STAMPEDE trial (MRC PR08):

Arm J overview

"Enzalutamide and abiraterone comparison" and trial update

Arm J
Hypotheses and rationale

STAMPEDE: Hypothesis

- Will addition of enzalutamide and abiraterone to standard-of-care improve survival in hormone-naïve Pca?

Hypotheses: LHRHa + Enzalutamide + Abiraterone + Prednisolone

MRC Clinical Trials Unit

1. Combination of abiraterone (+ prednisolone 5mg od) with enzalutamide is safe and well tolerated

Translational data suggest that:

2. Resistance to enzalutamide is associated with increased androgen synthesis

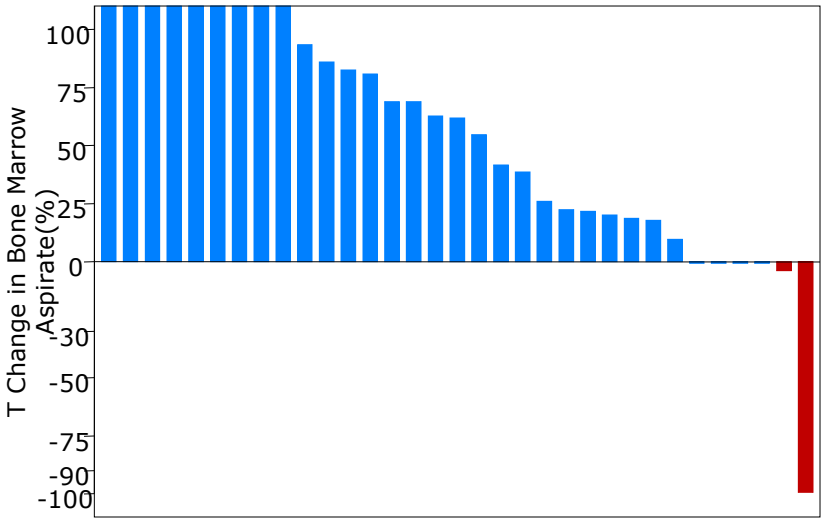
3. Resistance to abiraterone is associated with activation of "promiscuous" or over-expressed AR by residual ligands

4. Administration of both agents in combination but not in sequence will improve efficacy of inhibition of AR signalling

AR inhibition by enzalutamide associated with increased androgen biosynthesis

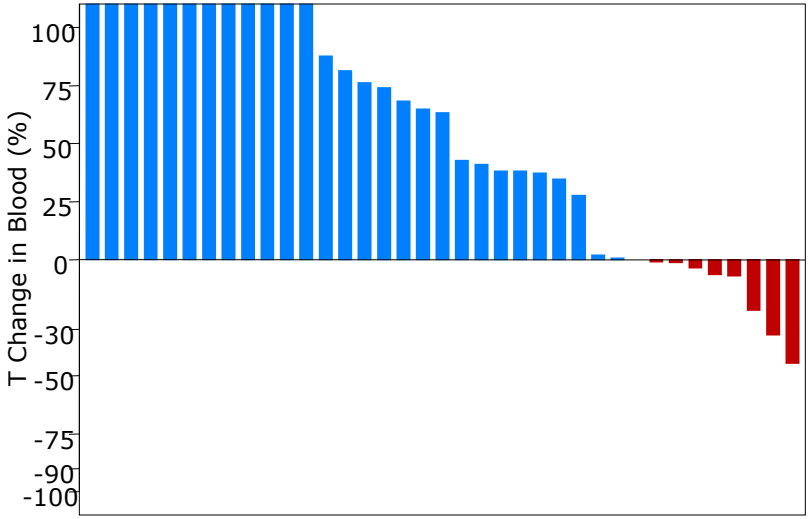
MRC Clinical Trials Unit

Bone Marrow



33 patients

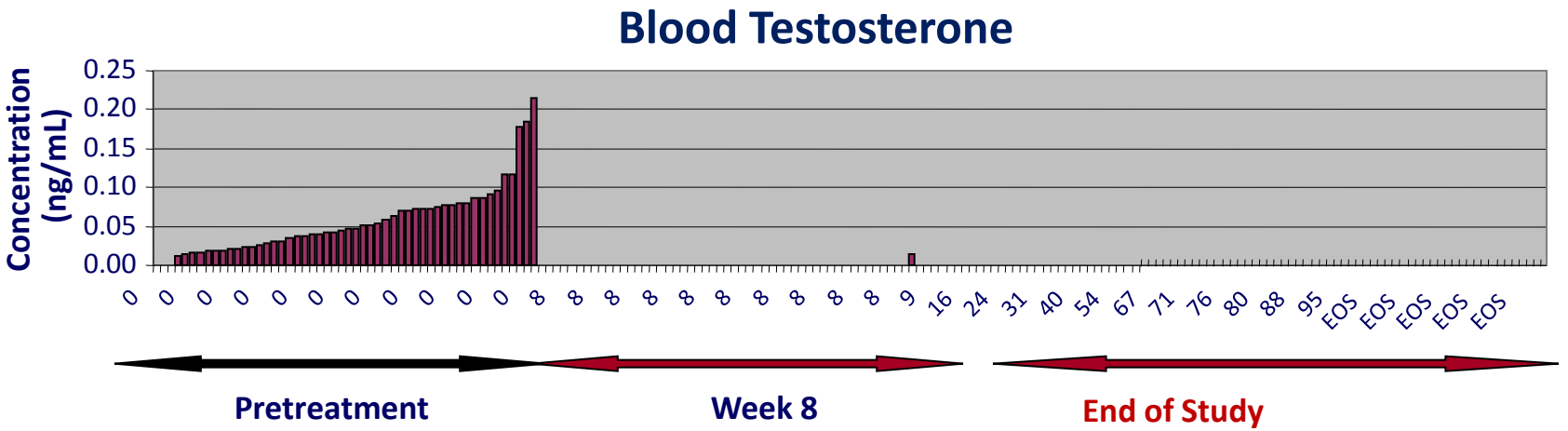
Blood

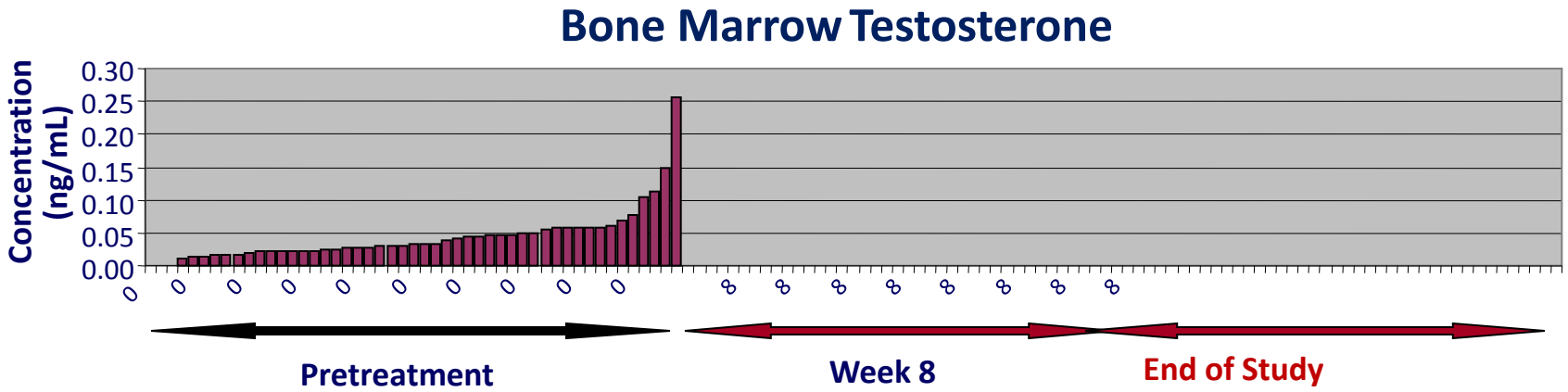


37 patients

Efstathiou et al. J Clin Oncol 2011; 29(Suppl)

Sustained depletion of testosterone by abiraterone





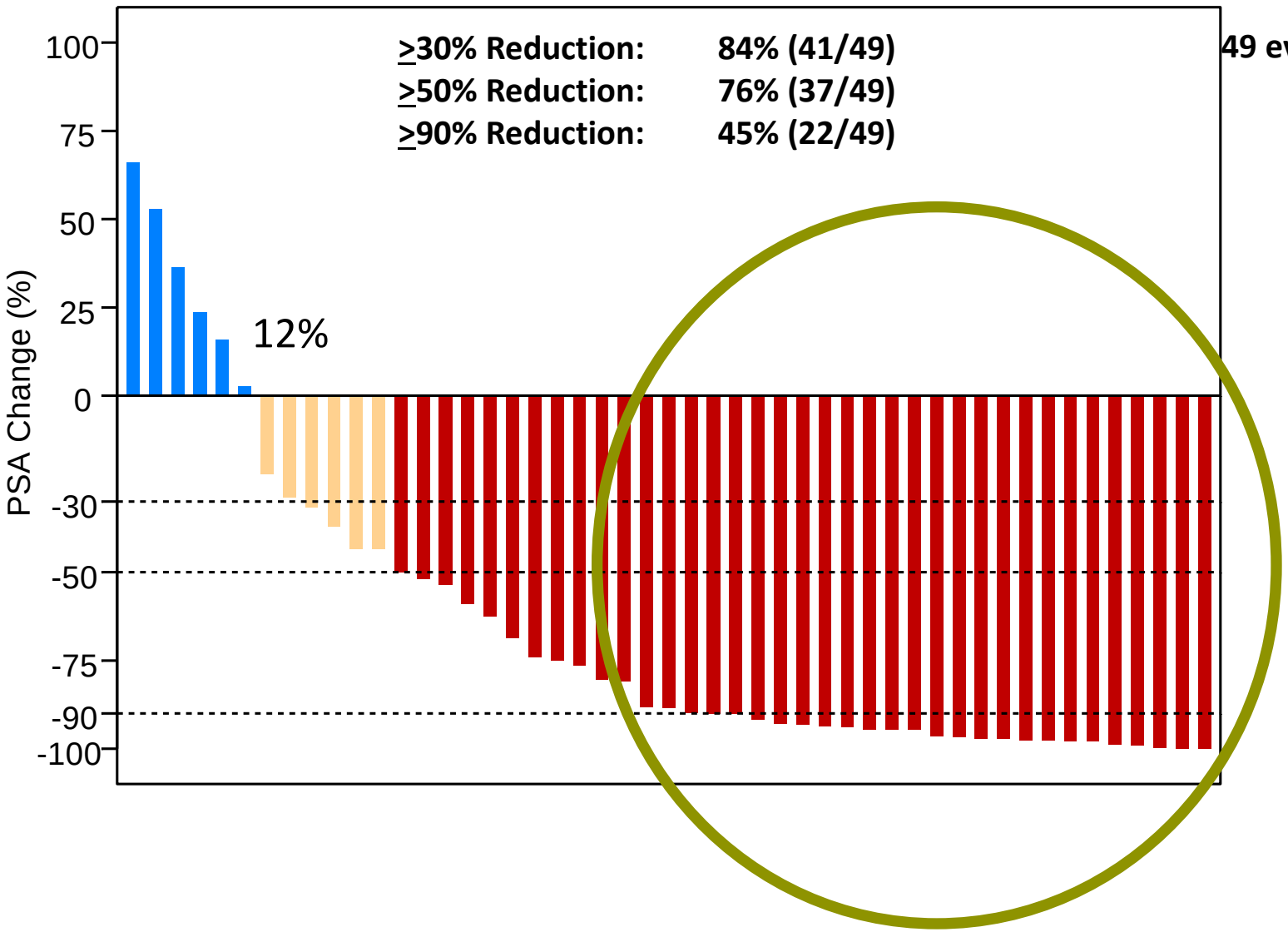
Efstathiou et al. J Clin Oncol 2012

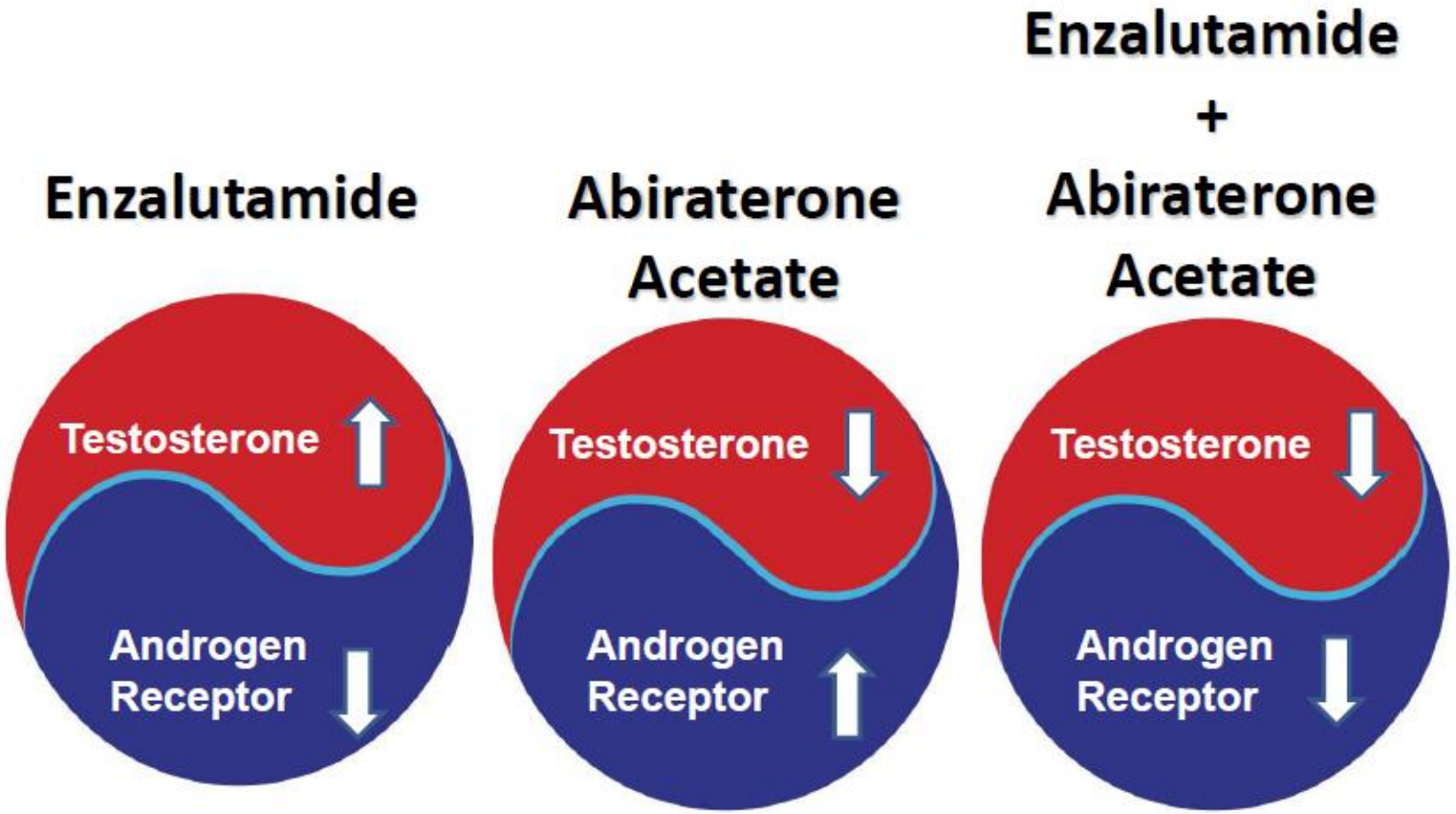
Phase Ib experience with Abiraterone + Enzalutamide

- 60 patients with metastatic CRPC treated at MDACC
- 57 patients evaluable
- No severe adverse effects
- Well tolerated

Efstathiou et al ESMO 2013

Maximum PSA change with combination




Enzalutamide
Testosterone
Androgen Receptor
Abiraterone Acetate
Testosterone
Androgen Receptor
Enzalutamide + Abiraterone Acetate
Testosterone
Androgen Receptor

Conclusion from Efstathiou et al

- **Confirms tolerability of combination in metastatic CRPC**

Limitations:

- Incomplete follow-up
- Not yet published in a peer reviewed journal
- Single-arm study of 2 highly active drugs
- Does not allow any conclusions on increased activity of combination

Abiraterone + Enzalutamide

- Enthusiasm from both manufacturers, physicians and patients

- Indirect comparisons with abi + pred in STAMPEDE Arm G
- Comparisons using network meta-analysis with enza alone

Other trials:

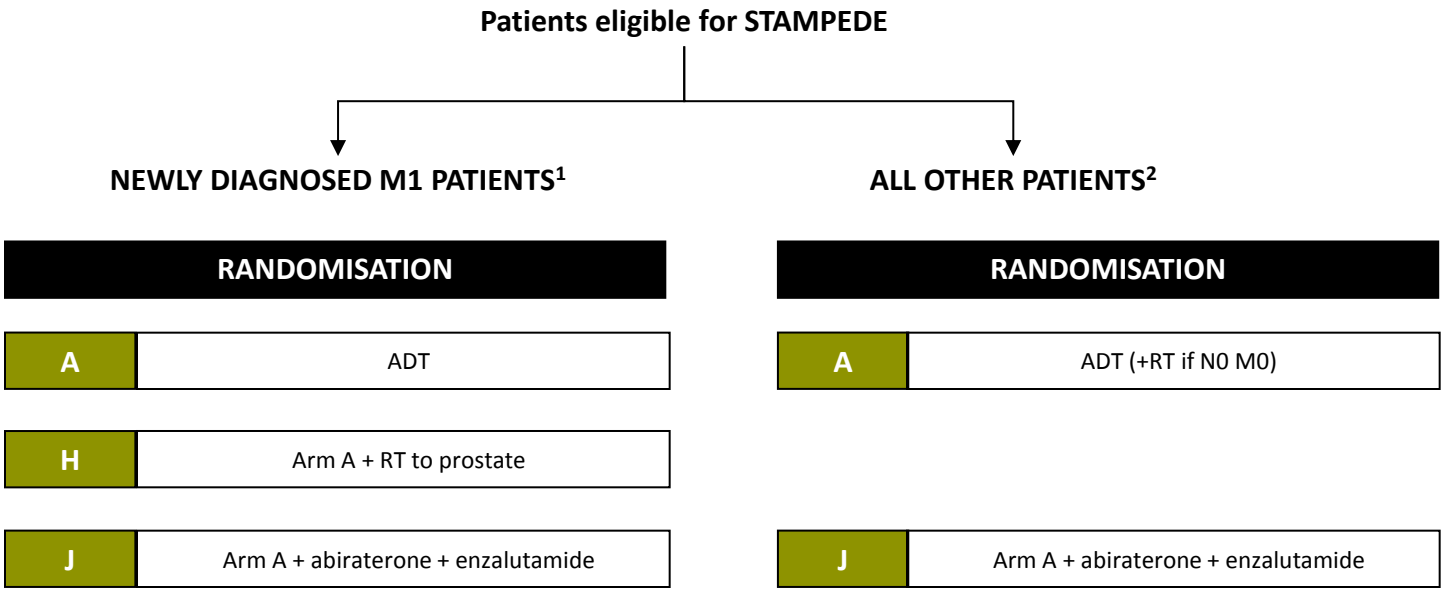
- Combination assessed vs enzalutamide alone in NCT01949337
    - US Co-operative group trial
    - **Metastatic CRPC**
    - N=1400
    - Primary end-point - survival

- PLATO study (Medivation sponsored)
    - **Metastatic CRPC**
    - Abi + enza vs abi alone after progression on enza alone

Abiraterone + Enzalutamide: possible concerns

- Long-term toxicities associated with more profound androgen suppression
- Priming of CRPC to earlier development of resistance
- Cost

STAMPEDE: Eligibility and trial design



[1] except pts with a contra-indication to RT

[2] all suitable pts with newly diagnosed locally advanced disease should also have RT[1]

Main Inclusion Criteria

Broad disease categories:

- Newly diagnosed high risk patients T3/4 N0 M0
- Newly diagnosed metastatic or nodal disease
- Previously treated relapsing patients

Updated exclusion criteria

- Patients with contra-indications to prednisolone
- Prior exposure to enzalutamide or abiraterone
- History of seizure
- Unexplained history of loss of consciousness
- Operation of heavy machinery during treatment
- Prior therapy with zoledronic acid or other bisphosphonates
- Active inflammatory bowel disease

Arm J: Treatment administrations

- 4 x 250mg abiraterone (empty stomach) + 5 mg od prednisolone
- 4 x 40mg enzalutamide (with or without food)
- Trial treatment to start within 4 weeks of randomisation
- Standard-of-care RT (to be stratified at randomisation)
  - Mandatory for N0M0 patients
  - Optional for N+M0

Arm J: Assessment of Treatment Duration

- **M+** patients, treatment should continue until **all progressions** occur:
    - PSA progression
    - Radiological progression
    - Clinical progression

It is accepted that these flexible criteria for stopping trial treatments are open to the investigator's interpretation and discretion.

All progressions must be reported as per the other arms

Arm J: Assessment of Treatment Duration

- **N0M0** patients or **N+M0** patients planned for RT treatment should continue until:
    - 2 years or
    - Disease progression as defined for M+ patients, whichever is sooner

- **N+M0** patients **not planned for radical radiotherapy** should continue until:
    - Disease progression as defined for M+ patients

Arm J: Treatment duration

- Treatment should be stopped if new systemic therapy is introduced (eg anti-androgens)
- Post progression dexamethasone 0.5mg can be given instead of prednisolone
- Selective discontinuation of either IMP depending on toxicity
- Toxicity data to be collected on FU forms until all progressions occur and patient stops treatment

Arm J: Safety analysis

- First safety review – first 50 patients allocated to Arm J on trial for ~6wks
- Second safety review – first 50 patients allocated to Arm J on trial for ~6mths
- Additional safety reviews at the request of the IDMC

Arm J
Activation Timelines

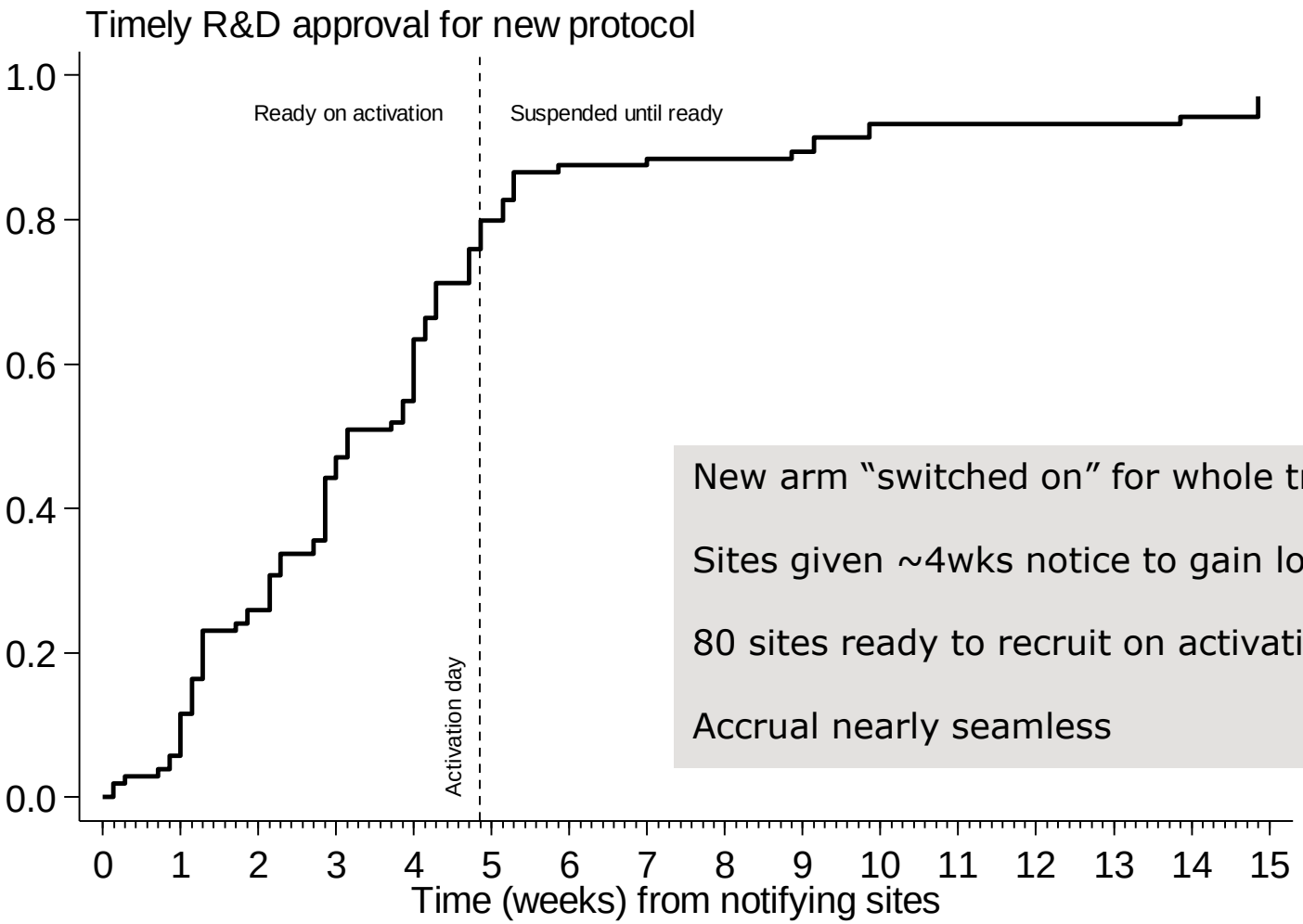
Activation timelines

- Activation plan as per “abiraterone comparison” and “M1/RT comparison”
- Activation date to be communicated in due course
- REC approval received in February 2014
- MHRA approval received in April 2014
- IMP distributor in set-up

Activation timelines

- "Switch on" date to be communicated in the future
- Approximately 4 weeks to gain local R&D approval
- Activation in mid-July 2014
- Additional support available:
  - Teleconferences
  - Trial website www.stampedetrial.org
  - CRF training
  - Pharmacy training

"abiraterone comparison" local approvals



New arm "switched on" for whole trial on set date

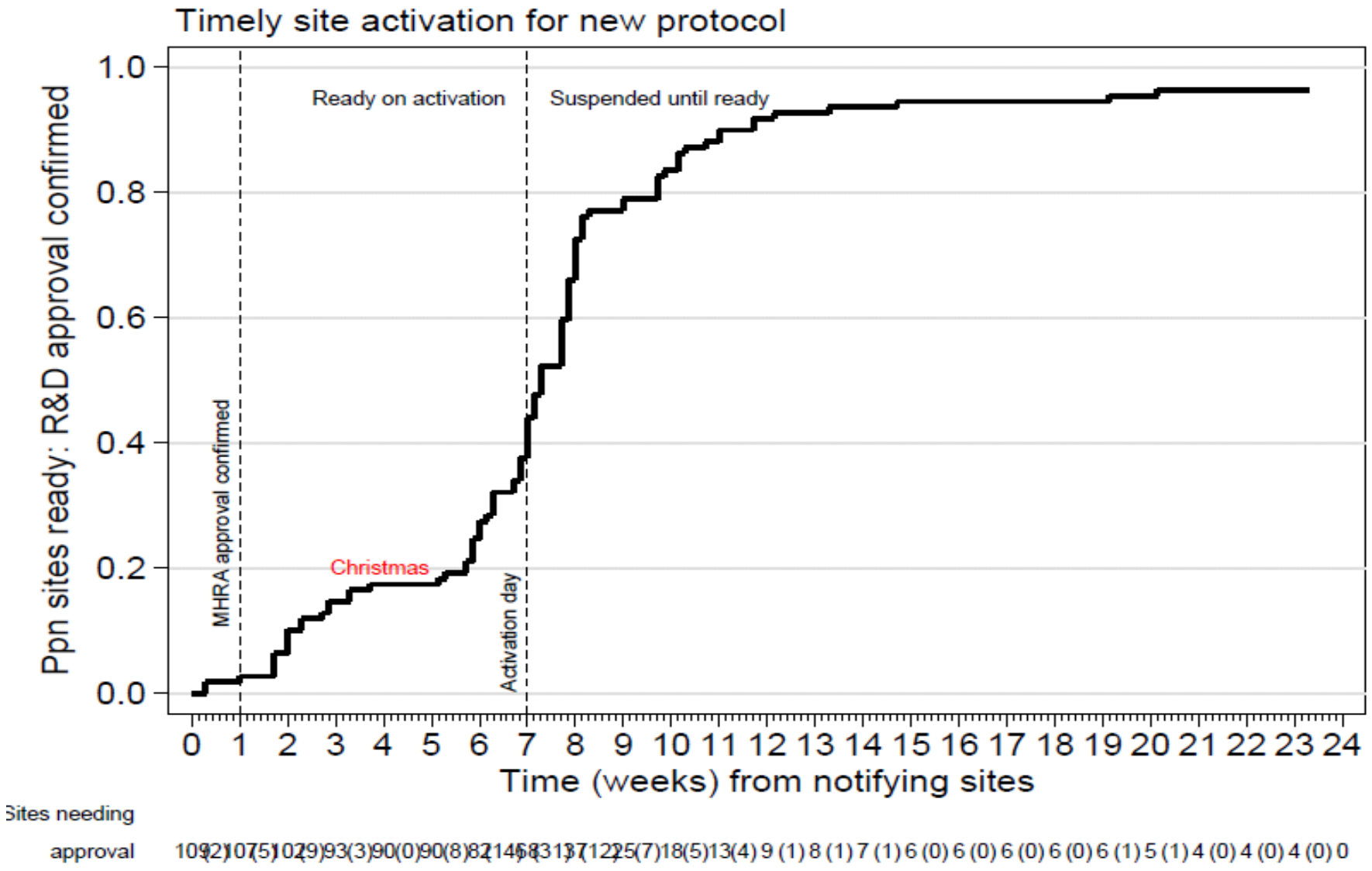
Sites given ~4wks notice to gain local approvals

80 sites ready to recruit on activation day!

Accrual nearly seamless

Sites needing approval	104	(6)	98	(21)	77	(19)	58	(11)	47	(26)	21	(8)	13	(0)	13	(1)	12	(1)	11	(4)	7	(0)	7	(0)	7	(0)	7	(1)	6	(3)	3

"M1/RT comparison" local approvals



CRF changes

- CRFs updated but overall structure unchanged
- CRFs guidelines training: Q2 2014 (14th, 16th ,19th May)
- CRFs guidelines being updated

Key CRFs changes

CRFs:Key Changes		
Minor Changes	**Medium**	**Major changes**
Bone Density Risk Factor	Randomisation	Abiraterone and Enzalutamide Treatment
Baseline	Follow-Up	Progression & Additional Treatment
Cardiovascular Assessment	Follow-Up (Post-Progression)	
Pathology	End of Treatment	
Pre-18 Week Bisphosphonate	Serious Adverse Event	
Post-18 Week Bisphosphonate	Death	
Docetaxel Treatment*	Early cessation of follow-up	
RT detail		
RT Acute Toxicity		
Palliative Radiotherapy		
Patient Transfer		
Co-enrolment		

STAMPEDE: general update
How to report FFS events

STAMPEDE Follow-up schedule

6 weekly	Randomisation to 24 weeks
12 weekly	24 weeks to 2 years
6 monthly	2 years to 5 years
Annually	thereafter

- Follow-up dates will be sent to you on a treatment and follow-up schedule each time you randomise a patient

- Please complete a follow-up form for each visit

Assessment of Treatment Failure

Types of progression:

1. Biochemical
2. Objective
   - Local
   - Lymph node
   - Distant metastatic
   - Skeletal related event

3. Symptomatic

Progression of each type need only be reported **once**

Complete an '**additional treatment update form**' if a patient receives additional treatment for a progression that you have already reported

Defining PSA Nadir & PSA Failure Categories

- PSA Nadir:
  - Lowest reported PSA level
  - Between randomisation and 24 weeks

- PSA Failure:
  - Depends on baseline PSA measurement and PSA nadir
  - 3 possible PSA failure categories, A, B and C

Defining PSA Relapse

PSA nadir is lowest value in first 24 weeks on trial

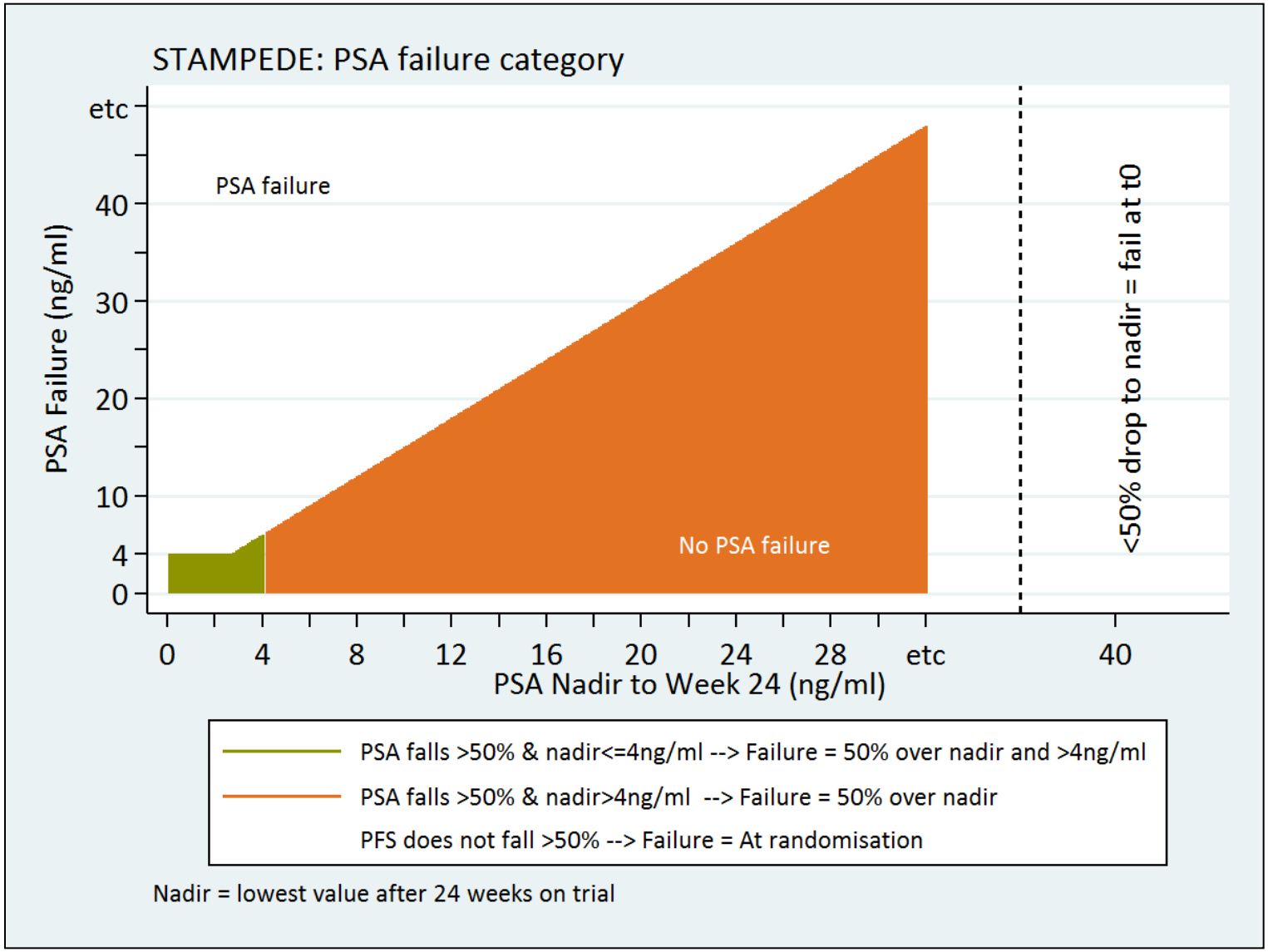
3 PSA failure categories:

- **PSA Failure Category A** – Nadir >50% baseline
  → Relapse = failed at time zero

- **PSA Failure Category B** – Nadir >4ng/ml but ≤50% baseline
  → Relapse = PSA increases by 50% above nadir

- **PSA Failure Category C** – Nadir ≤4ng/ml and ≤50% baseline
  → Relapse = PSA increases by 50% above nadir **and** >4ng/ml

Defining PSA Relapse



Reporting PSA Relapse

- Confirmatory PSA test between 1 week and 3 months later:
  - If value is ≥PSA progression value **then** report biochemical progression
- If clinician adds anti-androgens therapy before trial progression:
  - Report progression
- PSA progression emails are sent to sites approx. 3-monthly
  - Baseline and FU forms up to week 24 needed
  - Alternatively contact the trial team for help

Reporting progressions on CRFs

In case of progression:

- Follow up form for the relevant visit (i.e. week 36)
- Progression and Additional Treatment form
- End of treatment form (if applicable)
- Death form (if applicable)

Reporting progressions on CRFs

For patients on **Arms A, B, C, E and H**:

- Continue to follow-up as normal **and** report data on Follow-up (post-progression) form

- Ensure all **second-line treatments** are reported on CRFs

Reporting progressions on CRFs

For patients on **Arm G**:

- Continue to follow-up as normal **but**
  report data on Follow-up form until *all* types of progression are reported or treatment changes

- Ensure no further second-line treatment is given until:
  - all types of progressions are reported
  - trial abiraterone treatment is stopped

What to do post-progression

- Continue to follow up patients as normal until death
- Complete Follow up (Post-progression) form at each follow up visit
- Ensure additional treatment post progression are reported using the Additional Treatments form

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