TREATMENTS OVERVIEW

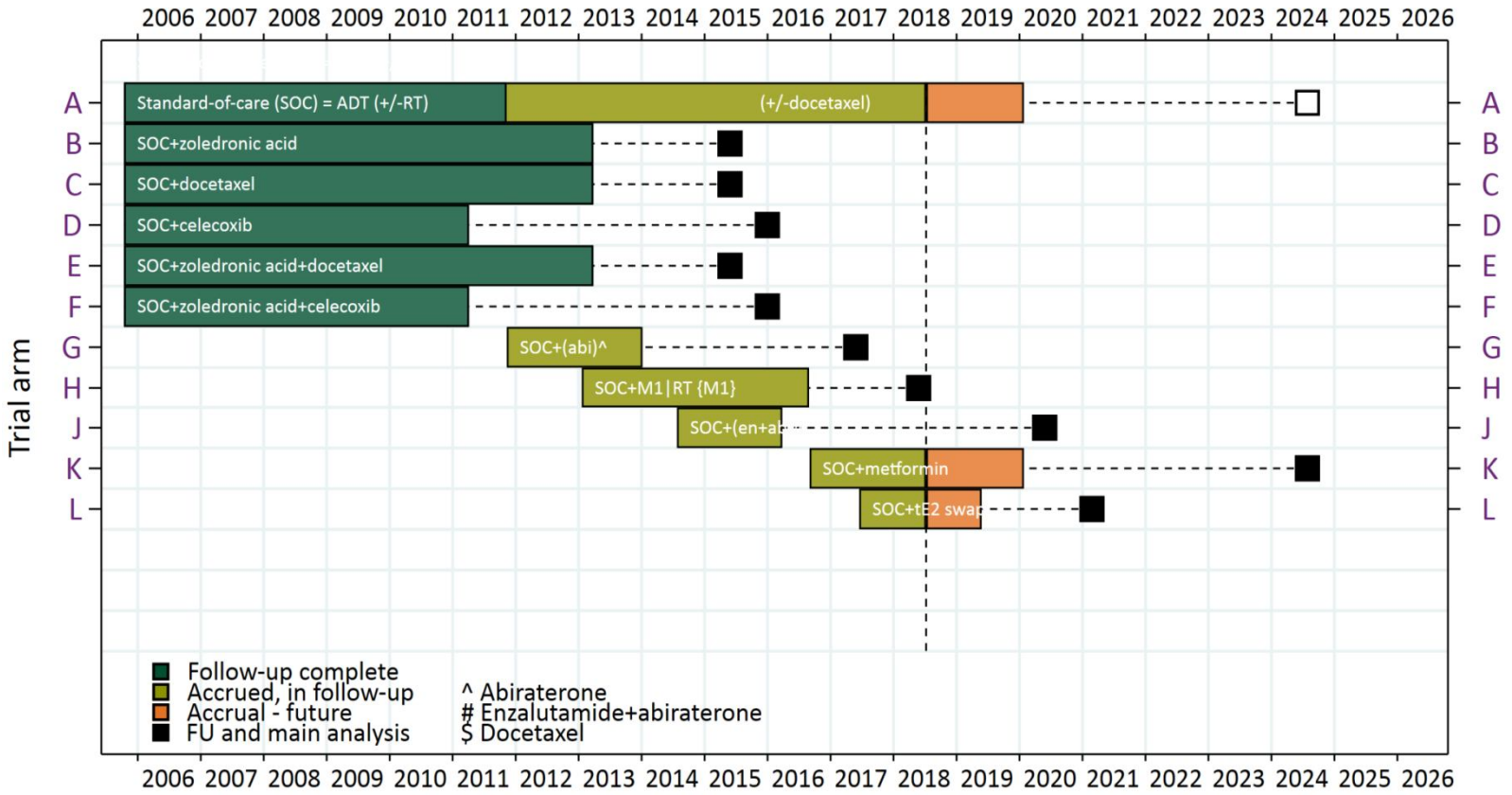
STAMPEDE

Systemic **T**herapy in **A**dvancing or **M**etastatic

Prostate Cancer: **E**valuation of **D**rug **E**fficacy

November 2018

STAMPEDE


2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026
Trial arm
A
B
C
D
E
F
G
H
J
K
L
Standard-of-care (SOC) = ADT (+/-RT)
(+/-docetaxel)
SOC+zoledronic acid
SOC+docetaxel
SOC+celecoxib
SOC+zoledronic acid+docetaxel
SOC+zoledronic acid+celecoxib
SOC+(abi)^
SOC+M1|RT {M1}
SOC+metformin
Follow-up complete
Accrued, in follow-up
Accrual - future
FU and main analysis
^ Abiraterone
# Enzalutamide+abiraterone
$ Docetaxel

PROTOCOL STANDARD-OF-CARE (SOC) TREATMENTS

Protocol SOC

Hormone Therapy

Permitted methods of ADT are:

- Bilateral Orchidectomy: Operations should be performed by appropriately trained surgeons. A total or sub-capsular orchidectomy may be performed
- LHRH Agonists: To be used according to local practice. The prophylactic use of anti-androgens to prevent tumour 'Flare' is recommended.
- LHRH Antagonists: To be used according to local practice. The prophylactic use of anti-androgens to prevent tumour 'Flare' is recommended.
- Duel Androgen Blockade: Long-term use of anti-androgens alongside LHRH agonists, according to local practice. Note this was previously referred to as maximum androgen blockade.
- Recommended methods of hormone therapy are given in Protocol Section 6.1.1.
- Other methods of ADT should be discussed with the STAMPEDE trial team.
- Planned duration of ADT should be at least 2 years.

Radiotherapy

- Radiotherapy is to be given as per local protocol as a standard non trial treatment.

Protocol SOC

Docetaxel

- Following the primary analyses results of the "Original Comparisons" and CHAARTED, docetaxel is now permitted as SOC.
- Investigators are strongly encouraged to consider giving docetaxel for participants with newly diagnosed metastatic disease or high-risk locally-advanced disease.
- Docetaxel is to be given as per local protocol as a standard non trial treatment.

Abiraterone Acetate

- Following the primary analyses of the results of the "Abiraterone Comparison" and LATITUTDE, abiraterone is now permitted as SOC.
- Following protocol 19.0 activation, SOC abiraterone will be permitted for participants within the metformin comparison
- SOC abiraterone is not permitted in any participants randomised prior to activation of protocol version 19.0.
- Abiraterone is to be given as per local protocol as a standard non trial treatment.

Protocol SOC

SOC

- In summary, SOC treatment is defined as being **one** of the following combinations:
  - ADT alone
  - ADT + Prostate Radiotherapy (RT)
  - ADT + Docetaxel
  - ADT + RT + Docetaxel
  - ADT + Abiraterone
  - ADT + RT + Abiraterone

CURRENT PROTOCOL RESEARCH TREATMENTS

Abiraterone Acetate

(Arms G & J)

Mechanism of Action

- Abiraterone inhibits the enzymatic activity of steroid 17alpha-monooxygenase, a member of the cytochrome p450 family that catalyses the 17alpha-hydroxylation of steroid intermediates involved in testosterone synthesis.
- Administration of this agent may suppress testosterone production by both the testes and the adrenals to castrate-range levels.

Zytiga®
(abiraterone acetate)
250 mg, 500 mg tablets

Abiraterone Acetate Management

(Arms G & J)

Dose

- 1000mg oral dose (4 tablets) daily together with prednisolone or prednisone 5mg daily. The tablets should be taken at least 2 hours after food, swallowed whole with some water. No food should be eaten for 1 hour afterwards.

Treatment Length

- M1 Patients, Relapsed Patients & N+M0 (without RT) Patients; treatment will continue until all categories of disease progression have occurred
- N0M0 Patients & N+M0 (with RT) Patients; treatment will continue until the earliest of; 2 years or all categories of disease progression have occurred
- In the event of a **missed dose** of either abiraterone, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

Contraindications

- Anti-androgens (i.e. bicalutamide) should not be given in combination due to the risk of toxicity
- Unusual or allergic reaction to past abiraterone acetate treatment
- Uncontrolled hypertension or uncontrolled heart failure
- Abnormal liver function or active or chronic liver disease

Abiraterone Acetate Management

(Arms G & J)

Toxicity Management

- The STAMPEDE protocol gives guidance on treatment dose reductions, pauses and discontinuation based on toxicity (Protocol Section 6.2).
- In patients hospitalized for intravenous potassium replacement or for Abnormal Liver Function, abiraterone should be permanently stopped.
  - If ALT > 5x ULN (Grade 3 toxicity) treatment should be withheld.
  - For severe hepatotoxicity (ALT ≥20x ULN), treatment should be discontinued & not be reintroduced.
- Abiraterone can be restarted at the treating clinician's discretion when toxicity has resolved and providing the patients should not already have stopped.
- If considering stopping treatment permanently, we encourage case-by-case discussions with MRC CTU at UCL in the first instance.
- There have been no reports of overdose during clinical trials. There is no specific antidote. In the event of overdose, drug should be withheld and supportive measures given (e.g. Monitor for arrhythmias, hypokalaemia & signs & symptoms of fluid retention).

Abiraterone Acetate Management

(Arms G & J)

Monitoring

Patients taking Abiraterone Acetate require additional monitoring:

- For participants receiving research abiraterone, BP, liver function tests (LFTs) and serum potassium monitoring is required 2-weekly in the first 12 weeks, then monthly until 12 months on treatment.
- For participants who have not experienced toxicity following 12 months of treatment, this may be reduced to every 2 months whilst research abiraterone continues.
- Increased monitoring is required in participants experiencing toxicity

Enzalutamide

(Arm J)

Mechanism of Action

- Enzalutamide is an Androgen Receptor Antagonist, and Cytochrome P450 3A4 Inducer, and Cytochrome P450 2C9 Inducer, and Cytochrome P450 2C19 Inducer.
- Enzalutamide inhibits the activity of prostate cancer cell ARs, which may result in a reduction in prostate cancer cell proliferation and, correspondingly, a reduction in the serum prostate specific antigen (PSA) level.

Enzalutamide Management

(Arm J)

Dose

- 160mg oral dose (4 capsules) daily, taken together at the same time every day, with or without food.

Treatment Length

- M1 Patients, Relapsed Patients & N+M0 (without RT) Patients; treatment will continue until all categories of disease progression have occurred
- N0M0 Patients & N+M0 (with RT) Patients; treatment will continue until the earliest of; 2 years or all categories of disease progression have occurred

Contraindications

- Anti-androgens (i.e. bicalutamide) should not be given in combination due to the risk of toxicity

Enzalutamide Management

(Arm J)

Toxicity Management

- The STAMPEDE protocol gives guidance on treatment dose reductions, pauses and discontinuation based on toxicity (Protocol Section 6.2).
- In patients who have a seizure while on treatment, enzalutamide should be permanently stopped.
- Enzalutamide can be restarted at the treating clinician's discretion when toxicity has resolved and providing the patients should not already have stopped.
- If considering stopping treatment permanently, we encourage case-by-case discussions with MRC CTU at UCL in the first instance.

Metformin

(Arm K)

Mechanism of Action

- Metformin hydrochloride is a biguanide hypoglycemic agent,
- Metformin inhibits complex I of the mitochondrial respiratory chain, thereby increasing the cellular AMP to ATP ratio and leading to activation of AMP-activated protein kinase (AMPK) and regulating AMPK-mediated transcription of target genes.
- This eventually prevents hepatic gluconeogenesis, enhances insulin sensitivity and fatty acid oxidation and ultimately leads to a decrease in glucose levels.

Metformin Management

(Arm K)

Dose

- Starting Dose - 850mg oral dose once daily.
- Target dose - 850mg oral dose twice daily (minimum 8 hours between)

Treatment Length

- M0 Patients; If ADT is stopped at 2 years, treatment will continue for a minimum of 3 years, or 1 year after the last administration of LHRH, whichever is later
- M1 Patients; treatment will continue whilst on ADT, including post progression.

Contraindications

- Acute metabolic acidosis (including lactic acidosis and diabetic ketoacidosis)

Metformin Management

(Arm K)

Toxicity Management

- The STAMPEDE protocol gives guidance on treatment dose reductions, pauses and discontinuation based on toxicity (Protocol Section 6.2).
- In patients whose GFR falls to ≤30ml/min/1.73m^2, metformin should be permanently stopped.
- Metformin can be restarted at the treating clinician's discretion when toxicity has resolved and providing the patient should not already have stopped.

Monitoring

- Renal function should be monitored **at least every 6 months** in participants with stable renal function, whilst on metformin. Increased monitoring of renal function required if renal function declines.

Transdermal Oestradiol (tE2)

(Arm L)

- Oestradiol Hemihydrate is the hemihydrate form of oestradiol, the most potent, naturally produced oestrogen.
- Oestradiol hemihydrate diffuses through the cell membrane and binds to and subsequently activates the nuclear oestrogen receptor found in the reproductive tract, breast, pituitary, hypothalamus, liver, and bone.
- Transdermal oestradiol is expected to mitigate the cardiovascular risk associated with oral oestrogen.

Transdermal Oestradiol (tE2) Management

(Arm L)

Dose

- Discontinue any treatment started with LHRH and anti-androgens before starting tE2 treatment.
- Induction Dose – Start on 4 patches changed twice weekly.
- Maintenance Dose – Reduces to 3 patches changed twice weekly once testosterone <1.7nmol/L.
- Consecutive patches should be applied to different sites. It is recommended that patches are placed on dry, intact and hairless skin and on areas where little wrinkling occurs, at the following sites only:
  - Shoulder girdle
  - Back
  - Upper arms
  - Buttocks

Treatment Length

- Upon evidence of disease progression and at the investigator's discretion, a switch to LHRH analogues is appropriate to facilitate the addition of further therapies where concurrent treatment with transdermal oestradiol is untested.

Contraindications

- Tamoxifen should not be taken with transdermal oestradiol patches.
- Patient who have been exposed to cyproterone acetate are not eligible for transdermal oestradiol patches.

Transdermal Oestradiol (tE2) Management

(Arm L)

Toxicity Management

- If oestradiol levels are consistently below 300 pmol/L or over 2000pmol/L, consult with MRC CTU team for guidance.
- If testosterone levels are consistently above 1.7 nmol/L, consult with MRC CTU team for guidance.
- If rashes develop, ensure patients are alternating the patch application site. Patients are permitted to use a low dose steroid cream prior to patch application.

Monitoring

- Hormone tests (testosterone and oestradiol) are required whilst the participant is receiving research transdermal oestradiol, at weeks 4, 12, 24, 48, 72, 96 and at all further visits.

PREVIOUS PROTOCOL RESEARCH TREATMENTS

Zoledronic Acid

(Arms B, E & F)

Mechanism of Action

- Zoledronic Acid binds to hydroxyapatite crystals in the bone matrix and inhibits farnesyl pyrophosphate (diphosphate) synthase, thereby preventing protein prenylation within the mevalonate pathway.
- This leads to the loss of downstream metabolites essential for osteoclast function, leading to the induction of apoptosis and eventually, osteoclast-cell death.
- By preventing osteoclast-mediated bone resorption, zoledronic acid decreases bone turnover and stabilizes the bone matrix.

Conclusions

- Addition of Zoledronic Acid was found to have no significant treatment effect as monotherapy (Arm B) or when coupled with Celecoxib (Arm F), or with Docetaxel (Arm E), when compared to SOC alone (Arm A).

Docetaxel

(Arms C & E)

Mechanism of Action

- Docetaxel is a microtubule inhibitor.
- Docetaxel binds specifically to the beta-tubulin subunit of microtubules and thereby antagonizes the disassembly of the microtubule proteins.
- This results in the persistence of aberrant microtubule structures and results in cell-cycle arrest and subsequent cell death.

Conclusions

- Addition of Docetaxel (Arm C) was shown to have a statistically significant improvement on overall survival when compared to SOC alone (Arm A).

Celecoxib

(Arms D & F)

Mechanism of Action

- Celecoxib is a nonsteroidal anti-inflammatory drug.
- Celecoxib selectively inhibits cyclo-oxygenase-2 activity (COX-2); COX-2 inhibition may result in apoptosis and a reduction in tumour angiogenesis and metastasis.

Conclusions

- Addition of Celecoxib (Arm D) was found to have significant treatment effect, when compared to SOC alone (Arm A). Recruitment was stopped to Arms D and F early in 2011.

Radiotherapy

(Arm H)

Mechanism of Action

- Radiotherapy works by damaging the DNA of cancerous cells.

Conclusions

- STAMPEDE will report on the Radiotherapy treatment effect in 2018.

More Information

For more detailed information, please see the STAMPEDE protocol, the FAQ section of the website or contact the trial team.

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