STAMPEDE 2

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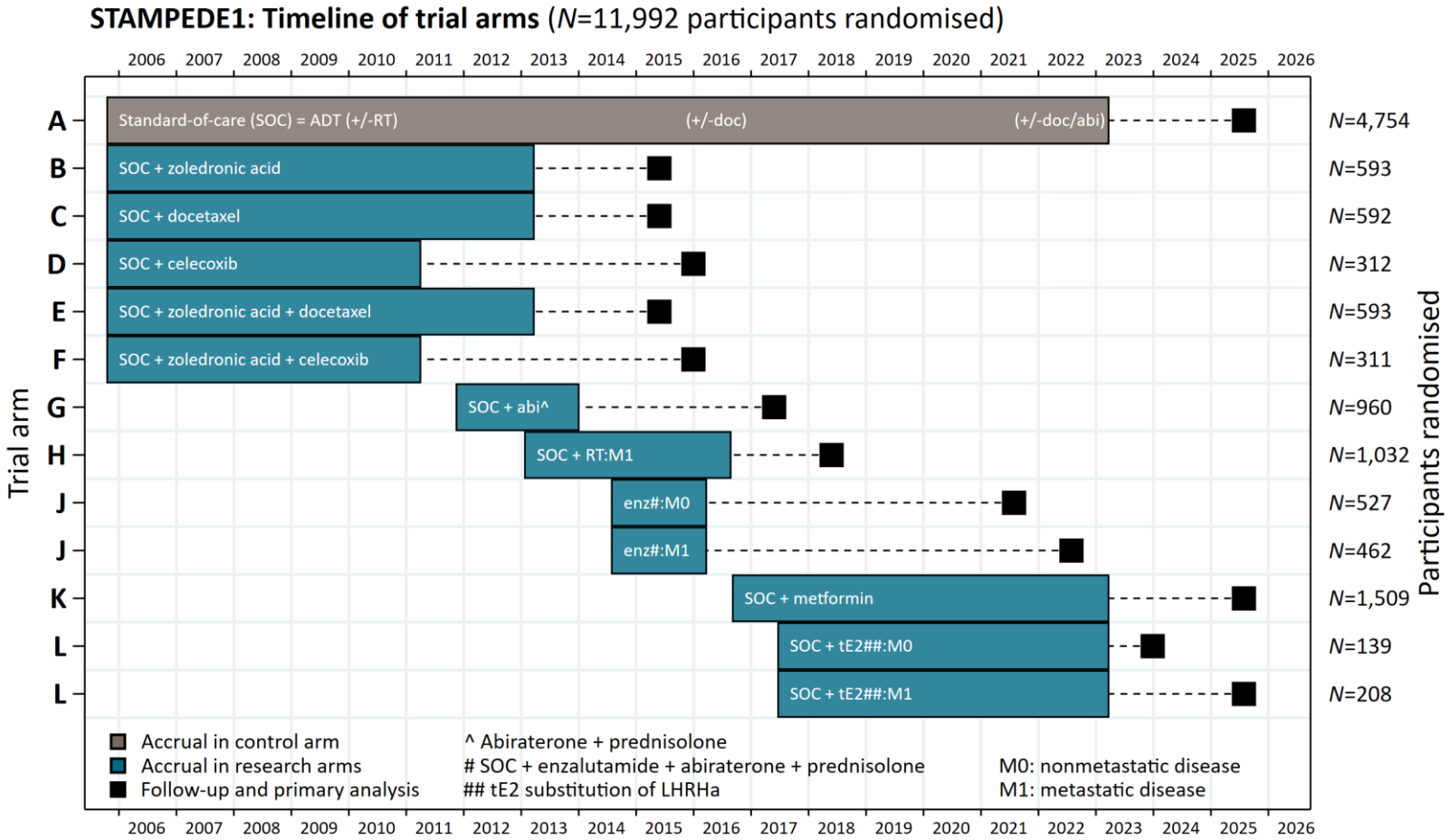
STAMPEDE – key features

- Multiple arms
- Simple broad inclusion criteria
- Simple endpoints
- Interim analyses to decide whether to stop or continue
- Arms need distinct mechanisms of action

Multiple arm trials – design benefits

- Answers to multiple questions
- Spin off translational benefits
- Broad inclusion criteria and range of therapies give valuable information about natural history


STAMPEDE1: Timeline of trial arms (N=11,992 participants randomised)
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026
Trial arm
A Standard-of-care (SOC) = ADT (+/-RT) (+/-doc) (+/-doc/abi) N=4,754
B SOC + zoledronic acid N=593
C SOC + docetaxel N=592
D SOC + celecoxib N=312
E SOC + zoledronic acid + docetaxel N=593
F SOC + zoledronic acid + celecoxib N=311
G SOC + abi^ N=960
H SOC + RT:M1 N=1,032
J enz#:M0 N=527
J enz#:M1 N=462
K SOC + metformin N=1,509
L SOC + tE2##:M0 N=139
L SOC + tE2##:M1 N=208
Participants randomised
Accrual in control arm
Accrual in research arms
Follow-up and primary analysis
^ Abiraterone + prednisolone
# SOC + enzalutamide + abiraterone + prednisolone
tE2 substitution of LHRHa
M0: nonmetastatic disease
M1: metastatic disease

MRC Clinical Trials Unit

Smarter Studies
Global Impact
Better Health

STAMPEDE

UCL

Radiotherapy to the primary tumour for men with newly-diagnosed metastatic prostate cancer: Survival results from STAMPEDE

CC Parker, ND James, CD Brawley, NW Clarke, G Attard, S Chowdhury, W Cross, DP Dearnaley, S Gillessen, C Gilson, RJ Jones, MD Mason, R Millman, C Eswar, J Gale, JF Lester, DJ Sheehan, AT Tran, MKB Parmar, MR Sydes.

MUNICH 2018 ESMO congress

The ROYAL MARSDEN NHS Foundation Trust

CANCER RESEARCH UK

Parker CC, et al. Poster presentation at the 2018 ESMO Congress; October 19–23, 2018; Munich, Germany. Abstract LBA5.

Radiotherapy as a Standard of Care in M1

OS

FFS

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gillessen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire L Amos, Roberto Alonzi, Amit Bahl, Alison Birtle, Omar Din, Hassan Douis, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Sai Jonnada, Sara Khaksar, Jason F Lester, Joe M O'Sullivan, Omi A Parikh, Ian D Pedley, Delia M Pudney, Denise J Sheehan, Narayanan Nair Srihari, Anna T H Tran, Mahesh K B Parmar, Matthew R Sydes*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†*

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S0140-6736(18)32486-3

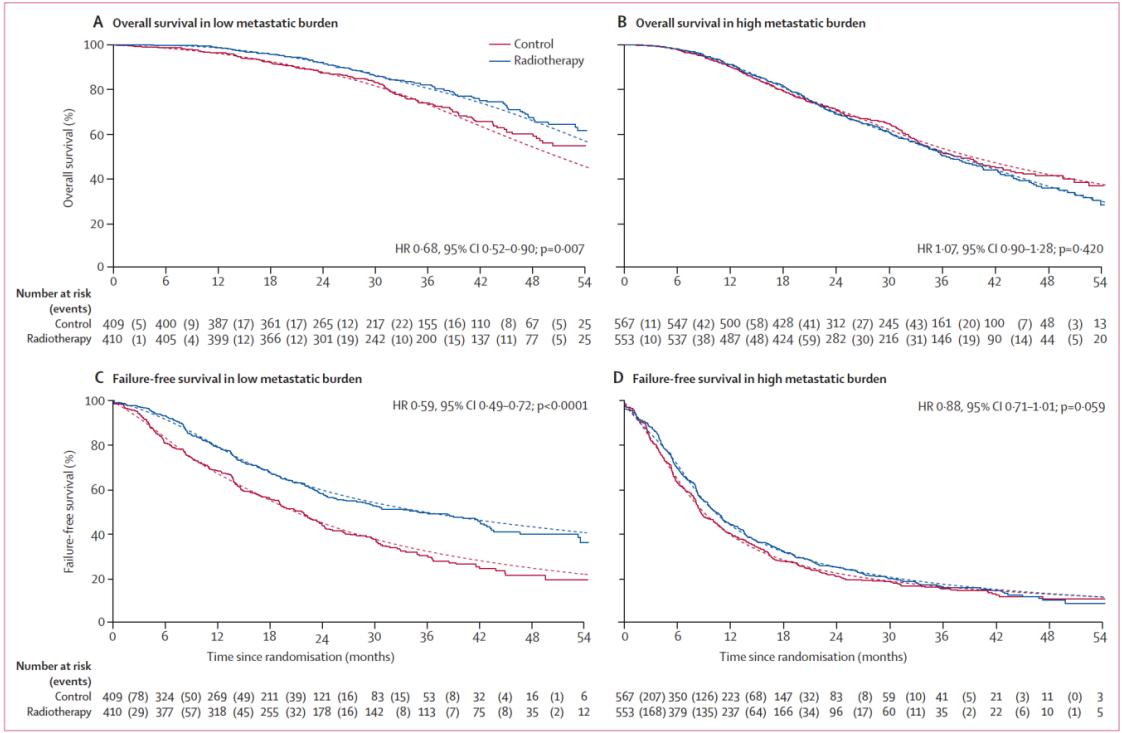
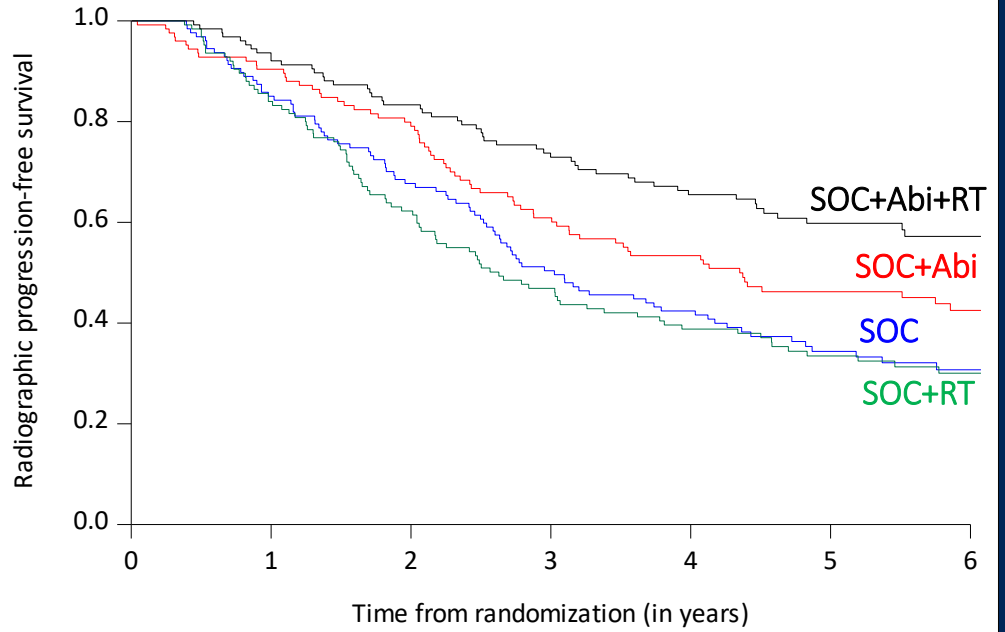


Figure 4: Overall survival and failure-free survival by treatment and metastatic burden

Low burden

High burden

rPFS (low volume population)



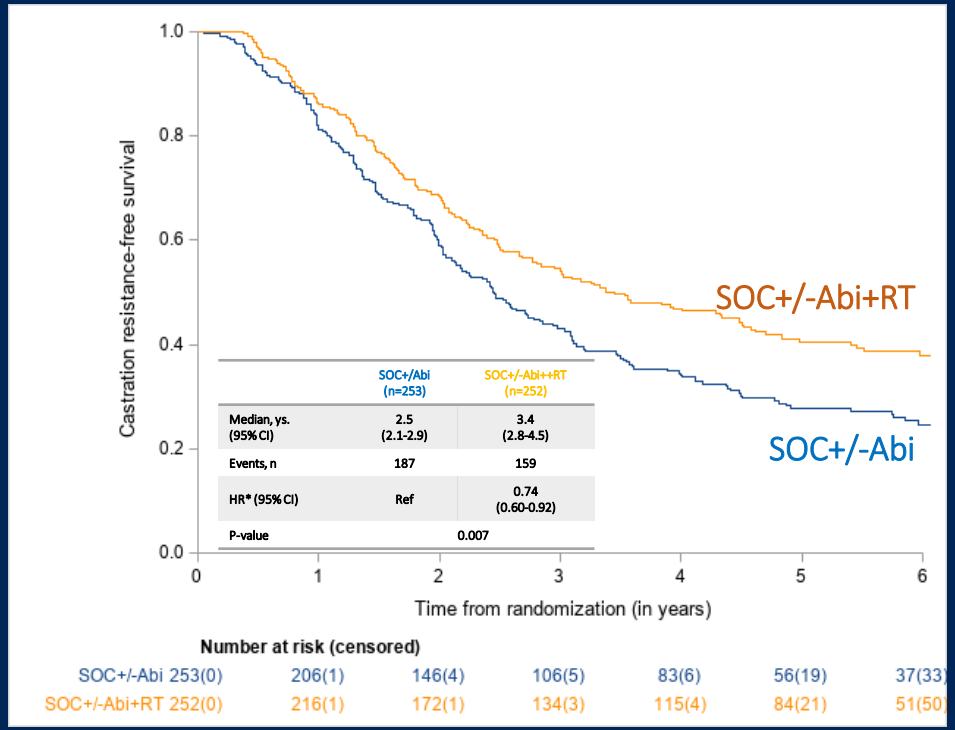
Number at risk (censored)

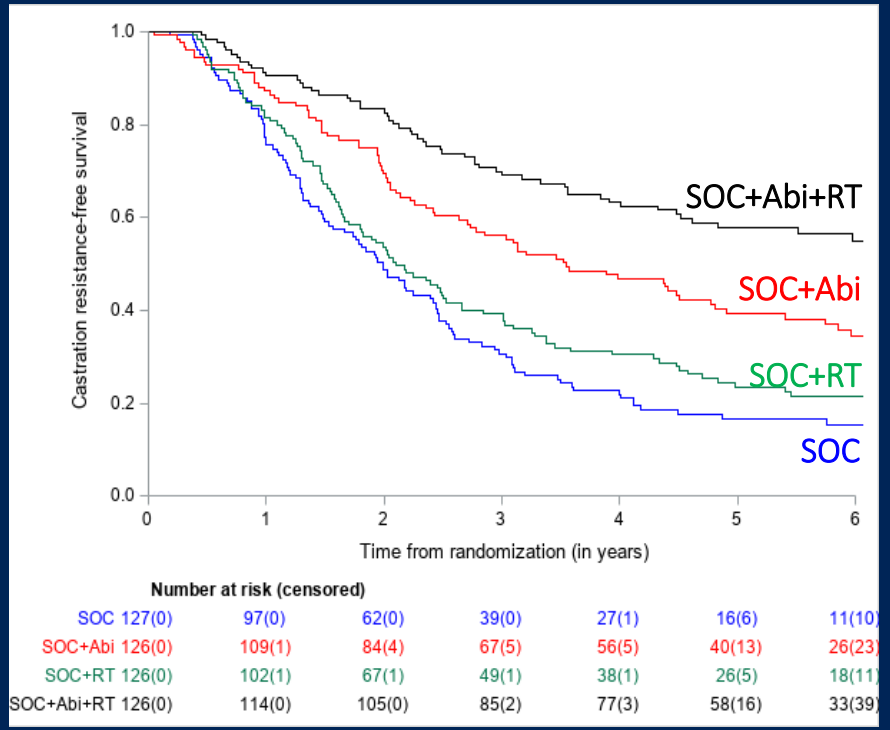
SOC	127(0)	108(0)	86(0)	64(0)	53(1)	34(11)	20(22)
SOC+Abi	126(0)	113(1)	96(4)	73(5)	64(5)	46(15)	31(27)
SOC+RT	126(0)	105(1)	77(2)	58(2)	48(2)	36(8)	23(18)
SOC+Abi+RT	126(0)	116(0)	105(0)	89(3)	79(4)	60(17)	34(41)

	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (99.9% CI)	3.0 (2.3-4.8)	2.6 (1.7-4.6)	4.4 (2.5-7.3)	7.5 (4,0-NE)
Events, n.	87	89	74	55
HR (99.9%CI)*	Ref	1.11 (0.67-1.84)	0.76 (0.45-1,28)	0.50 (0.28-0.88)
Global p-value	<0.0001			
HR (99.9% CI)*	Ref	1.08 (0.65-1.80)	Ref	0.65 (0.36-1.19)
P-values arms w/wo Abi	0.61		0.02	

*Adjusted on stratification factors (PS, type of castration, docetaxel)

Castration Resistance Free-Survival (low volume pop.)

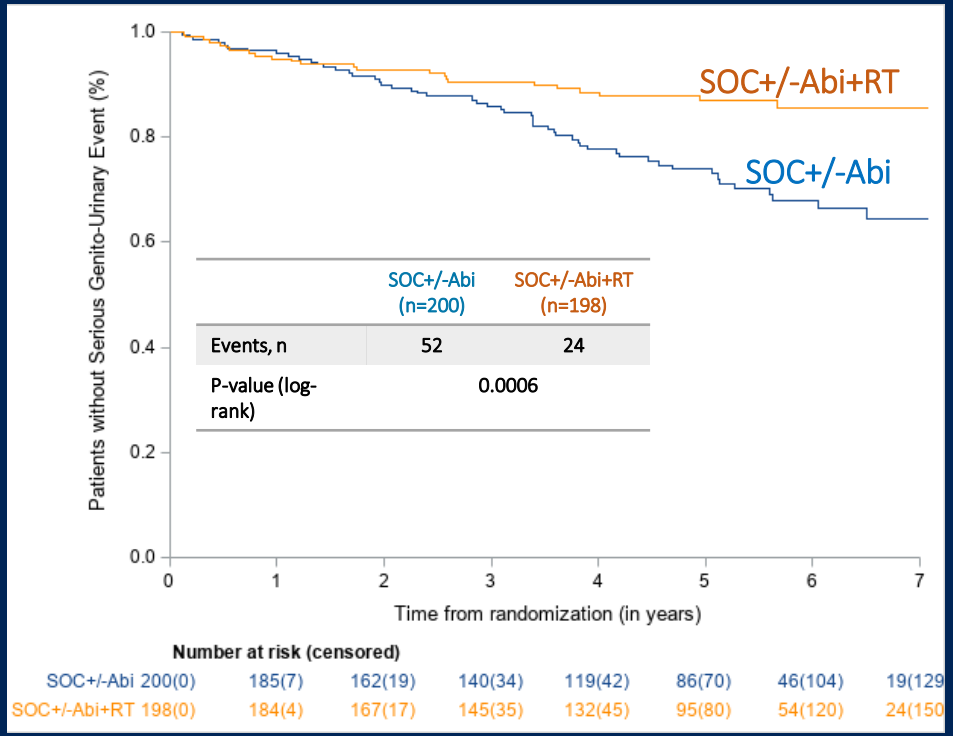




interaction p-value = 0.15

*Adjusted on abiraterone and stratification factors (PS, type of castration, docetaxel)

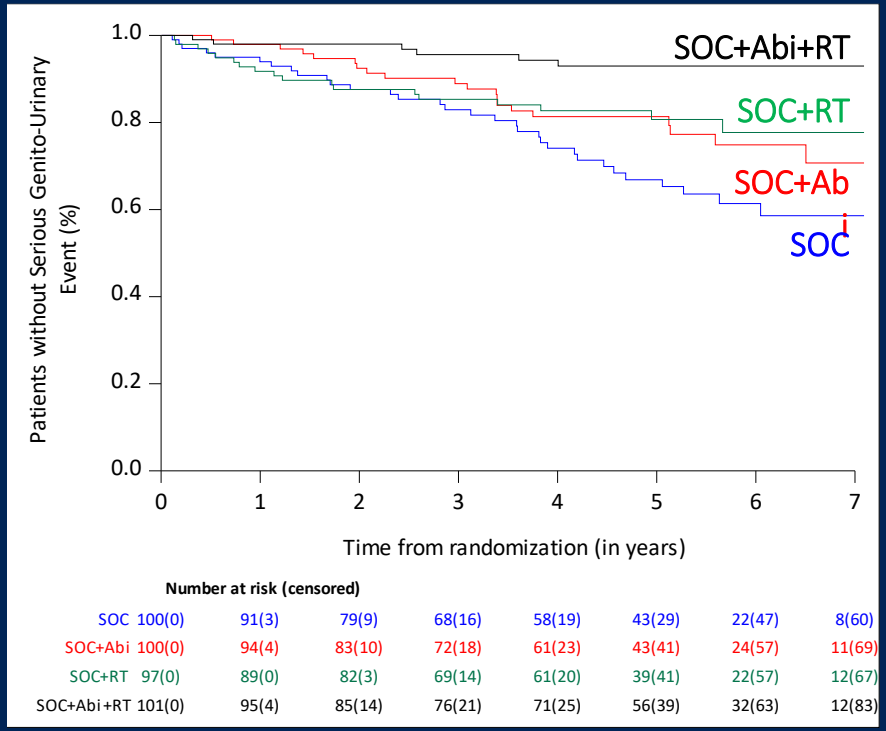
Time to Serious Genito-Urinary events (low volume pop.)



	SOC+/-Abi (n=200)	SOC+/-Abi+RT (n=198)
Events, n	52	24
P-value (log-rank)	0.0006	

Number at risk (censored)

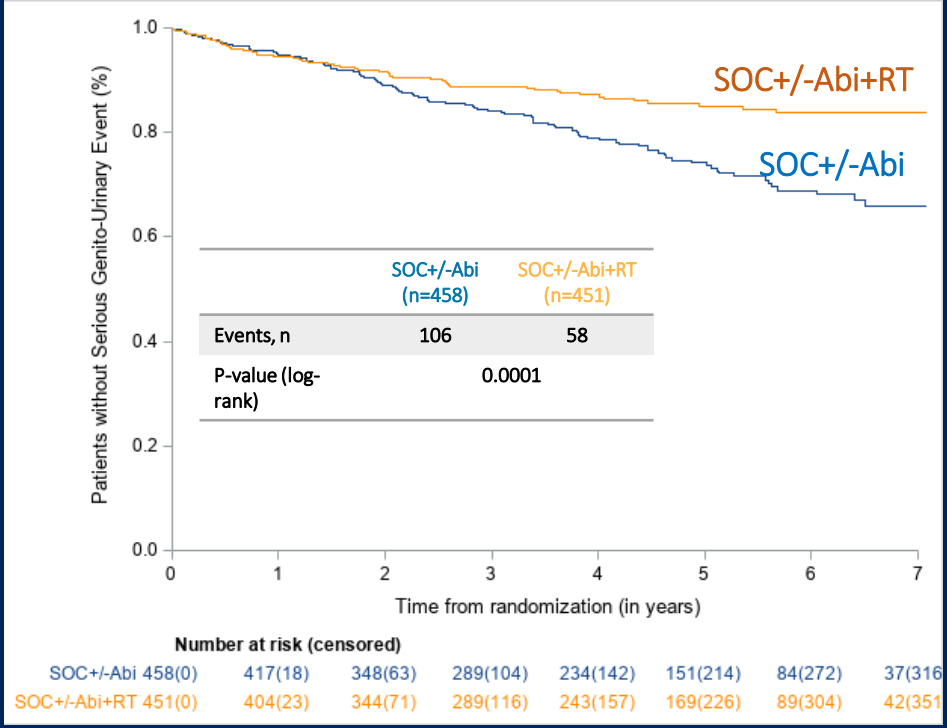
SOC+/-Abi 200(0)	185(7)	162(19)	140(34)	119(42)	86(70)	46(104)	19(129
SOC+/-Abi+RT 198(0)	184(4)	167(17)	145(35)	132(45)	95(80)	54(120)	24(150

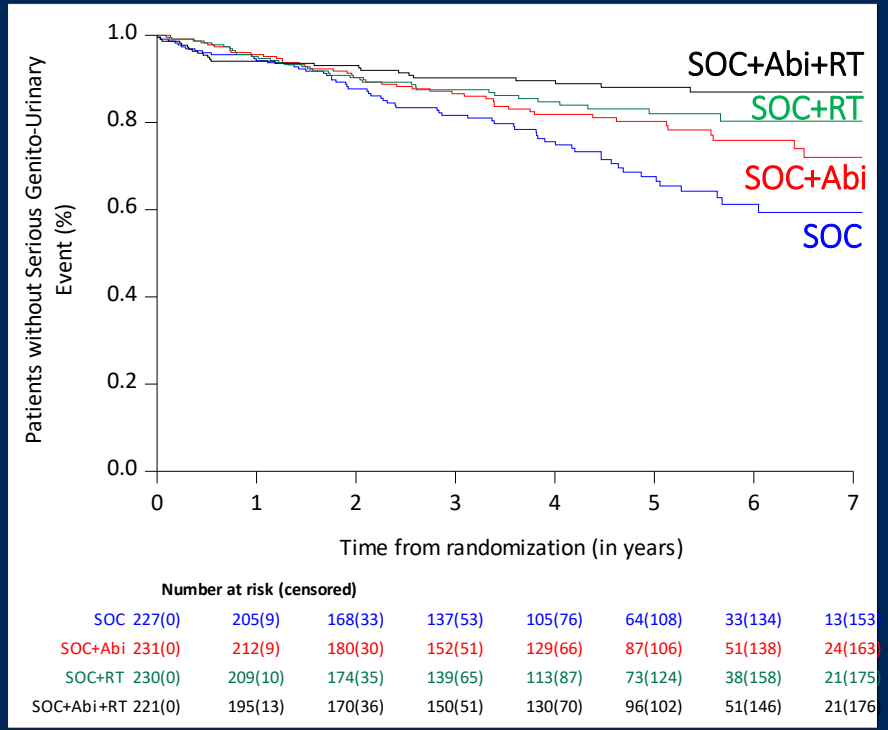


Number at risk (censored)

SOC 100(0)	91(3)	79(9)	68(16)	58(19)	43(29)	22(47)	8(60)
SOC+Abi 100(0)	94(4)	83(10)	72(18)	61(23)	43(41)	24(57)	11(69)
SOC+RT 97(0)	89(0)	82(3)	69(14)	61(20)	39(41)	22(57)	12(67)
SOC+Abi+RT 101(0)	95(4)	85(14)	76(21)	71(25)	56(39)	32(63)	12(83)

Time to Serious Genito-Urinary events (overall pop.)

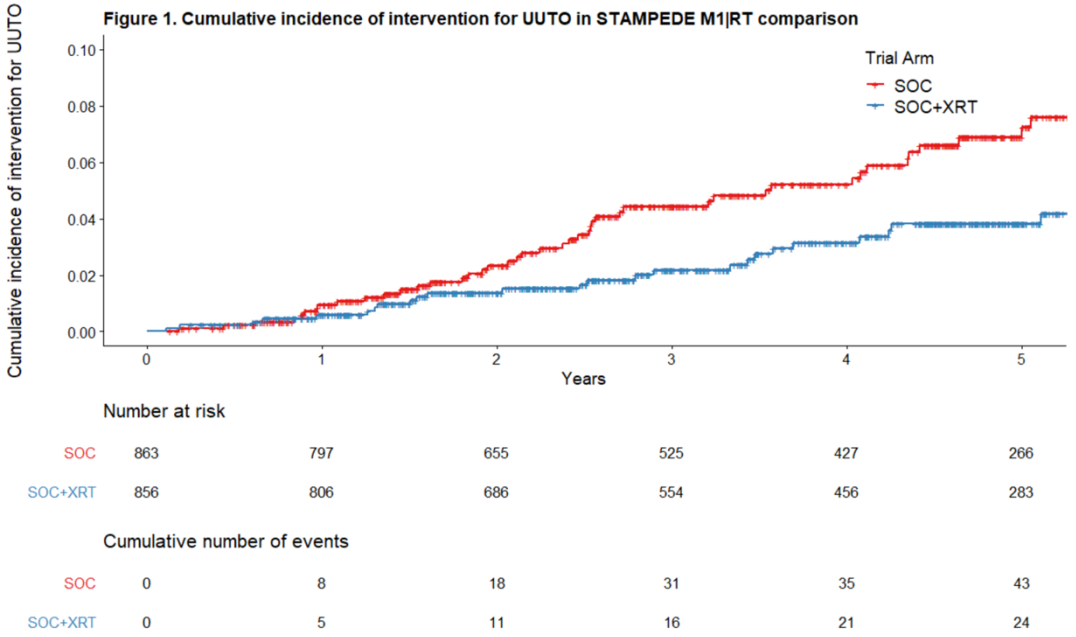




Prostate radiotherapy reduces long-term risk of obstructive uropathy in metastatic hormone sensitive prostate cancer (mHSPC): results from the STAMPEDE M1-RT comparison

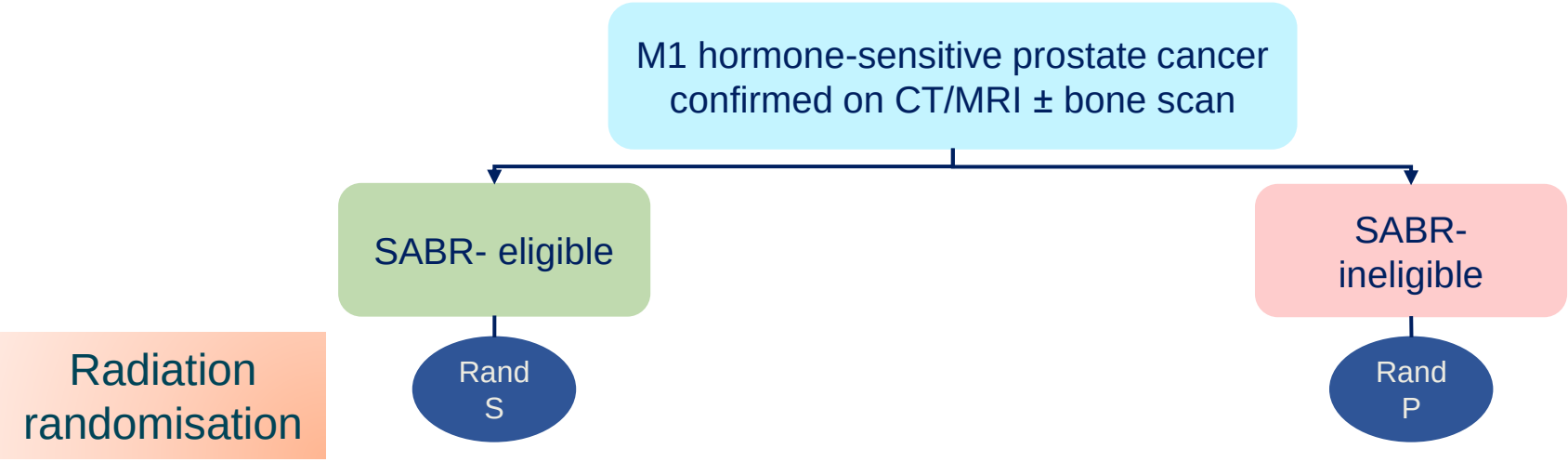
Craig Jones, Laura Murphy, Macey Murray, Louise Brown, Mahesh Parmar, Nick James, Chris Parker, Matthew R Sydes, Noel Clarke, Ashwin Sachdeva

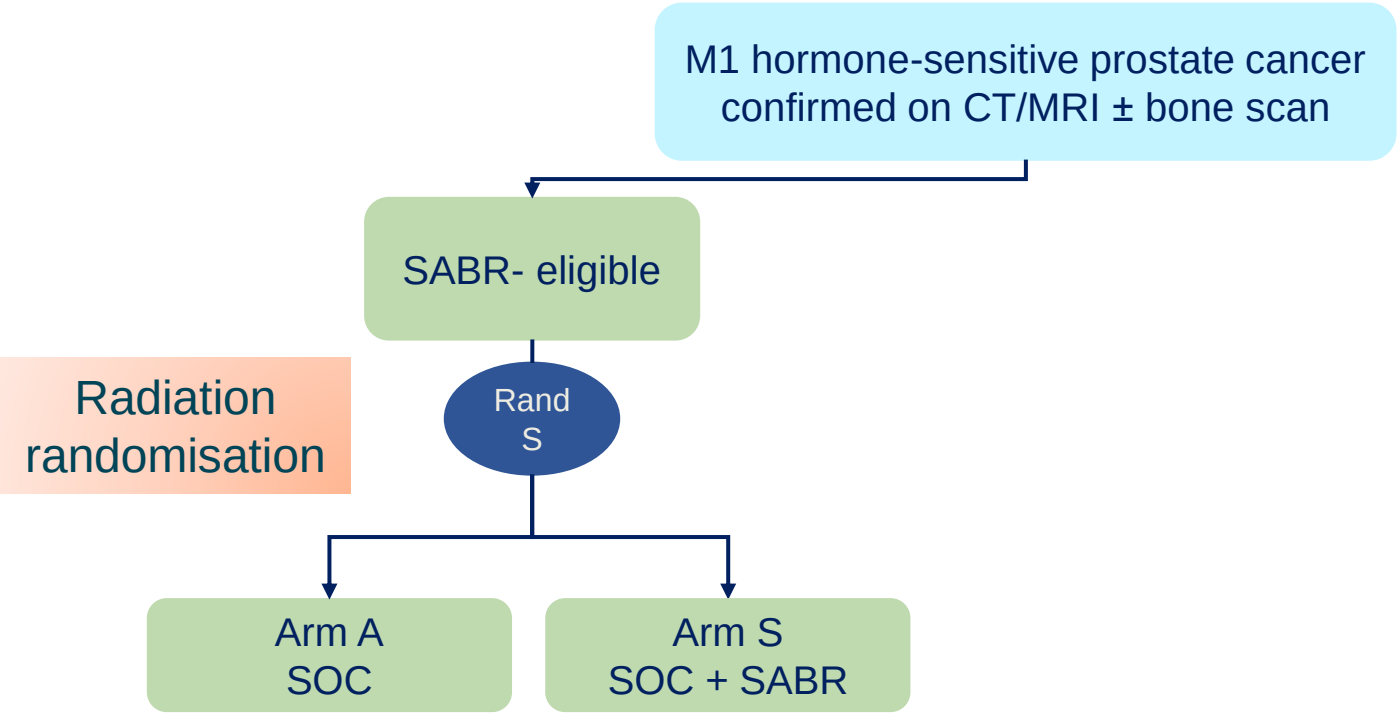
Prostate radiotherapy reduces long-term risk of obstructive uropathy in metastatic hormone sensitive prostate cancer



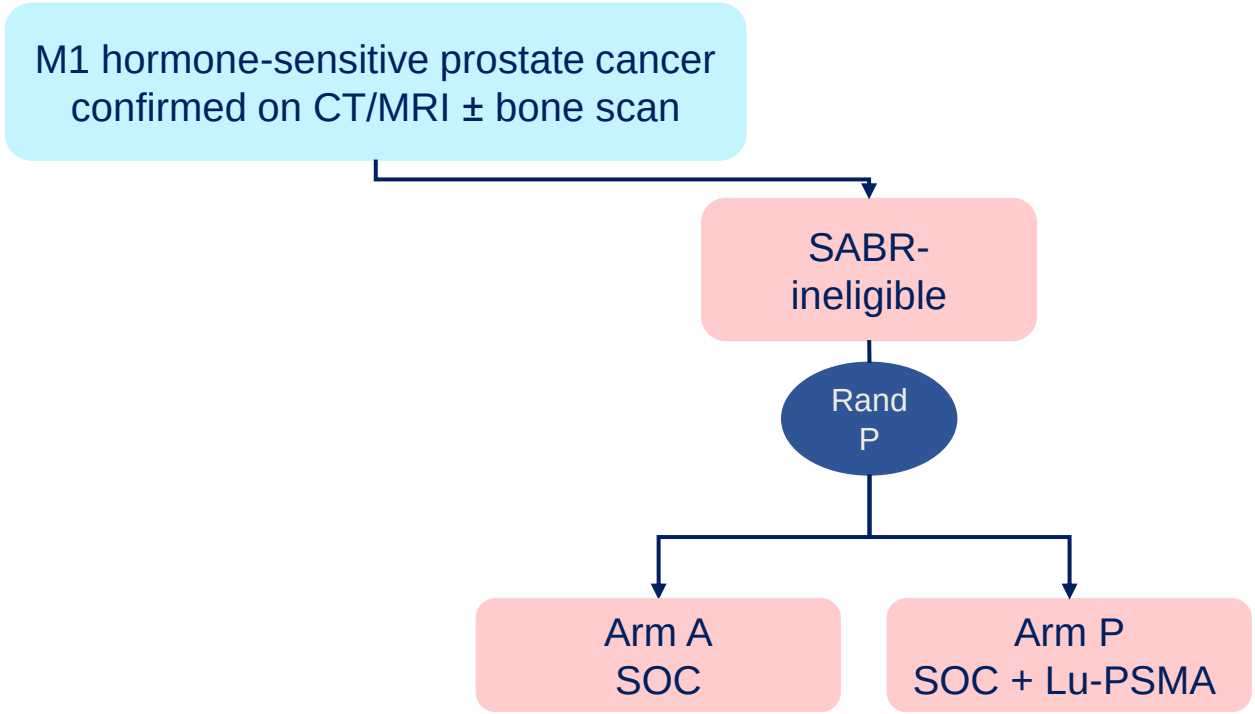
Unpublished – not for distribution

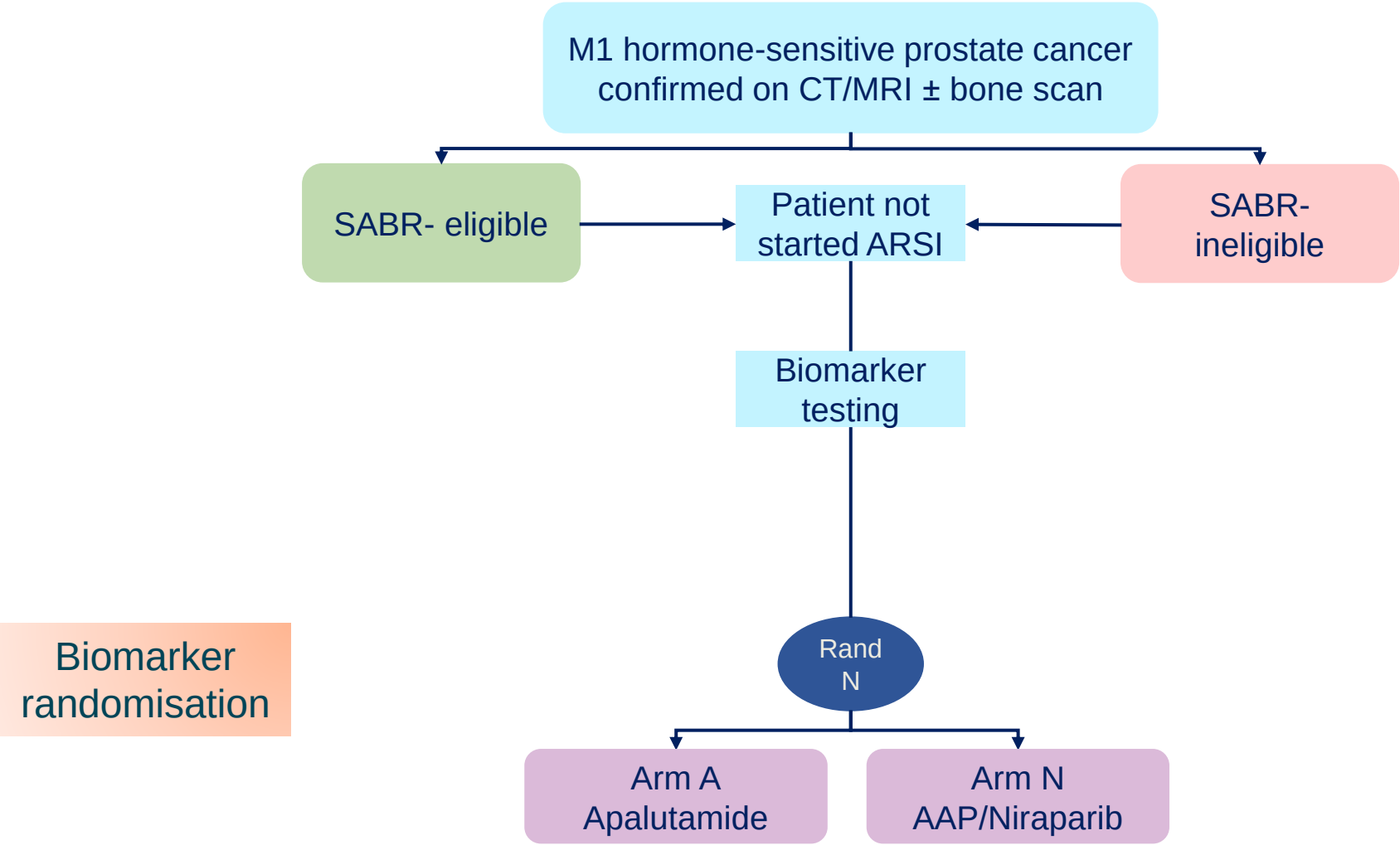
The STAMPEDE2 trial

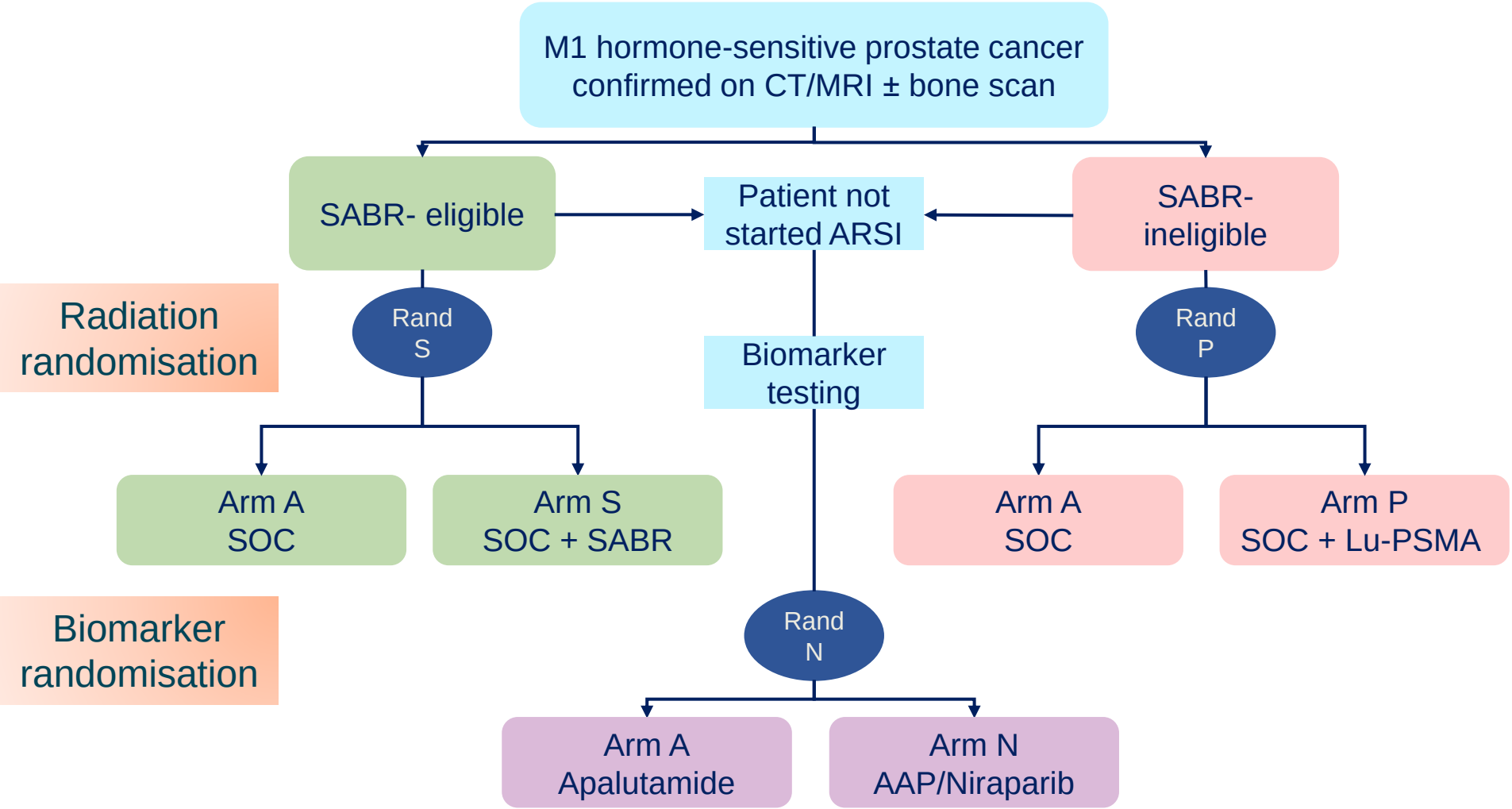

M1 hormone-sensitive prostate cancer confirmed on CT/MRI ± bone scan
SABR- eligible
SABR- ineligible
Radiation randomisation
Rand S
Rand P

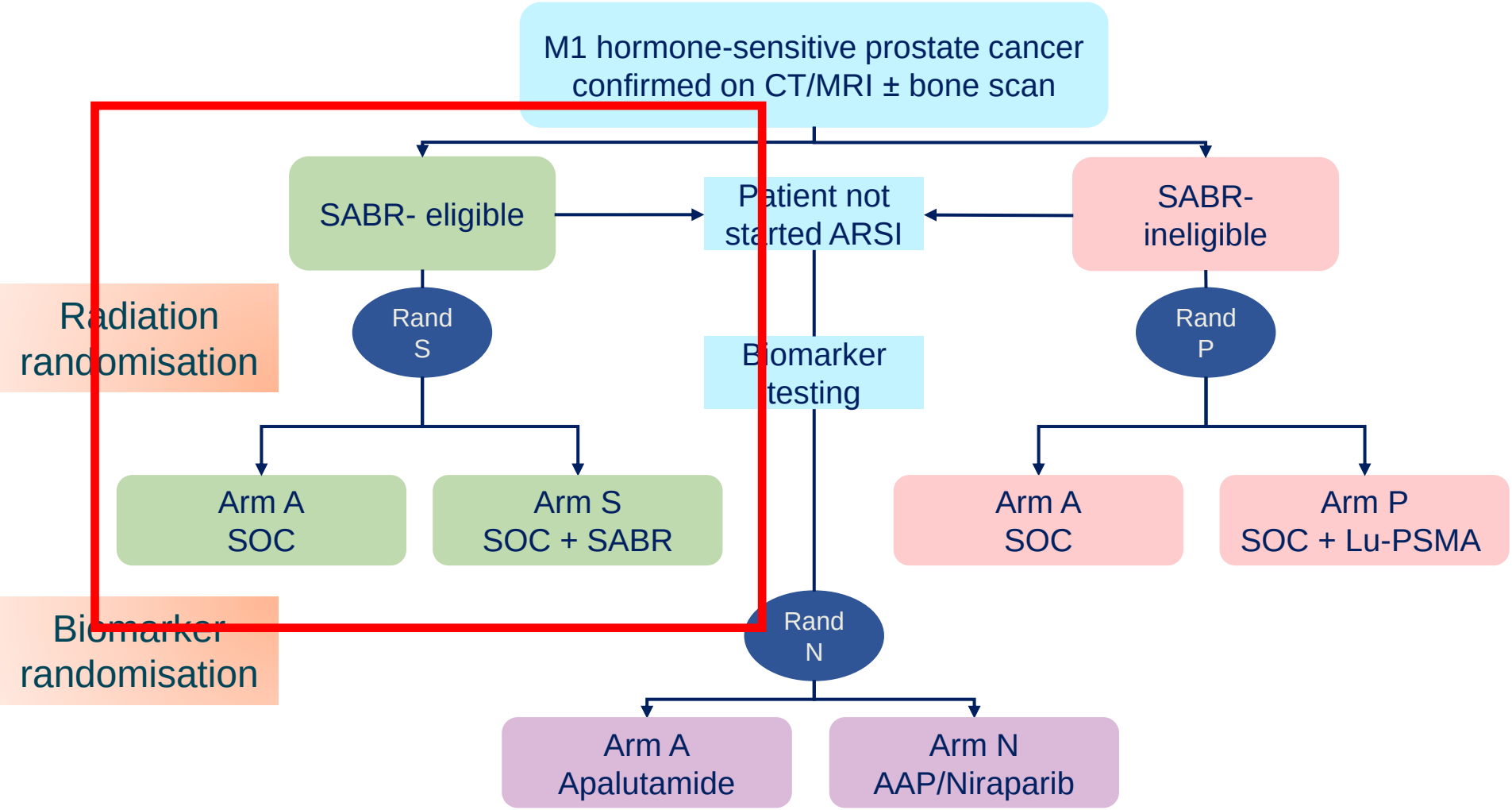

M1 hormone-sensitive prostate cancer confirmed on CT/MRI ± bone scan
SABR- eligible
Radiation randomisation
Rand S
Arm A SOC
Arm S SOC + SABR

Radiation randomisation



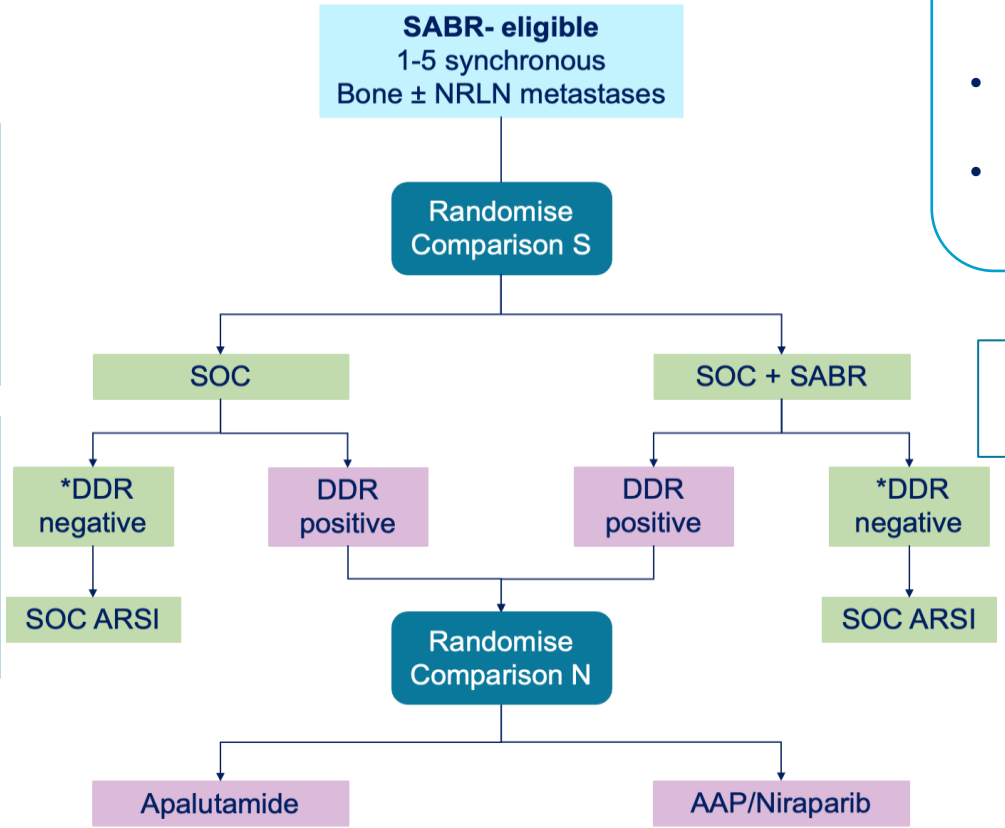

M1 hormone-sensitive prostate cancer confirmed on CT/MRI ± bone scan
SABR- eligible
Patient not started ARSI
SABR- ineligible
Biomarker testing
Biomarker randomisation
Rand N
Arm A Apalutamide
Arm N AAP/Niraparib


M1 hormone-sensitive prostate cancer confirmed on CT/MRI ± bone scan
SABR- eligible
Patient not started ARSI
SABR- ineligible
Radiation randomisation
Rand S
Rand P
Biomarker testing
Arm A SOC
Arm S SOC + SABR
Arm A SOC
Arm P SOC + Lu-PSMA
Biomarker randomisation
Rand N
Arm A Apalutamide
Arm N AAP/Niraparib


M1 hormone-sensitive prostate cancer confirmed on CT/MRI ± bone scan
SABR- eligible
Patient not started ARSI
SABR- ineligible
Radiation randomisation
Rand S
Biomarker testing
Rand P
Arm A SOC
Arm S SOC + SABR
Arm A SOC
Arm P SOC + Lu-PSMA
Biomarker randomisation
Rand N
Arm A Apalutamide
Arm N AAP/Niraparib

STAMPEDE2: Comparison S

Inclusion criteria:
- 1-5 synchronous bone ± NRLN mets
- CT/MRI ± bone scan detected
- SABR technically & clinically suitable

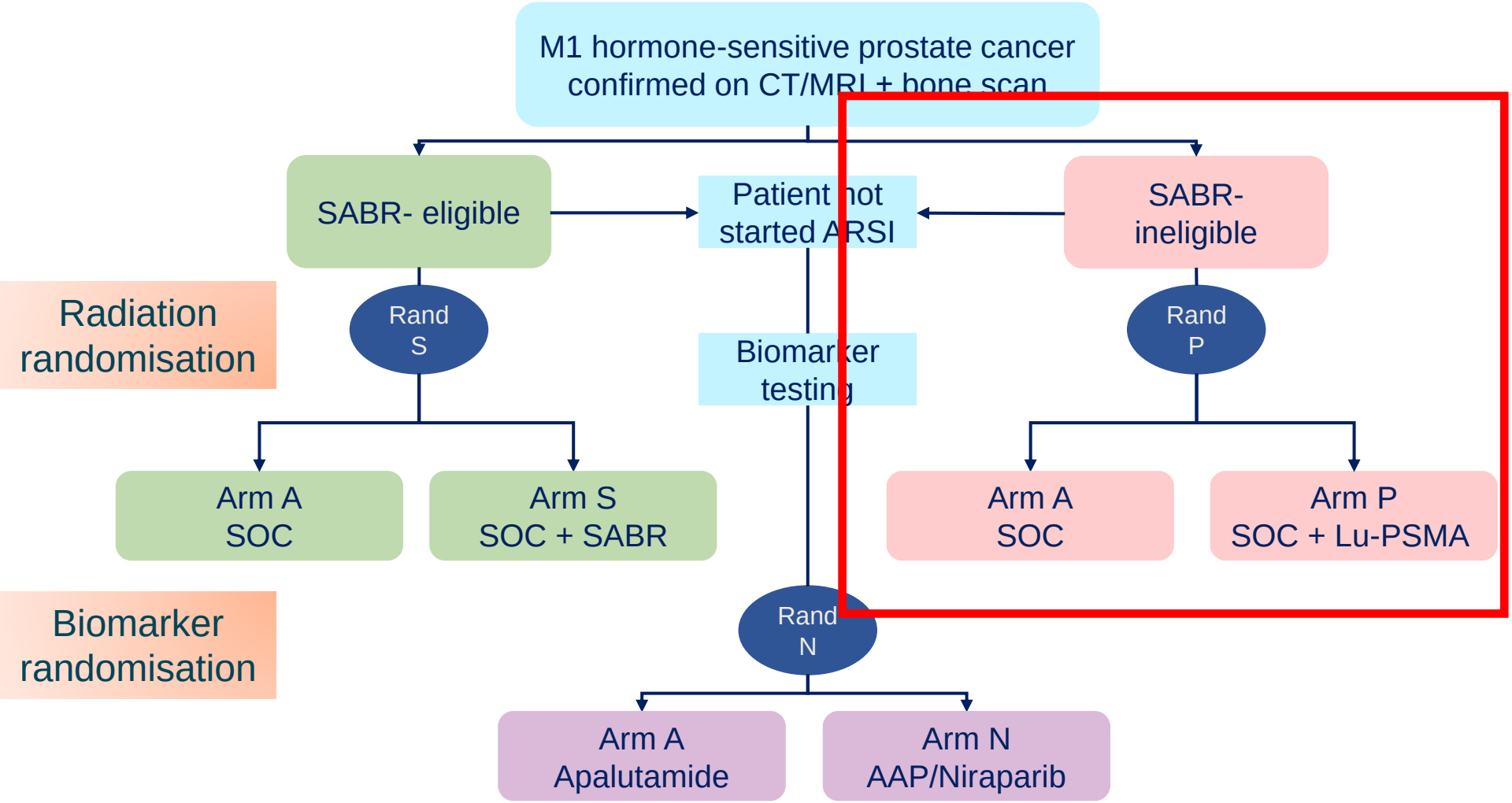


* Or DDR unknown

Systemic therapy
ADT
ARSI of choice if DDR-/unknown
± Docetaxel

Prostate RT (± pelvic)
36.25Gy in 5f
60Gy in 20f
(47Gy to LNs, 51Gy boost)

SABR to metastases
27-30Gy in 3-5f


M1 hormone-sensitive prostate cancer confirmed on CT/MRI + bone scan
SABR- eligible
Patient not started ARSI
SABR-ineligible
Radiation randomisation
Rand S
Biomarker testing
Rand P
Arm A SOC
Arm S SOC + SABR
Arm A SOC
Arm P SOC + Lu-PSMA
Biomarker randomisation
Rand N
Arm A Apalutamide
Arm N AAP/Niraparib

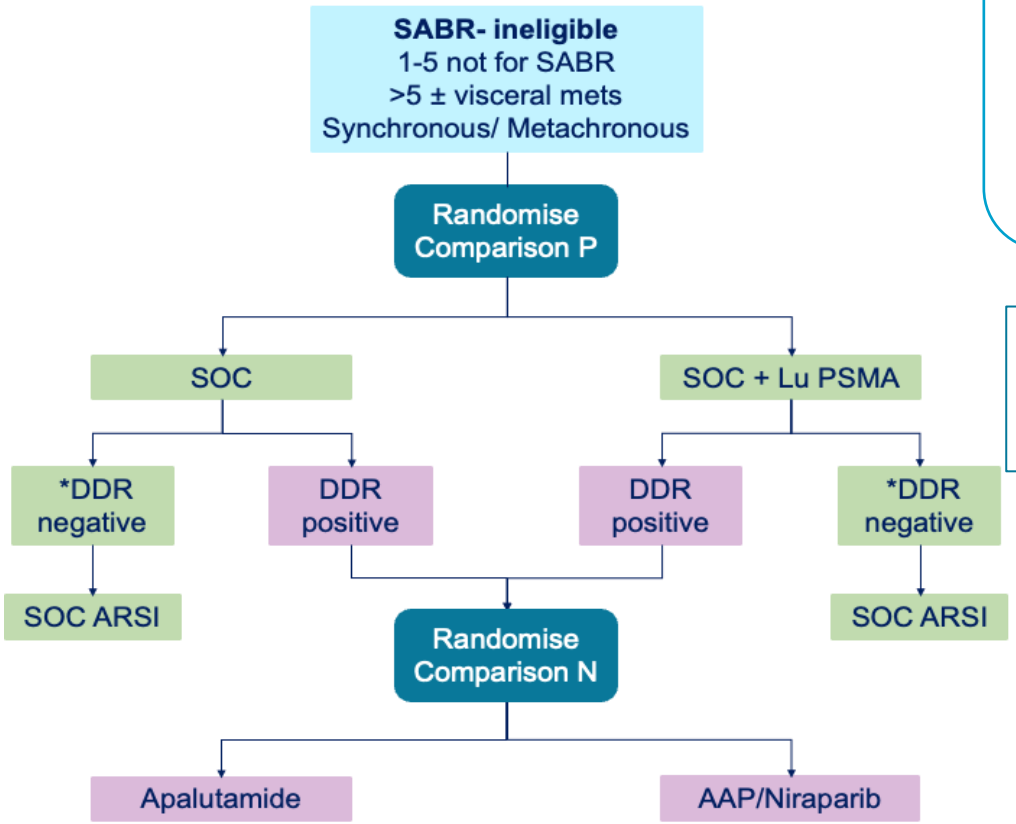
STAMPEDE2: Comparison P

Inclusion criteria:
- Any M1 disease
- Detected on CT/MRI ± bone scan detected
- Not suitable for SABR

Systemic therapy
ADT
ARSI of choice if DDR-/unknown
± Docetaxel

^Prostate RT
36Gy in 6f weekly

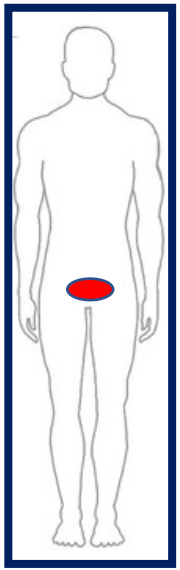
^{177}Lu-PSMA-617
7.4GBq D1 & D8
6 weekly (x3)



* Or DDR unknown

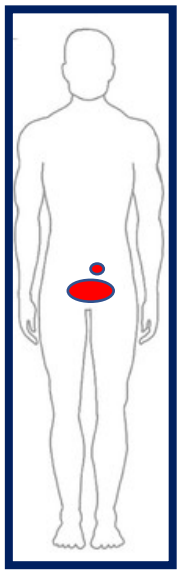
How to deal with new generation imaging?

De novo prostate cancer therapy



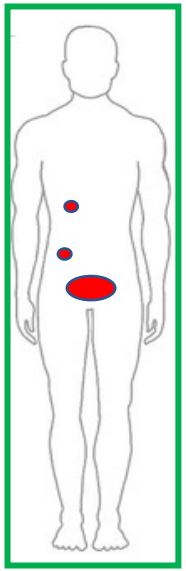
PRIMARY DISEASE

ADT + Prostate RT



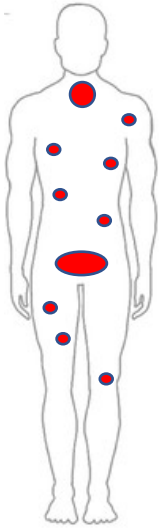
NODE+ DISEASE

ADT + Prostate + nodal RT +ARTI



LOW-VOLUME
< 4 bone lesions

ADT+ ARTI + Prostate RT
? Add MDT



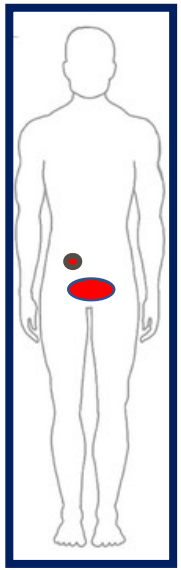
HIGH-VOLUME CHARTTED
≥ 4 bone lesions

ADT + Docetaxel + ARTI

STANDARD IMAGING (BONE SCAN + CT scan)

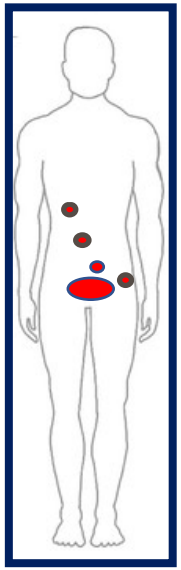
Low risk localized → **Full blown metastatic**

The stage migration in the *de-novo* setting



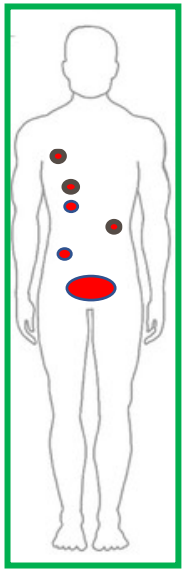
PRIMARY DISEASE

ADT + Prostate RT ?+ nodal RT



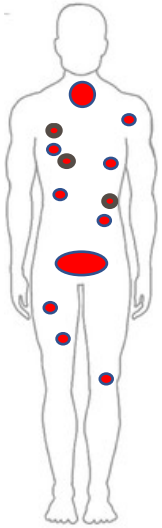
NODE+ DISEASE

ADT + Prostate + nodal RT + ARTI ?+ PA Nodal RT



LOW-VOLUME < 4 bone lesions

ADT+ ARTI + ~~Prostate RT~~ ~~? Add MDT~~



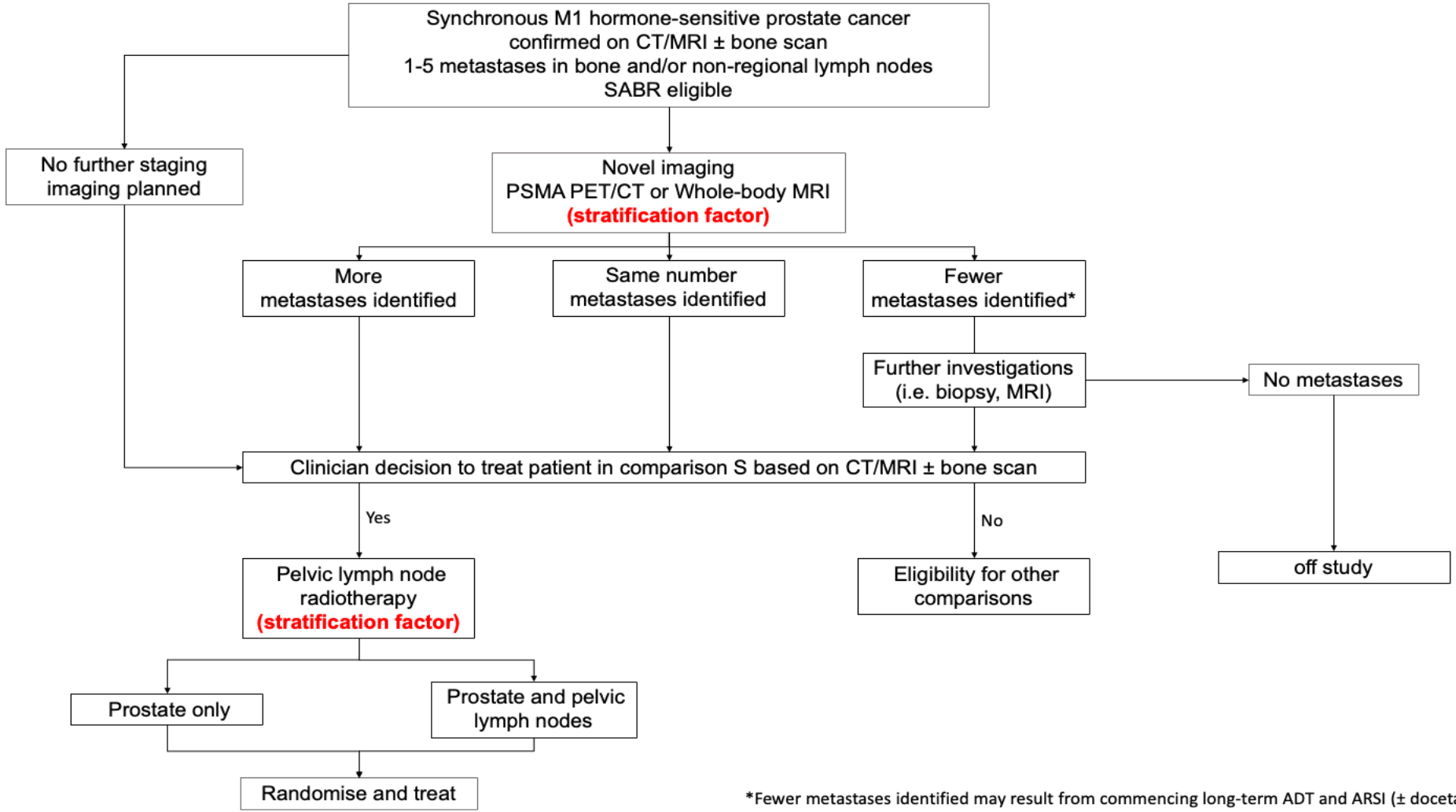
HIGH-VOLUME CHARTTED ≥ 4 bone lesions

ADT + Docetaxel + ARTI

STANDARD IMAGING (BONE SCAN + CT scan)

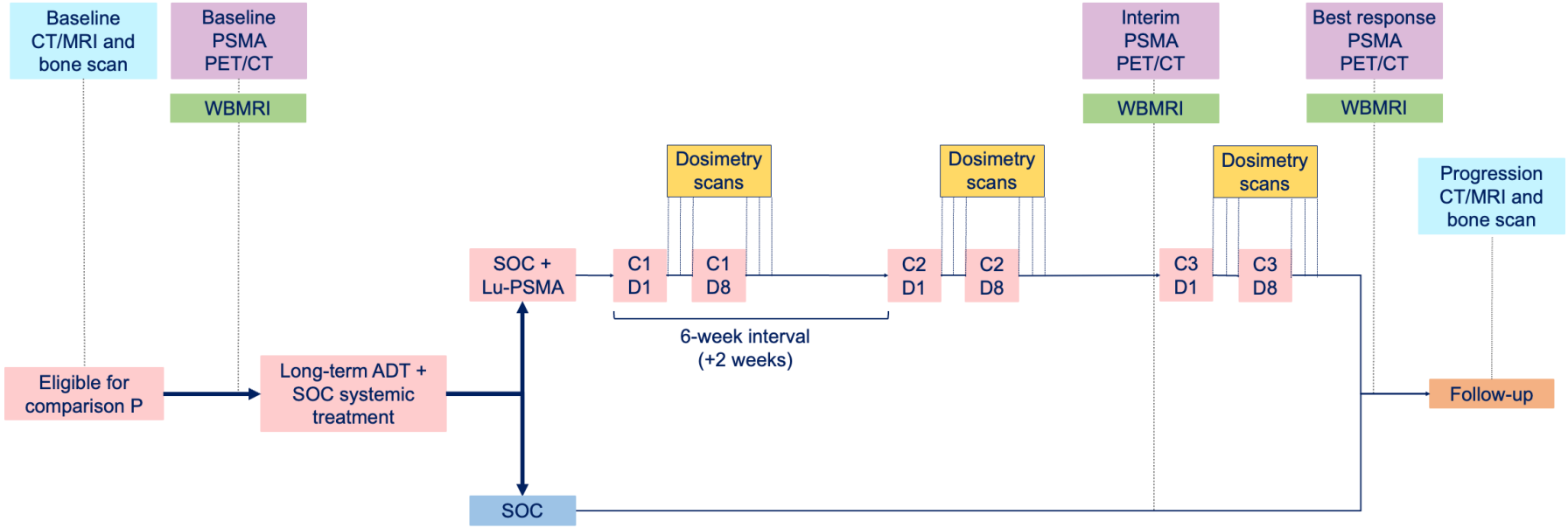
+ PSMA-PET

Low risk localized — **NEXT-GENERATION IMAGING (PSMA PET-CT)** — **Full blown metastatic**



*Fewer metastases identified may result from commencing long-term ADT and ARSI (± docetaxel)
This scenario is most likely to occur if new generation imaging are performed post-randomisation

Comparison P: run-in safety phase



Endpoints and other considerations

- Endpoints
  - Metastatic progression free survival
  - Overall survival
- Randomisation stratified by (amongst other things)
  - access to new generation imaging
  - Intention to use docetaxel
- Partial 2x2 design efficient as get data in DNA damage repair cases with all modalities
- Modular design allows centres to participate in 1, 2 or all 3 randomisations – facilitates international participation

Acknowledgements

12,000 patients who have joined the trial & their families + friends who have supported them

>3,000 site staff at >100 hospitals

www.stampedetrial.org

Sanofi, Novartis, Janssen, Clovis, Pfizer and Astellas pharma

Medical Research Council & Cancer Research UK

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