Stampede Trial website: http://www.stampedetrial.org/
- Prostate Cancer UK Best Practice Pathway: https://prostatecanceruk.org/about-us/projects-and-policies/best-practice-pathway
- Sydes, M.R. et al (2018) ‘Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol’ *Annals of Oncology,* 29(5): 1235-1248

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