

Radiotherapy (RT) to the primary tumour for men with newly-diagnosed metastatic hormone-naïve prostate cancer

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Honoraria for Advisory Boards:

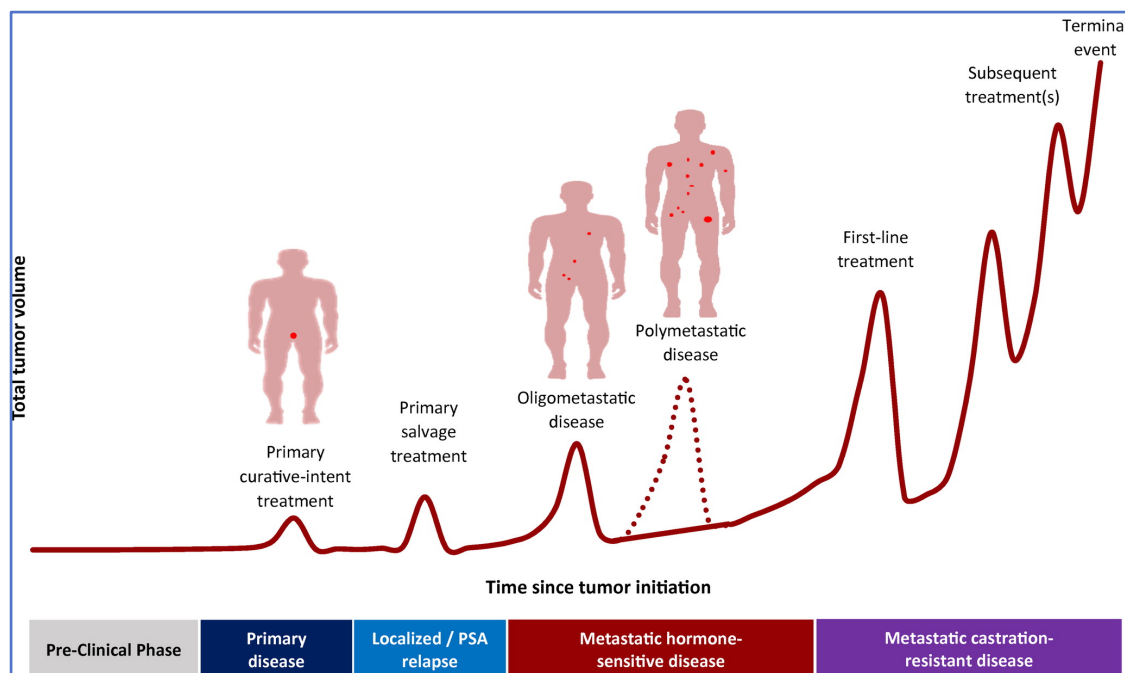
AstraZeneca, Onxeo, BlueLine Biosciences

Structured Research Grants:

GenomeDx

No role on execution or analyses of this trial

Oligometastatic Disease – Clinical Concept

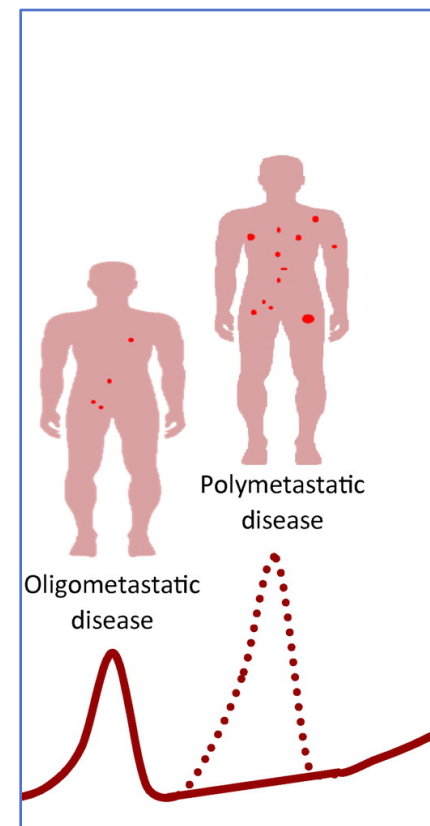


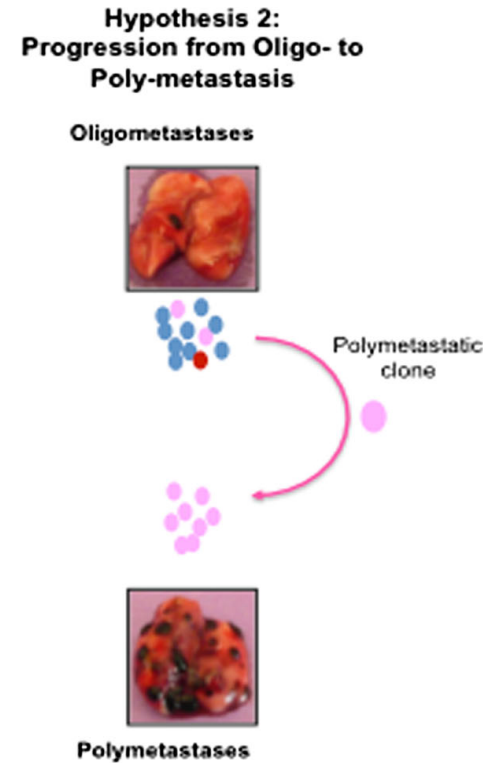
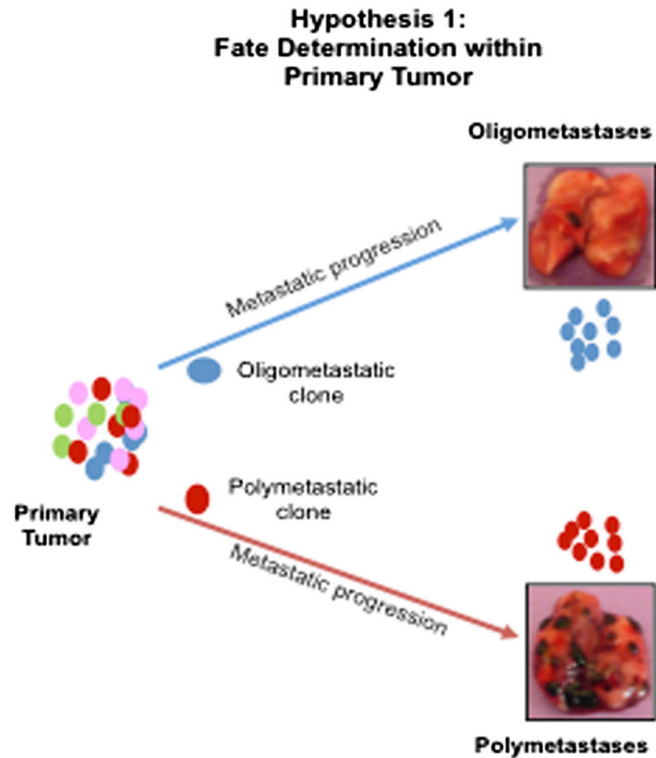
Trial	High Volume	Low Volume
Glass et al ¹²	(Extensive disease) Appendicular skeletal metastases and/or visceral metastases	(Minimal disease) Nodal metastases and/or axial skeletal metastases
CHAARTED trial ⁷³	≥ 4 bone metastases with one or more outside the vertebral bodies and pelvis and/or visceral metastases (extranodal)	All others
STAMPEDE trial ⁷²	Same as the CHAARTED trial	Same as the CHAARTED trial
GETUG-AFU15 trial ⁷⁴	Same as the CHAARTED trial	Same as the CHAARTED trial
LATITUDE trial ⁷⁵	Two or more of the following: visceral metastases, > 3 bone metastases, Gleason score ≥ 8	Only one of the following: visceral metastases, > 3 bone metastases, Gleason score ≥ 8

Ryan and colleagues, Eur Urol, 2019

Oligometastatic Disease – Biological Concept

- Coined by Hellman and Weichselbaum (JCO, 1995)
- ***Implicit in this concept:***
 - potentially a less aggressive disease course;
 - unique subset of patients might benefit (in terms of disease progression and/ or OS) from aggressive localized therapies;
 - have unique biologic characteristics which would differentiate its disease course;
 - have unique clinical and molecular characteristics allowing for a therapeutic window of treatment with multimodal therapy;
 - limited to specific organs and in limited numbers .
- Benefit of surgical and ablative mastectomy for lesions to lung, liver, brain





Biology: could change based on tumour or host characteristics, local and systemic treatments

Weischelbaum et al; 2014

Rationale for Treating Primary in the Metastatic Setting

CLINICAL

- Retrospective and Level I (RT) data suggest possible improvements in survival
- Local symptomatic progression may be reduced-*rare*
- Lethal cancer clones may be left in situ following systemic therapy-*unknown*
- Cytoreductive surgery and radiotherapy is safe in well-selected patients-*probably true*

BIOLOGICAL (*unknown in HSPC M1 setting*)

- May alter secondary polymetastases wave from primary or oligometastases
- May alter immunomodulatory responses or growth factors/cytokines
- Metastases may heterogenous:
 - genomics (somatic/germline),
 - immune surveillance,
 - AR signaling
 - TME

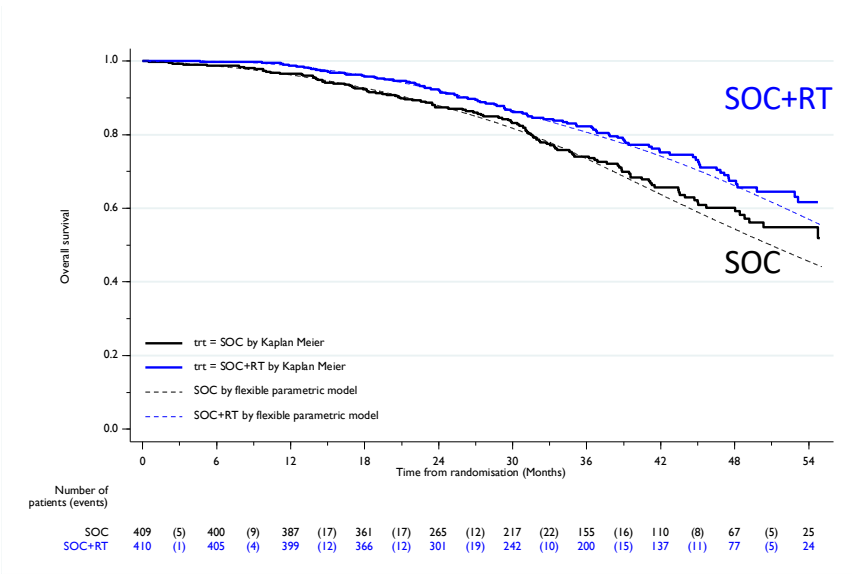
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial



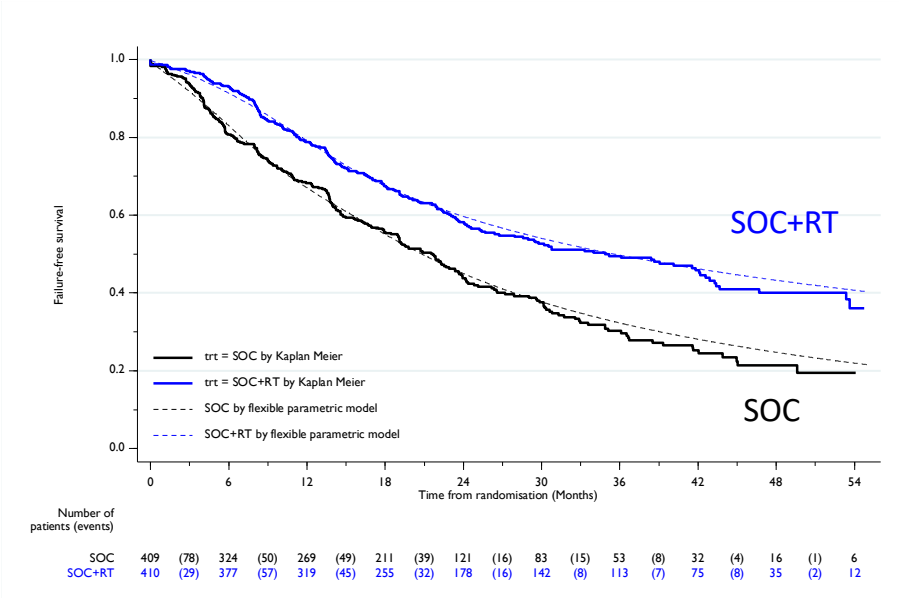
Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Deamaley, Silke Gillessen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, 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 Parkh, 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†



Parker et al; Lancet, October 21, 2018



Overall Survival



Failure Free Survival

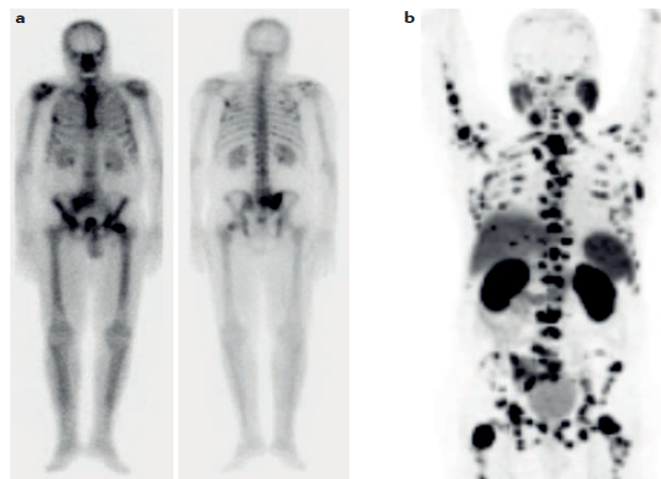
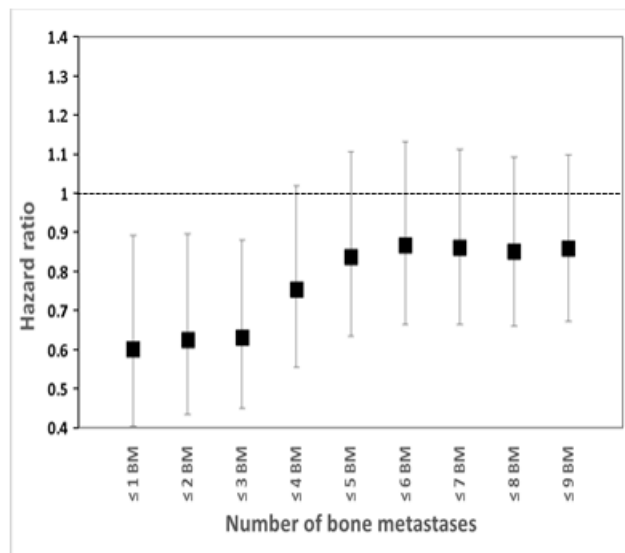


ADVANCED PROSTATE CANCER
CONSENSUS CONFERENCE: APCCC 2019
29-31 August 2019, Basel/Switzerland

Pre-specified analysis
Low burden



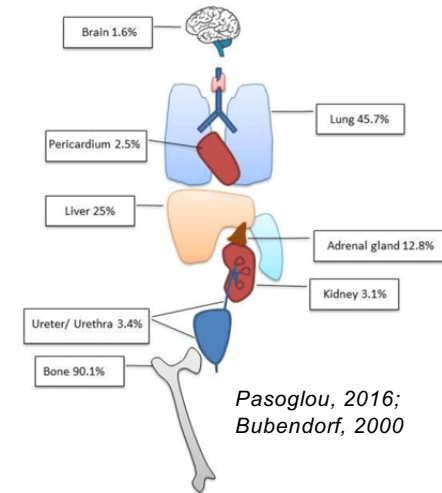
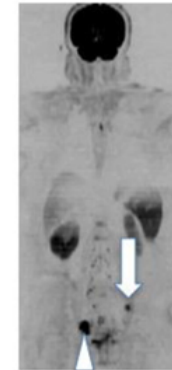
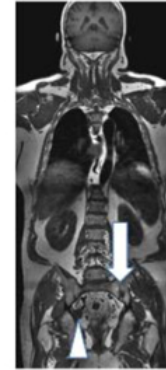
Bone Scanning and The Threshold Effect of Disease Burden (Pre-specified/cf. CT scans)



The Bone Scan is PREDICTIVE of Response to Radiotherapy to the Primary Site When the Bone Metastasis Number is 4 or Less (LN and Bone mets both have OS effect from radiotherapy)

courtesy of Adnan Ali and Noel Clarke

Does The Imaging Really Matter ?



Would future patients benefit from modern imaging including PSMA, wbMRI , NAF or PET-Choline ?

- Bone scan (+ CT scan) is **PREDICTIVE** in this study & available in almost all countries
- Novel/Modern imaging is unlikely to change the overall result of the study given the profound HR for low volume disease- might it fine-tune the patients who would benefit ?
 - more sensitive scans could decrease the proportion of patients amenable to local RT plus systemic therapy
- **European Organisation for Research and Treatment of Cancer (EORTC) Imaging Group**
 - clinical algorithms and trials needed to integrate modern imaging methods into the care pathway to identify oligometastatic disease (*Lecouvet et al. Lancet Oncology; 2018*)

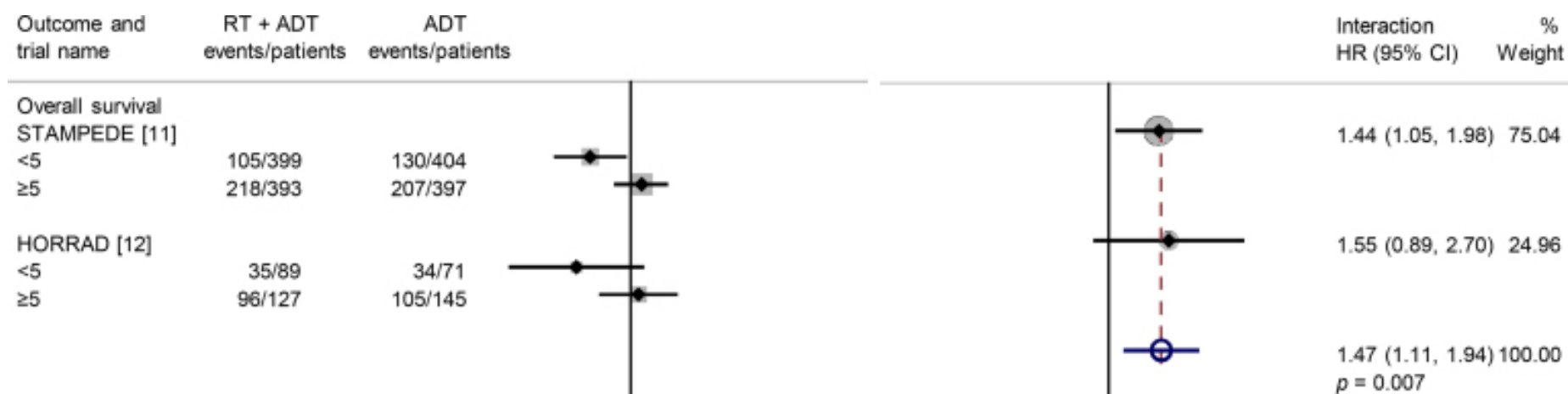


PROSTATE RADIOTHERAPY FOR METASTATIC HORMONE-SENSITIVE PROSTATE CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

Prospectively planned before results before any trial results known




Led by MRC Clinical Trials Unit at UCL in collaboration with STAMPEDE and HORRAD investigators

2126 men, 90% of men randomised to RT + ADT vs ADT; S Burdett et al., *Eur Urol.* 2019 Jul;76(1):115-124

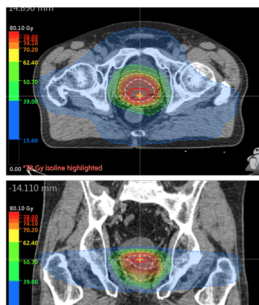


There was 7% improvement in 3-yr survival in men with fewer than five bone metastases.

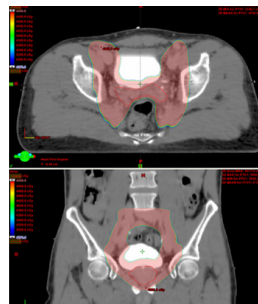
Does The Radiotherapy Dose and Volume Matter ?

36 Gy / 6f / 6 weeks	179/480	182/497	0.27		1.01 (0.82, 1.25)
55 Gy / 20f / 4 weeks	212/546	188/532			0.86 (0.71, 1.05)
Overall					0.92 (0.80, 1.06)

Prostate Alone

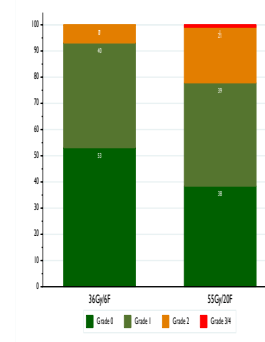


Prostate + PELVIS

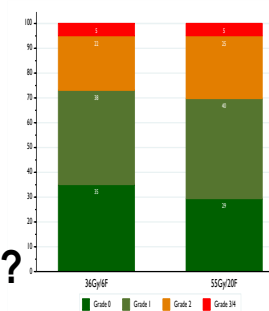


VOLUME

Bowel



Bladder



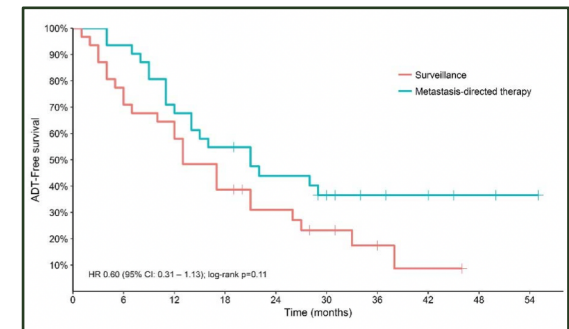
**RTOG
Toxicity**

**Benefit
for T3/T4 ?**

- Controversy regarding whole pelvis RT
 - may be a biological issue for immune responses with non-irradiated nodes needed for maximum IO effects
- Longer term follow-up required for late toxicity and RT benefit on obstruction and QOL in T3 and T4 disease

Future Role of Metastasis-Directed Therapy in Oligometastatic Prostate Cancer ?

- Multiple retrospective studies suggesting that metastasis-directed therapy may be efficacious
- **STOMP (Randomised Phase II)** has started to validate the role for metastasis-directed therapy
 - 62 patients with biochemical recurrence after definitive therapy with fewer than three extracranial metastatic lesions were randomly assigned to surveillance or metastasis-directed therapy (either SBRT or surgery)
 - median ADT- free survival for surveillance was 13 months compared with 21 months for the metastasis-directed therapy arm (HR 0.60)



Ost et al; JCO, 2017

- *Gomez et al; Lancet Oncology; 2016*, Local consolidative therapy; with or without maintenance therapy; three or fewer metastases from NSCLC; **OS Benefit**
- *Palma et al; Lancet 2019*; Ablate all (max 5) metastases, primary controlled; **OS benefit**
- On- going phase III clinical trials, including CORE and PCX IX, will provide overall survival data for metastasis-directed therapy.

SURGERY VERSUS RADIOTHERAPY ?

- Retrospective reviews (e.g. three from the U.S. SEER database and one from Munich Cancer registry) suggest mCSPC with N+ disease may benefit from best systemic therapy plus radical prostatectomy.
 - The 5 and 10 year overall survival rate in German cohort was 84% and 64% respectively following RP + SOC systemic therapy; without RP it was 60% and 28% respectively.(Engel et al., Eur Urol 2012).
- Prostate surgery is being tested in feasibility and RCT trials: **g-RAMMP** trial (NCT02454543), SWOG 1802 and **TROMBONE** feasibility study is completed in the UK.
 - If positive, these trials would start to inform a trial between surgery and radiotherapy in terms of efficacy and QOL.
 - It would also start to inform whether local glandular RT, versus removal of the prostate entirely, is the basis of the biology behind the clinical observation.

STAMPEDE M: Primary RT +/- SABRE (and development of a Surgery Sub-trial)

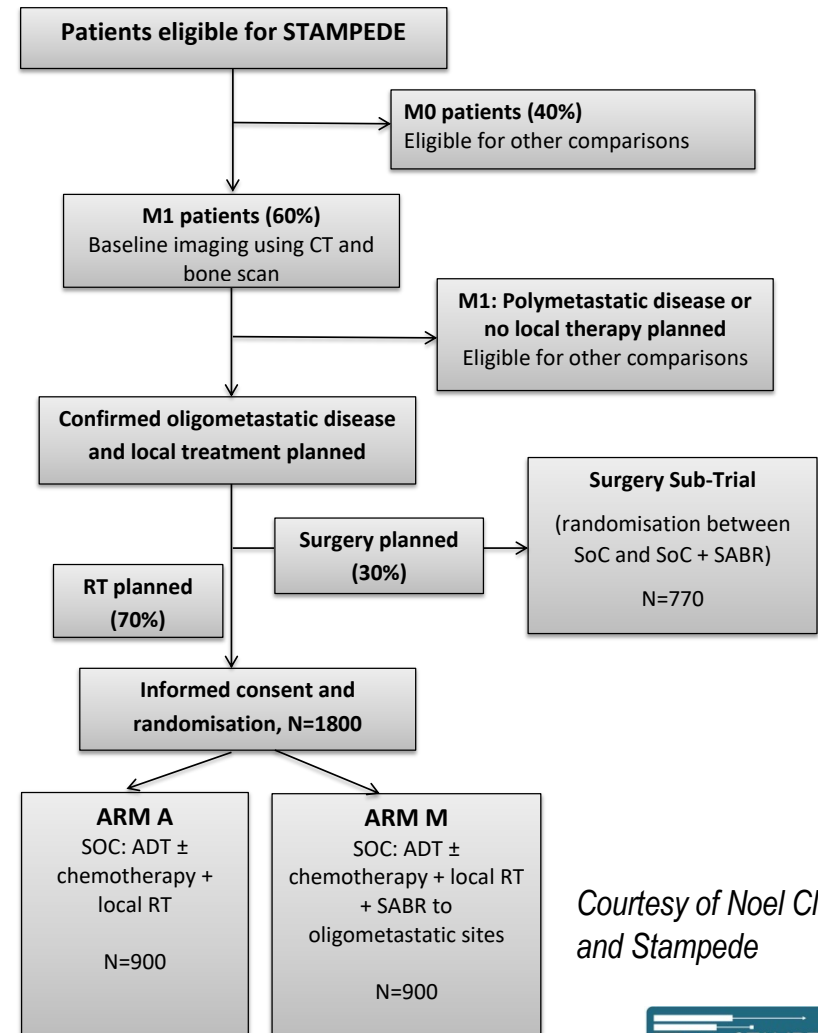
- Trial powered on the established SOC:
Local RT+ Systemic Treatment

Final outcome = Overall Survival

Target HR = 0.75

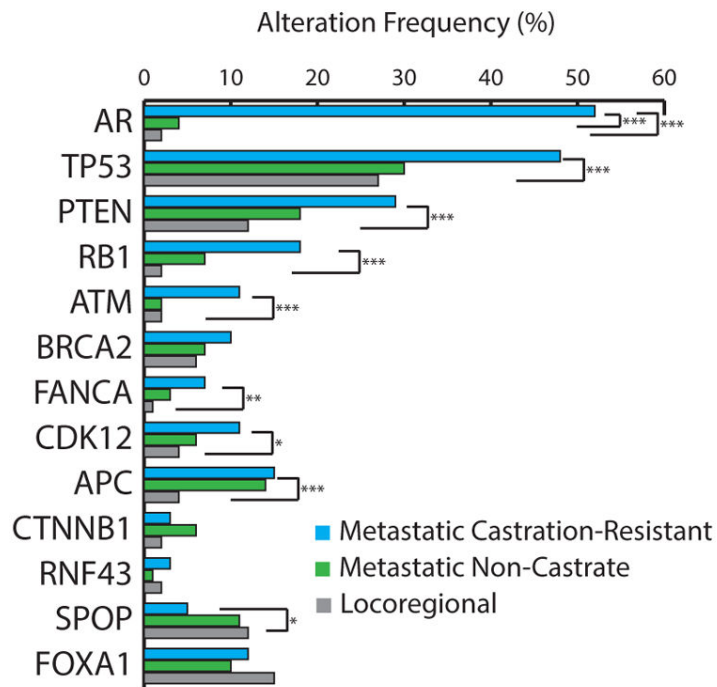
Target for Radiotherapy Treated = 1800
patients (6 years recruitment, 2 years
FU)

-sub-stratify 1-3 vs 4-5 mets and pelvic
lymph node radiotherapy

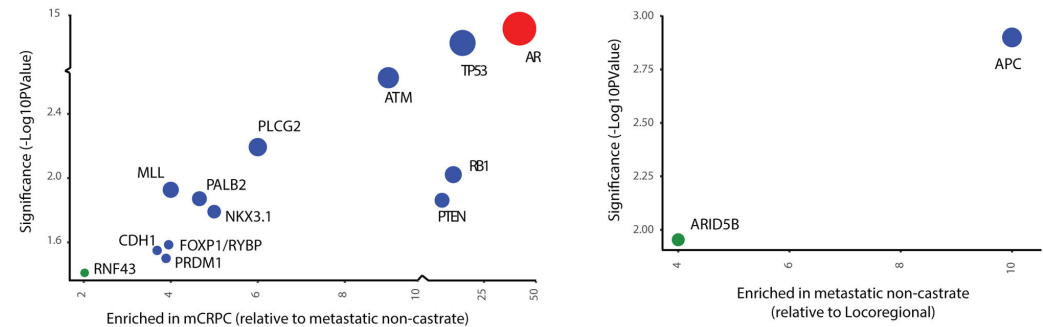


*Courtesy of Noel Clarke
and Stampede*

Do We Know The Biological State of the M1 HSPC Disease We Are Treating ?



Abida et al; JCO 2017



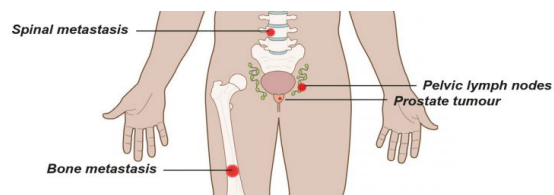
Paucity of data on the genomic and immune cell heterogeneity within untreated primary and metastases in N1 and M1 disease

- MOVEMBER Gap6 project
- Combi-Mets Study-Chris Hovens
- (Pan-Prostate Cancer Genomics Group)

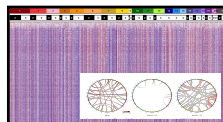
TxNxM1 Disease at MANCHESTER MDTs



*PIMO to label hypoxic cells
mpMRI and PSMA*



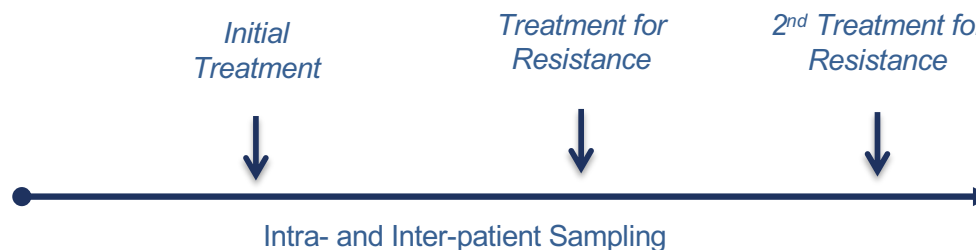
Primary Tissues- Localised High Risk
Primary Tissues- mCSPC/mCrpc
Metastatic Samples-lymph nodes
and bone mets)



NEW GENOMIC Data

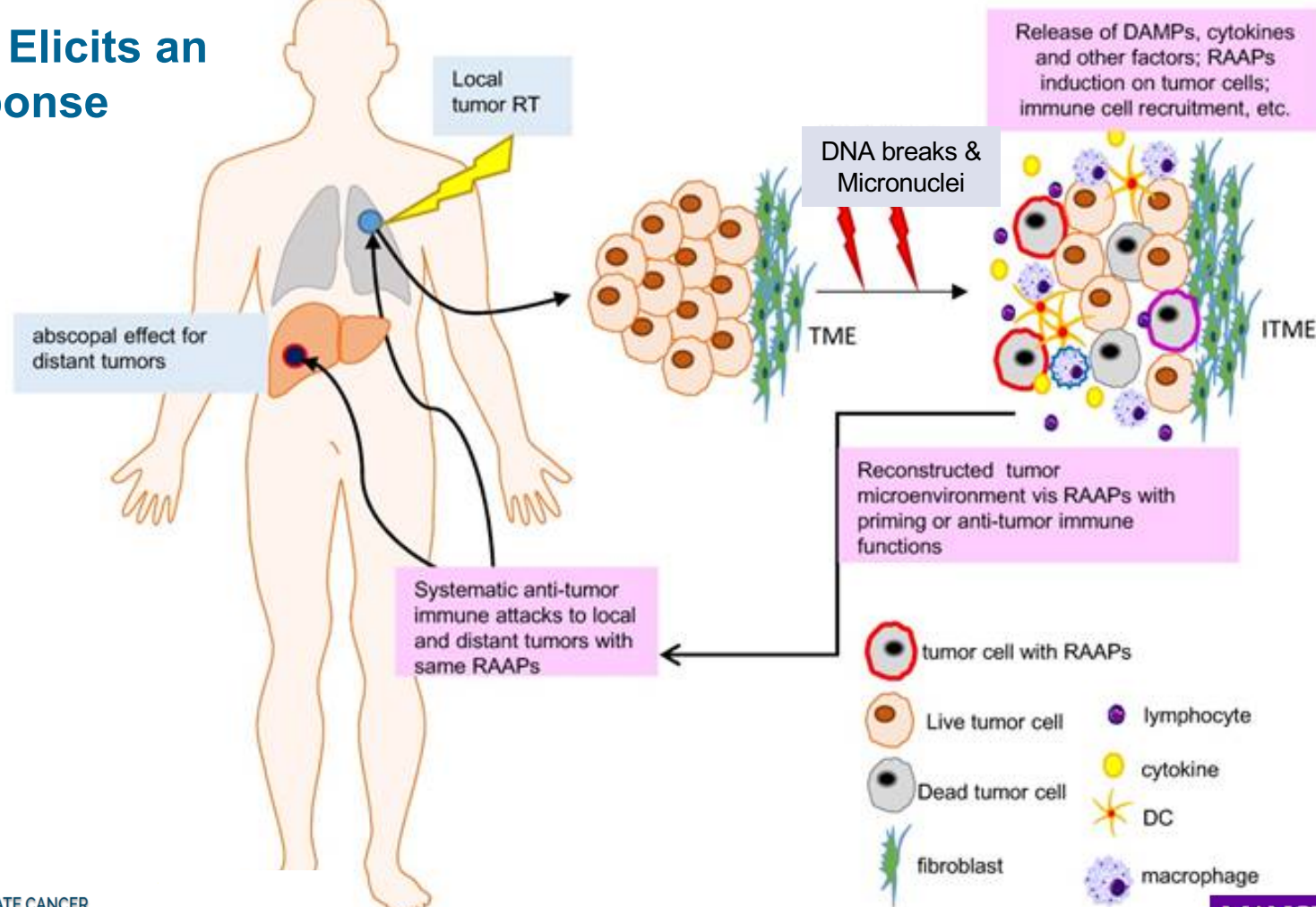
Untreated bone mets
Untreated lymph node mets
ctDNA for genetic instability

HYPROGEN: TME heterogeneity and resistance signals



OCTOBER 2019 with Oing, Gillessen, Clarke

Radiotherapy Elicits an Immune Response



Some Conclusions

LEVEL 1 Evidence

- **RT should be added to SOC systemic therapy in newly-diagnosed M1 (low) prostate cancer**
 - consider similar treatment for patients with N1 disease (retrospective data and this trial results with extrapolation)
 - SOC: ADT plus docetaxol or ABI - awaiting PEACE-1
 - RT is a treatment that is effective for OS and relatively inexpensive (if prostate RT alone)
 - RT is well-tolerated even with 36Gy/6: important concept for increasing ageing population with co-morbidities
- Surgical trials ongoing to determine if removal of prostate gives similar result:
 - appears to be well tolerated
 - important to continue these trials as will validate approach
 - if similar OS effect not observed, supports that the translational biology rests solely with RT

***It's not yet about choice;
hopefully soon it will be about biology***

Some Speculations

- **Future trials should answer questions regarding roles for:**
 - different RT and surgical volumes (pelvic lymph nodes?)
 - surgery versus radiotherapy
 - modern imaging
 - germline changing systemic therapies (including immunotherapy)
 - increased efficacy of ablative therapies and heterogeneity in responses
- **More information required regarding the biology:**
 - do HS metastases have altered microenvironments
 - immunolandscape- prior to and during therapy
 - missing information on genetics of mCSPC for nodal and bone metastases