Managing metastatic CRPC

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Objectives

1. Evidence for treatments
   - Docetaxel
   - Cabazitaxel
   - Abiraterone
   - Enzalutamide
   - Radium-223
2. How to manage pts on treatment and side effects
3. Access, funding and sequencing
4. Current clinical trials
5. Case history

Docetaxel (Taxotere)

- Microtubule stabiliser (spindle poison)
- TAX 327- NEJM 2004
- Doc plus pred vs mitoxantrone plus pred, **after MAB,** n=1009
  - Median OS 18.9m vs 16.5m (2.4m benefit)
  - Improvement in pain + QoL **and OS for first time**
- NICE TA101 June 2006

Docetaxel (Taxotere)

- CHAARTED / E3805 – ASCO June 2014
  - Doc x6 plus ADT vs ADT as 1st line, n=790
  - Unblinded at interim analysis
  - Median OS 57.6m vs 44.0m (13.6m benefit)
  - Benefit due to high vol pts (visceral mets or 4 or more bone mets)
  - 1 pt died due to docetaxel
  - Controversial!

Docetaxel (Taxotere)

- 75mg/m^2 every 3 weeks, max 10 cycles plus pred 5mg BD
- Myelosuppression, hypersensitivity, hair loss, fatigue, rash, neuropathy
- Review every 3 weeks, FBC, U+E, LFT

Cabazitaxel (Jevtana)

- Microtubule stabiliser (spindle poison)
- TROPIC trial Lancet 2010
- Cabaz plus pred vs mito plus pred, max 10 cycles after failure of docetaxel, n=755
  - Median OS 15.1m vs 12.7m (2.4m benefit)
  - 83% vs 58% G3/4 neutropenia
- NICE TA255 May 2012

Cabazitaxel (Jevtana)

- 25mg/m^2 every 3 weeks, max 10 cycles plus pred 5mg BD
- GCSF
- S/E as per docetaxel, more hypersensitivity

Abiraterone (Zytiga)

- CYP (cytochrome P450) isoenzyme 17 inhibitor, - blocks 3 sources of androgen biosynthesis by testes, adrenals and tumour
- COU-AA-301- NEJM June 2011
- Abi plus pred vs placebo plus pred, **post docetaxel,** n=1195
  - Unblinded at interim analysis
  - Median OS 14.8m vs 10.9m (3.9m benefit)
  - Median FU 12.8m
- NICE TA259 June 2012

Abiraterone (Zytiga)

- COU-AA-302 – NEJM Jan 2013, OS update ESMO Sept 2014 in **chemo naïve** met CRPC, asymp or mildly symptomatic
  - Abi plus pred vs placebo plus pred, n=1088
  - Unblinded at interim analysis as PFS improved 16.5m vs 8.3m
  - 44% crossed over
  - Median OS 34.7 vs 30.3m (4.4 m benefit)
  - Median time to chemo 25.5m vs 16.8m
  - Median FU 49.2m
- CDF

Abiraterone (Zytiga)

- 1000mg OD (4 tabs) + pred 5mg BD
- No food 2 hours before + 1 hour after
- See every 2 weeks for first 3 months, then every 4 weeks
- U&E, LFT, BP, fluid retention (chest, legs)

Abiraterone (Zytiga)

- When to stop?
- Post ADT – unequivocal clinical progression e.g. need for RT or surgery, opiates, declining PS
- Post chemo – PSA progression (>25%) PLUS radiographic progression PLUS clinical progression
- CTCs / other biomarkers?

Radium-223 dichloride (Alpharadin / Xofigo)

- Alpha particle emitter, range 2-10 cell diameters, targets bone
- ALSYMPCA- NEJM July 2013
- Ra-223 vs plac x6, n=921, prev chemo or declined / not fit enough, bone only or LN<3cm
  - Unblinded at interim analysis
  - Median OS 14.9m vs 11.3m (3.6m benefit)
- CDF

Radium-223 dichloride (Alpharadin / Xofigo)

- 50 kBq/kg IV every 4 weeks x6
- CT CAP (exclude visceral mets) + BS (eclude superscan), no imminent fracture risk
- Adequate BM function
- Weekly FBC
- S/E- BM suppression, fatigue, G1/2 diarrhoea , flare. No diff in AEs / treatment discontinuation
- Radiation Protection advice
- ALP response better than PSA

Enzalutamide (Xtandi)

- Androgen receptor inhibitor
  1. Competitively inhibits androgen binding to receptor (cytoplasm)
  2. Inhibits receptors from translocation into nucleus (nuclear membrane)
  3. Inhibits receptor binding to DNA (nucleus)
- AFFIRM- NEJM Sept 2012
- Enza vs placebo, **post docetaxel**, n=1199
  - Unblinded at interim analysis
  - Median OS 18.4m vs 13.6m (4.8m benefit)
  - Median FU 14.4m
- NICE TA316 July 2014

Enzalutamide (Xtandi)

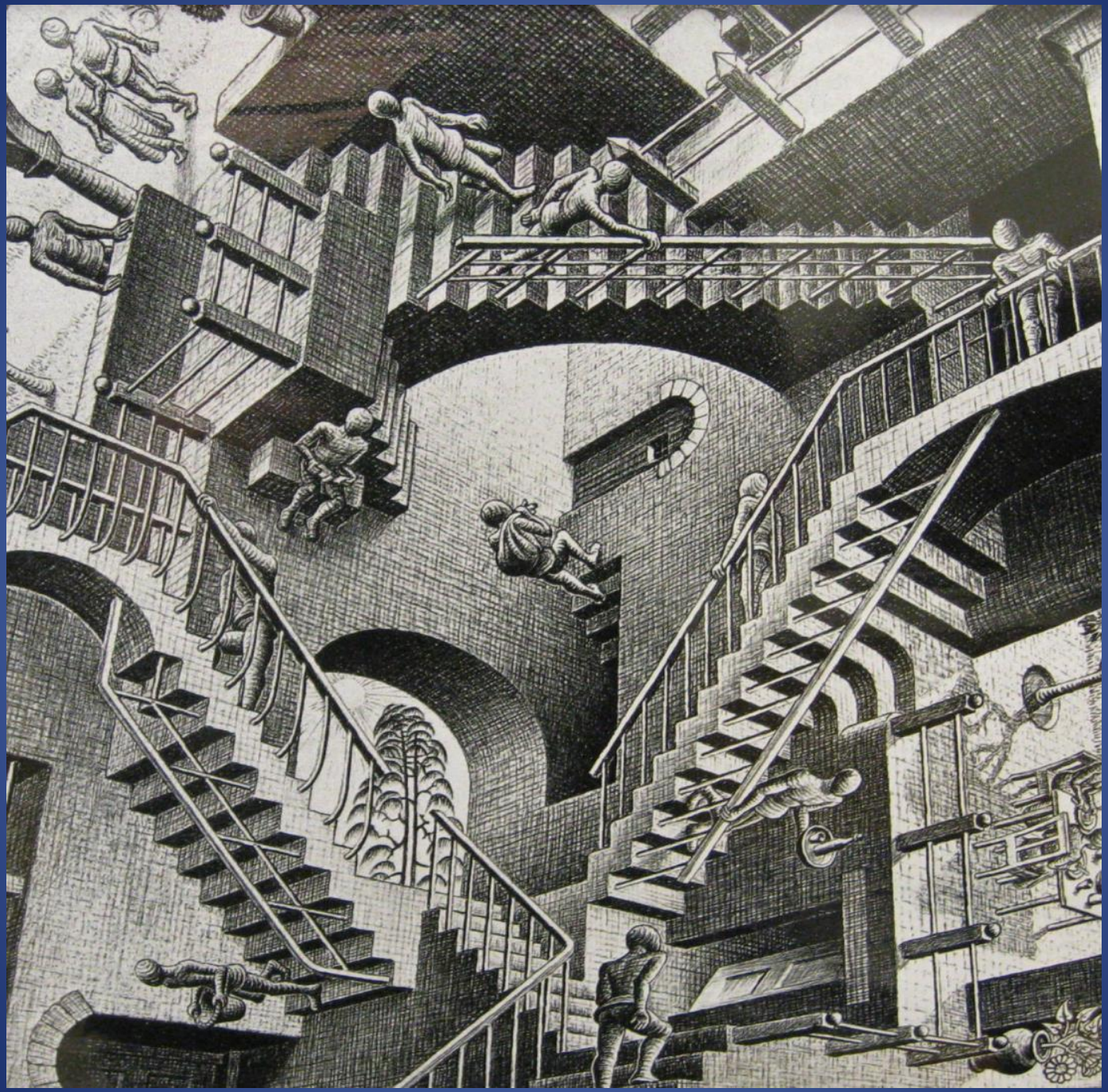
- PREVAIL – GU ASCO Feb 2014, NEJM July 2014 in **chemo naïve** met CRPC, n=1717
  - Enza vs placebo
  - Unblinded at interim analysis as 30% reduction in risk of death, 81% reduction of radiographic progression
  - Median OS 32.4m vs 30.2m (2.2m benefit)
  - Delayed time to initiation of chemo
- CDF

Enzalutamide (Xtandi)

- 160mg OD (4 tabs)
- With / without food
- See every 4 weeks
- No specific monitoring recommended
- S/E – headache, hot flushes, hi BP, 0.8% seizures
- CYP enzyme inducer, full effect at approx 1 month, can affect levels of:
    - Warfarin, opiates, antibiotics, antiepileptics, betablockers, cardiac meds, T4, statins
- When to stop – as per abi

Access to drugs

- NICE approved:
  - Doc for hormone refractory (June 2006)
  - Cabaz post doc (May 2012)
  - Abi post doc (June 2012)
  - Enza post doc (July 2014). If prev abi NHS England won't fund
- NICE rejected:
  - Abi pre chemo (Aug 2014) – available via CDF
- NICE considering:
  - Enza pre chemo, due Sept 2015 – available via CDF
  - Rad-223 in process – available via CDF
  - ?? Up front docetaxel



Sequencing

- New Dx, fit, hi vol mets– discuss upfront docetaxel x6
  - Pro – apparent large survival benefit
  - Con – toxic treatment, not yet NICE approved
- After failure of combined CAB, PS 0/1– enzalutamide via CDF, unless seizure risk, polypharmacy.
  - Pro - no pred, fewer visits, less liver toxicity and hi BP
  - Con – less clinical experience, drug interactions
- If not appropriate for enza – abi
- If intolerant of enza in first 3 months and no progression - abi

Next steps

- Enza... Radium-223 (bone only)… docetaxel… cabazitaxel… abi ???
- Order changes regularly depending on trial results / funding / experience with sequential therapies

Current clinical trials

- STAMPEDE – over 5000 pts recruited, current comparison arm ADT + enza + abi
- RE-AKT – enza + AZD5363 vs plac + enza - prev abi + doc
- CANTATA – doc rechallenge vs cabaz - prev doc
- TOPARP – olaparib - biomarkers

Mr WA

- 71 yo man, Jan 2009 L neck swelling
- CT – neck, SCF, mediastinal, retroperitoneal, iliac LN
- Bone scan – clear
- PSA 2614
- Neck node biopsy – poorly differentiated carcinoma, IHC consistent with prostate

Mr WA

- Jan 2009 – Zoladex, PSA nadir 43
- Nov 2009 - PSA 73, bicalutamide added, PSA nadir 19
- July 2010 – PSA 70, bic stopped, DES started
- Nov 2010 – PSA 393, referred to oncology

Mr WA

- Dec 2010 – see in oncology, PSA 802
  - DES stopped, pred started
  - Asymp apart from small neck lump, PS 0
  - Doesn't want chemo
- May 2011- PSA 180

Mr WA

- Sept 2011 – fatigue, increasing neck lump, PSA 707
- Docetaxel x10 completed Apr 2012
- PSA post chemo - 16
- June 2012 - 12.5
- Aug 2012 – 32.6

Mr WA

- Sept 2013 – PSA 606, CT shows increasing LN, well
- “Window of opportunity”
- Cabazitaxel x10 completed Apr 2014
- PSA post chemo - 16
- May 2014 - 12.3
- Jul 2014 – 18.4

Mr WA

- Dec 2014 – PSA 317.5
- CT – no cervical or mediastinal LN, small RP LN, increasing pelvic LN vs Sept 2013 (pre – cabazitaxel)
- PS 0, asymptomatic
- What next?

Summary

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