STAMPEDE: "Metformin comparison"

Overview

Sponsor number:	**MRC PR08**
ISRCTN number:	**ISRCTN78818544**
EUDRACT number:	**2004-000193-31**
CTA number:	**00316/0026/001-0001**

Hypotheses and rationale

Hypothesis

- Will the addition of metformin to the standard-of-care
  - Improve survival in hormone-naive PCa?
  - Mitigate adverse side effect linked to long-term ADT?

Background and rationale

- Long-term ADT
  - ⬆ risk of insulin resistance
  - ⬆ hyperglycaemia
  - ⬆ dyslipidaemia
  - ⬆ obesity

- 50% pts on ADT will develop metabolic syndrome
  - Cardiovascular morbidity
  - Mortality

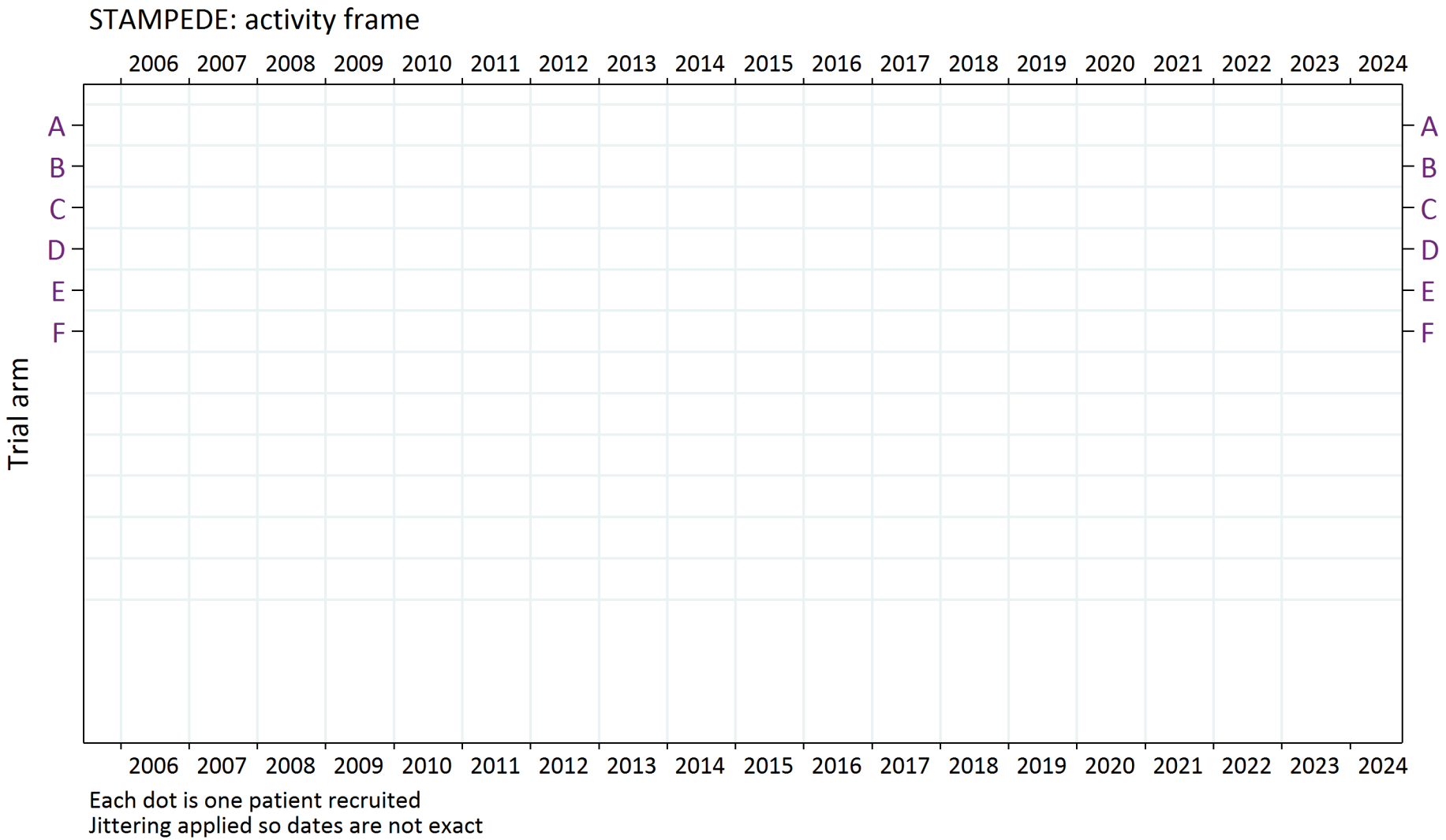
- Metformin
  - Counteracts effects of metabolic syndrome
  - Anti-cancer effects

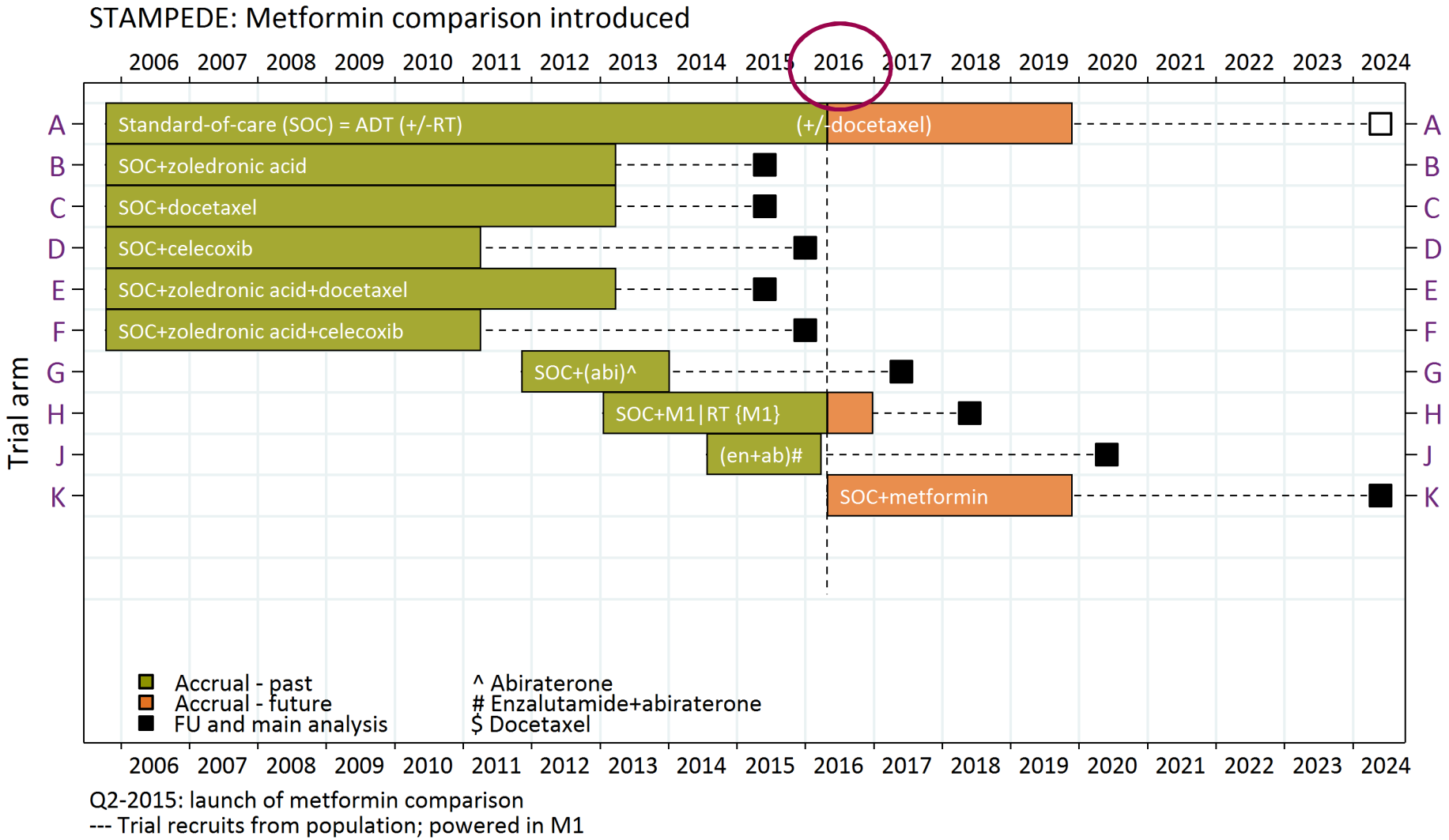
Background and rationale

- Full details on scientific and clinical rationale to be posted on STAMPEDE website

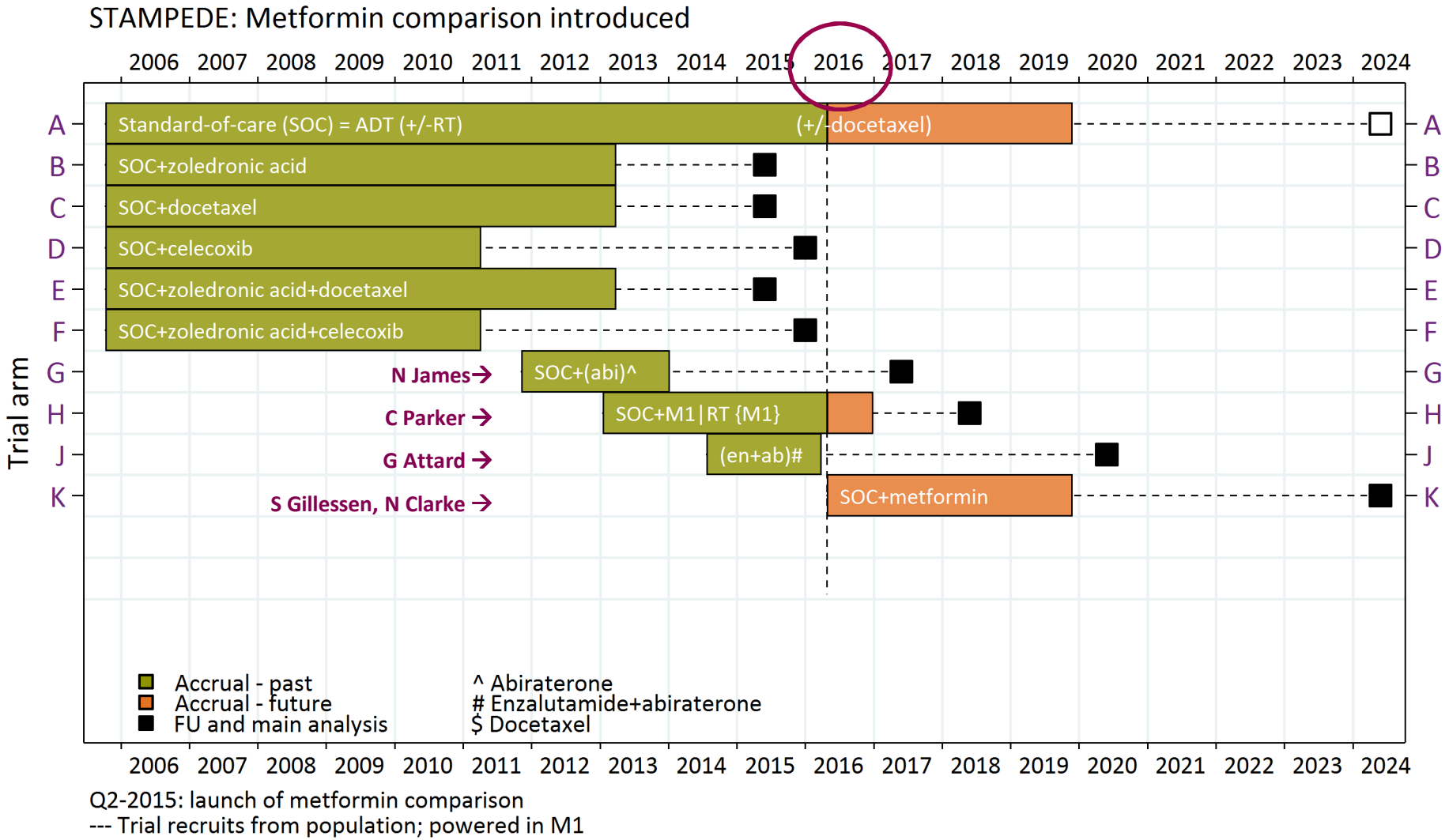
www.stampedetrial.org

Trial design


STAMPEDE: activity frame
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024
A
B
C
D
E
F
Trial arm
Each dot is one patient recruited
Jittering applied so dates are not exact



Q2-2015: launch of metformin comparison
--- Trial recruits from population; powered in M1

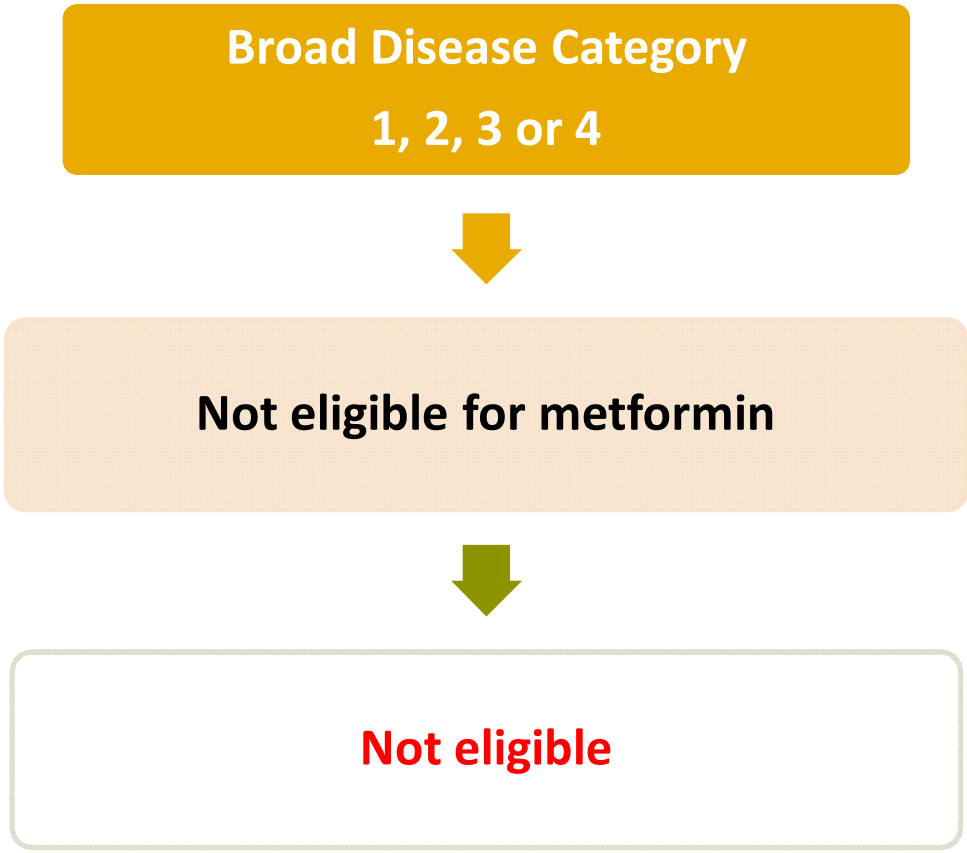

STAMPEDE: Metformin comparison introduced
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024
Trial arm
A Standard-of-care (SOC) = ADT (+/-RT) (+/-docetaxel)
B SOC+zoledronic acid
C SOC+docetaxel
D SOC+celecoxib
E SOC+zoledronic acid+docetaxel
F SOC+zoledronic acid+celecoxib
G N James → SOC+(abi)^
H C Parker → SOC+M1|RT {M1}
J G Attard → (en+ab)#
K S Gillessen, N Clarke → SOC+metformin
Accrual - past
Accrual - future
FU and main analysis
^ Abiraterone
# Enzalutamide+abiraterone
$ Docetaxel
Q2-2015: launch of metformin comparison
--- Trial recruits from population; powered in M1

Trial design

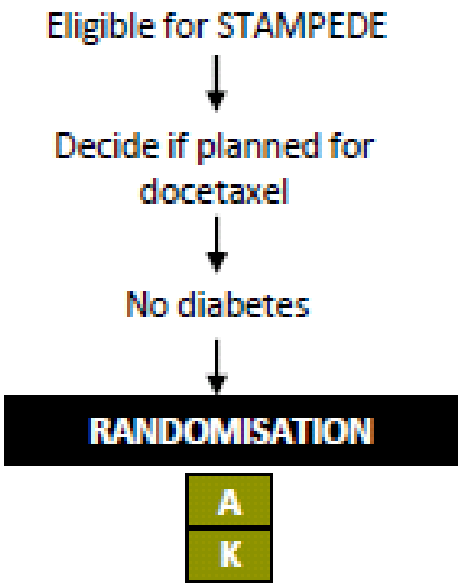
- “M1|RT comparison” closed 02-Sep-2016
- “Metformin comparison” opened 05-Sep-2016

Trial design

- "M1|RT comparison" closed 02-Sep-2016
- "Metformin comparison" opened 05-Sep-2016



Trial design



Key	
A	Standard-of-care (SOC)
K	SOC + metformin

SOC = ADT ± Docetaxel ± RT

Design parameters “metformin comparison”

Stage	Type	1^0 OM	HR_A	Power	Sig.	Critical HR	Control Events
1	Activity	OS	0.80	90%	0.40	0.965	104*
2	Efficacy	OS	0.80	90%	0.025	-	374*

* M1 pts

FFS: failure-free survival
HR: hazard ratio
OM: outcome measure
OS: overall survival

Eligibility

Inclusion criteria: general

Newly-diagnosed:

:: High-risk T3/4 N0 M0

:: $T_{any}N1M0$

:: $T_{any}N_{any}M1$

Previously treated, now relapsing

:: PSA ≥4ng/ml with doubling time <6 months

:: PSA ≥20 mg/ml

:: N+

:: M1

:: Intention to treat with ADT

:: Histologically confirmed adenocarcinoma

:: WHO 0-2

:: Written informed consent

Full criteria

www.stampedetrial.org

Inclusion criteria: metformin comparison

- No diabetes mellitus
- HbA1c <48 mmol/mol (equivalent to < 6.5% of total Hb)
- Creatinine clearance ≥60 ml/min /m^2
- No history of metabolic acidosis or pre-disposing conditions
- No current or previous treatment with metformin
- No contra-indications to metformin

Screening

Imaging

- CT or MRI of pelvis and abdomen
- Bone Scan (or equivalent e.g. whole body MRI, choline PET-CT)
- Chest X-ray (only if chest not included in CT/MRI)

Blood tests

- PSA
- Creatinine clearance
- Full blood count
- Urea and Electrolytes
- HbA1c

Other

- BP
- ECG

Screening

Imaging

- CT or MRI of pelvis and abdomen
- Bone Scan (or equivalent e.g. whole body MRI, choline PET-CT)
- Chest X-ray (only if chest not included in CT/MRI)

Blood tests

- PSA
- Creatinine clearance
- Full blood count
- Urea and Electrolytes
- HbA1c Mandatory

Other

- BP
- ECG

Health-related findings

- Screening might detect new diagnosis of diabetes
  - New letter developed to inform GP
  - Management as per standard clinical practice

Framework on the feedback of health-related findings in research
March 2014

Reference:
http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtp056059.pdf

Baseline investigations

- Baseline tests required
  - Within 4 weeks before or after randomisation
  - Before starting research treatment

- Testosterone (pre-ADT, if available)
- Serum corrected calcium
- Phosphate
- Magnesium
- Albumin

- Fasting glucose
- Fasting triglycerides
- Non-fasting total cholesterol, LDL and HDL

Baseline investigations

- Baseline tests required
  - Within 4 weeks before or after randomisation
  - Before starting research treatment

- Testosterone (pre-ADT, if available)
- Serum corrected calcium
- Phosphate
- Magnesium
- Albumin

- Fasting glucose
- Fasting triglycerides
- Non-fasting total cholesterol, LDL and HDL

} Mandatory

Concomitant medications

- Information on long-term (>6months) use of con-meds
  - Statins
  - Metformin
  - Aspirin
  - Bisphosphonates or Denosumab/calcium and Vitamin D
  - Opiate pain killers
  - ACE inhibitors or angiotensin II antagonist
  - Vitamin B12

For more information see CRF training slides

Trial Treatment

Starting trial treatment: metformin

- Arm K patients should start metformin
  - As soon as possible after randomisation, ideally
    - ≤4 weeks from randomisation
    - ≤12 weeks from starting ADT

- Metformin and docetaxel can be given concurrently
  - i.e. don't wait until after chemotherapy

- Formulation
  - Immediate release (IR)
  - Sustained release (SR)

- To be taken with or after food
  - SR with evening meals

- Starting dose = 850mg OD
- If tolerated (after 1 month) = 850mg BID

Treatment duration: M0 patients

- Metformin should continue as long as ADT

- If ADT is stopped after 2 years
  - Metformin continues for a minimum of 3 years **OR**
  - 12 months after the last LHRH injection (whichever is longer)

- If LHRH is re-started whilst patient on metformin
  - Metformin should continue while on ADT

- If metformin stopped 12 months after last LHRH injection
  - Metformin should not be re-started

Treatment duration: M1 patients

- Metformin treatment continues:
  - As long as ADT
  - Post-progression
  - While on second-line treatments
    - Unless patient joining new IMP trial (CRPC setting)

Contraindications

- Metformin should be **permanently stopped** if
  - eGFR ≤60ml/min/1.73m^2 (contradiction in protocol on page 47)

- Metformin should be **paused** if

	RISK FACTOR
Iodinated contrast agents	Pause metformin 24 hours prior to receiving contrast and re-start 48 hours post administration.
Anaesthesia (peridural; spinal or general)	Pause metformin 48 hours prior to procedure and re-start no earlier than 48 hours following procedure, providing oral intake re-established and renal function is stable and at baseline.
Surgery	Pause metformin 48 hours prior to procedure and re-start no earlier than 48 hours following procedure, providing oral intake re-established and renal function is stable and at baseline.
Dehydration e.g. nausea, vomiting or diarrhoea	Pause metformin and re-start only when oral intake is re-established and renal function is stable and at baseline.
Obstructive uropathy e.g. urinary retention or ureteric obstruction	Pause metformin and re-start only when renal function confirmed to be stable and at baseline.

Treatment breaks

- Discuss with trial team if
  - Treatment breaks >3months OR
  - 50% doses missed

- If metformin stopped for >2wks
  - Re-start at 850mg OD
  - Escalate to full dose after 1 month

Management of metformin-related toxicities

- GI toxicities

Toxicity event	Action
Grade 1	Ensure metformin is taken with or after food. Consider switching to 750 mg sustained release preparation if available. If unavailable consider a 1 week treatment pause and re-start at 850mg once daily and attempt an escalation after 1 month. If necessary, remain at 850mg OD. If unable to tolerate 850mg OD or sustained release preparations are not available consider dose reduction to 500mg OD.
Grade 2 or higher	Reduce to 850mg OD and if symptoms improve to grade 1 or better, re-attempt dose escalation after 1 week. If symptoms recur at grade 2 or higher, pause treatment for 2 weeks. Re-start at 850mg sustained release or if not available 500mg OD. Re-attempt a dose escalation 2 months later. Continue at the maximum tolerated dose providing symptoms ≤ grade 1.

Management of metformin-related toxicities

Correction GI toxicities Table 12 Protocol v15.0

- **Grade 1 toxicity** at 850mg BID
  - A. Change to 750mg SR BID OR
  - B. 1 week treatment pause then restart 850mg OD IR & attempt an escalation after 1 month OR
  - C. Reduce to 500mg OD (IR or SR) if both A&B unsuccessful & attempt dose escalation after 1 month, aiming to continue at the maximum tolerated dose

- **Grade 2 or higher** at 850mg BID
  - A. Reduce to 500mg OD IR; re-attempt dose escalation after 1 week if symptoms improve.
  - B. Stop treatment for 2 weeks if A unsuccessful then re-start 750mg OD SR after 2 weeks & re-attempt dose escalation 2 months later aiming to continue at the maximum tolerated dose

Management of metformin-related toxicities

- B12 deficiency
  - Start haematinics including vitamin B12
- Lactic acidosis
  - Discontinue immediately
  - Consider haemodialysis
- Overdose
  - Consider hospital admission
  - Clinical management as per standard practice

Interactions

Clinical use	Drug	Recommentation
Anti-hypertensives and other cardiac disease	ACE inhibitors/angiotension II receptor blockers e.g. ramipril, lisinopril, Irbesartan	Monitor renal function until confirmed to be stable and providing eGFR remains >60mls/min/m^2. Repeat test if necessary
	Diuretics e.g Frusemide, budesonide	
Antibiotics	Aminoglycoside antibiotics e.g Gentamycin or amikacin	Hold metformin during treatment and re-start providing renal function confirmed to be stable and eGFR remains >60mls/min/m^2
Analgesia	NSAIDS **e.g.** Ibuprofen, diclofenac, naproxen	Avoid if possible If no alternative increase renal monitoring to until confirmed to be stable and providing eGFR remains >60mls/min/m^2

Assessment and Procedures

Cardiovascular and metabolic outcomes

OUTCOME OF INTEREST	TIMING OF ASSESSMENT	CRF
Eligibility screening		
HbA1c	Prior to randomisation	Randomisation
Baseline		
Lipid profile (cholesterol, HDL, LDL)	Randomisation	Baseline
Fasting glucose	Randomisation	Baseline
Fasting triglyceride	Randomisation	Baseline
Weight and BMI	Randomisation	Baseline
Waist circumference	Randomisation	Baseline
Follow-up		
HbA1c	6 months 12 months 24 months	FU
Fasting glucose	6 months 12 months 24 months	FU
Fasting triglyceride	6 months 12 months 24 months	FU
Lipid profile (cholesterol, HDL, LDL)	Annual	FU
Metabolic and cardiovascular events		
New diagnosis of diabetes	As and when metabolic and cardiovascular event occurs	FU
Cardiac event: myocardial infarction or revascularization (e.g PCI or CABG)	As and when metabolic and cardiovascular event occurs	FU
Stroke or transient ischaemic event	As and when metabolic and cardiovascular event occurs	FU

Cardiovascular and metabolic outcomes

OUTCOME OF INTEREST	TIMING OF ASSESSMENT	CRF
Eligibility screening		
HbA1c	Prior to randomisation	Randomisation
Baseline		
Lipid profile (cholesterol, HDL, LDL)	Randomisation	Baseline
Fasting glucose	Randomisation	Baseline
Fasting triglyceride	Randomisation	Baseline
Weight and BMI	Randomisation	Baseline
Waist circumference	Randomisation	Baseline
Follow-up		
HbA1c	6 months 12 months 24 months	FU
Fasting glucose	6 months 12 months 24 months	FU
Fasting triglyceride	6 months 12 months 24 months	FU
Lipid profile (cholesterol, HDL, LDL)	Annual	FU
Metabolic and cardiovascular events		
New diagnosis of diabetes	As and when metabolic and cardiovascular event occurs	FU
Cardiac event: myocardial infarction or revascularization (e.g PCI or CABG)	As and when metabolic and cardiovascular event occurs	FU
Stroke or transient ischaemic event	As and when metabolic and cardiovascular event occurs	FU

Follow-up

All patients, all research arms

- FU and PSA measurements
  - 6 weekly for first 6 months
  - 12 weekly up to year 2
  - 6 monthly up to year 5
  - Annually thereafter

Arm A and K patients

- Additional metabolic and cardiovascular outcomes

Arm K patients

  - 6 monthly renal function tests (U&Es)

Follow-up: telephone consultations

- Telephone FU permitted
  - Pt discharged from oncology or urology service
  - Poor health
  - Travelling to hospital clinic difficult
- All data to be collected
  - Liaise with GP for required blood tests
- CRF can be considered source data
  - File note required
- Details of telephone consultation in patient's notes
  - Telephone FU log can be used (where available)
- Telephone FU checklist to be provided by STAMPEDE team

Recruitment tools

- Eligibility checklist to be provided to sites
  - Copy **not** required by STAMPEDE team

- Flowchart on treatment and FU to be provided to sites

- PSA progression calculator
- Hb1Ac calculator
- Creatinine clearance converter

- More information on how to report FU & progression via CRF training sessions

For more information see CRF training slides

Safety reporting

TREATMENT	SAE	SAR	SUSAR
ADT	Up to 30 days after last injection or progression (whichever is sooner	Indefinitely	Indefinitely
Docetaxel (Research)	Up to 30 days after last treatment	Indefinitely	Indefinitely
Docetaxel (SOC)	Up to 30 days after last treatment	Indefinitely	Indefinitely
Zoledronic Acid	Up to 30 days after last treatment	Indefinitely	Indefinitely
Celecoxib	Up to 30 days after last treatment	Indefinitely	Indefinitely
Research RT (Arm H)	Up to 30 days after last treatment	Indefinitely	Indefinitely
Abiraterone	Up to 30 days after last treatment	Indefinitely	Indefinitely
Enzalutamide	Up to 30 days after last treatment	Indefinitely	Indefinitely
Metformin	Up to 30 days after last treatment	Indefinitely	Indefinitely

Safety reporting exemptions

- Hospitalisation or prolongation of existing hospitalisation for the following SOC docetaxel-related events:
  - Febrile neutropenia
  - Thrombocytopenia
- Report event as toxicity on FU CRF
- Reporting via MHRA Yellow Card Scheme still apply
  https://yellowcard.mhra.gov.uk
- Exemption does **not** apply if event results in death

Arm K activation

Activation process

- Activation documentation 05-Aug-2016
- Arm H closed 02-Sep-2016
- Arm K opened 05-Sep-2016

Activation process

- Activation process as per previous research comparisons
  - Temporary suspension of recruitment if requirements not met by activation date

- Activation requirements
  - R&D approval
  - Amendment acknowledgment (to be signed by research team)
  - PI acknowledgment
  - Pharmacy acknowledgment
  - Training attended

- Activation checklist provided to sites

- Copies of new protocol (A5) and CRFs circulated

More training

- Rationale (via website)
- CRF training
- Pharmacy training