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Cancer Center

De-novo oligometastatic disease:
Consensus and controversy on aims, options, and rationale

Michael J. Morris, MD

Prostate Cancer Section Head

www. MSKCC.org

Conflicts of Interest

- Uncompensated consultant: Astella, Bayer, Endocyte
- Compensated: Advanced Accelerator Applications, Blue Earth, Tokai, Tolmar, Oric
- Research (institutional): Bayer, Sanofi, Endocyte, Progenics, Corcept, Roche/Genentech

De novo oligomets: a unique treatment opportunity

- Untreated primary
- Untreated metastatic disease
- Limited distribution
- Prolonging OS or achieving cure is probably most feasible when attempted early – before lethal treatment-related biology emerges

AR-directed therapy improves OS in M1 Disease

- Data is the *best level evidence that we have in medicine*: mutually supportive well conducted phase III randomized prospective trials

Trial	Population	Regimen	Primary Endpoint	HR
Stampede James NEJM 2017	Mo and M1	ADT vs. ADT/AAP	OS	0.63 (0.52-0.76)
Latitude Fizazi NEJM 2017	M1, High Risk	ADT vs. ADT/AAP	OS	0.62 (0.51-0.76)
Enzamet Davis, NEJM 2019	M1, All comers	ADT vs. ADT/Enza	OS	0.67 (0.52-0.86)
Titan Chi NEJM 2019	M1, All comers	ADT vs. ADT/Apa	OS	0.67 (0.51-0.89)

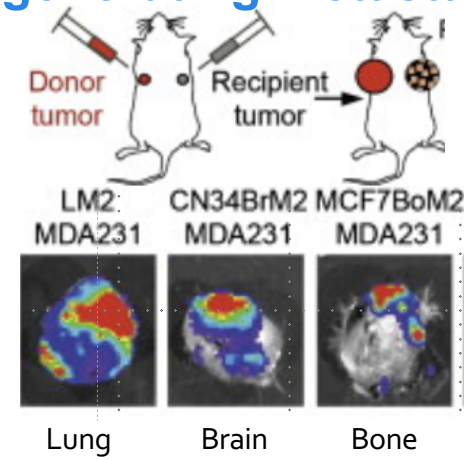
Mixed data re: docetaxel: oligomets are a subset of "low-volume/low risk"

Study	Population	HR
STAMPEDE	Mo and M1	HR=0.78 (0.66-0.93); *P*=.006
CHAARTED	Total pop	HR=0.73 (0.59-0.89); *P*<.0018
	High volume	HR=0.63 (0.50-0.79); *P*<.0001
	Low volume	HR=1.04 (0.70-1.55); P=.86
Getug 15	Total pop	HR=0.88 (0.68-1.14); *P*=.3
	High volume	HR=0.78 (0.56-1.09); *P*=.14
	Low volume	HR=1.02 (0.67-1.55); *P*=.9

Sweeney C, Annals of Oncology 27, 2016
Sweeney CJ, N Engl J Med 373:737-746, 2015
James ND The Lancet 387:1163-1177, 2016
Fizazi K N Engl J, 2017

The primary may be an active participant in tumor self seeding and generating metastatic disease

A



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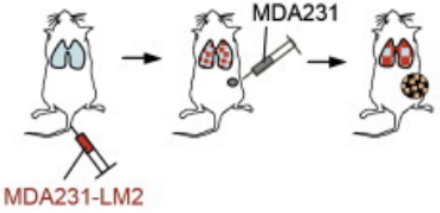

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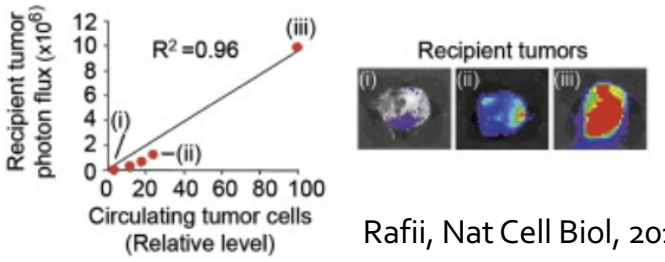

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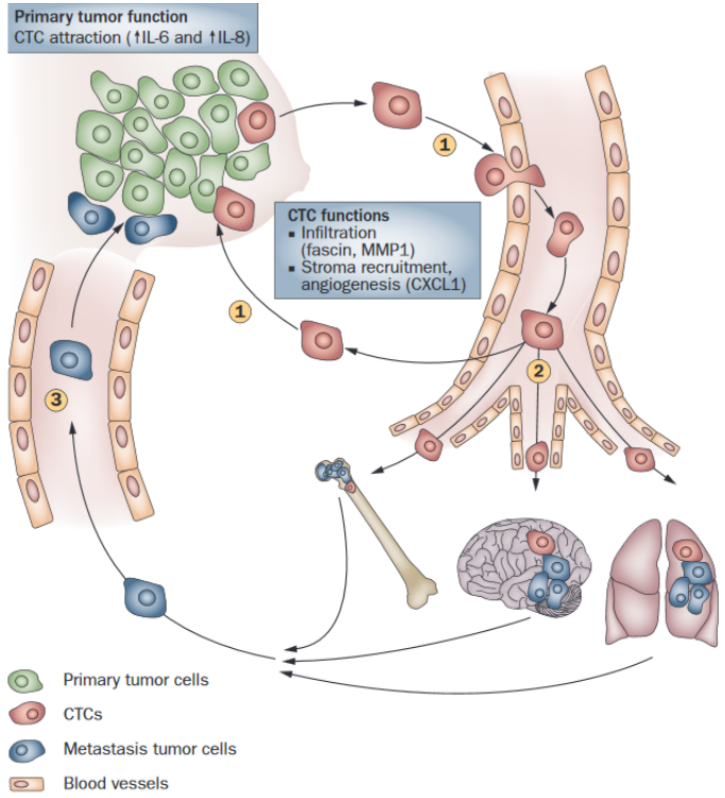

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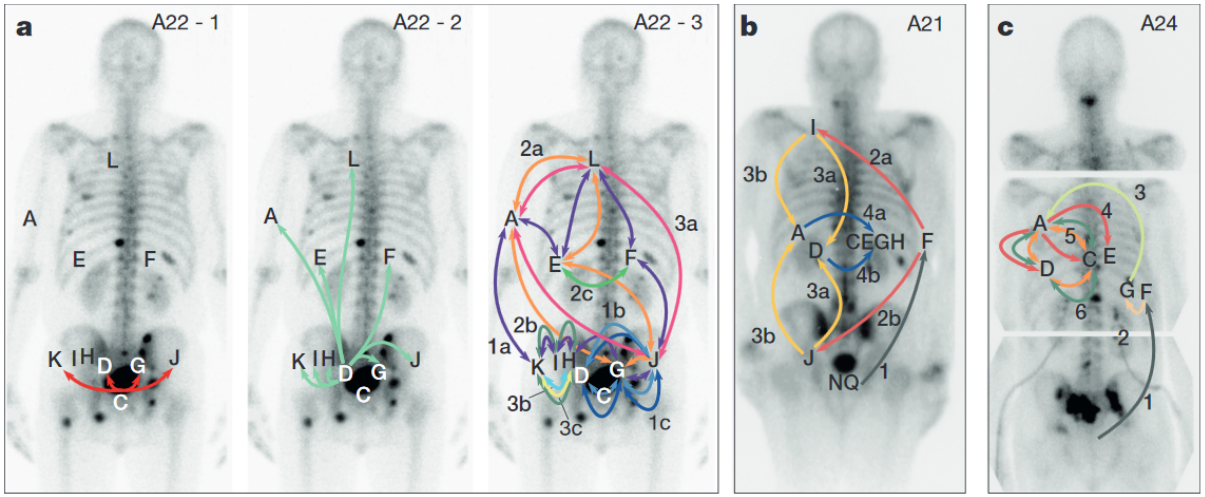
Rafii, Nat Cell Biol, 2010; Kaplan, Nature, 2006; Comen, Norton, Massague, Nat Rev Oncol 2011; Kim, Cell, 2009

LETTER

doi:10.1038/nature14347

The evolutionary history of lethal metastatic prostate cancer

Gunes Gundem[1], Peter Van Loo[1,2,3], Barbara Kremeyer[1], Ludmil B. Alexandrov[1], Jose M. C. Tubio[1], Elli Papaemmanuil[1], Daniel S. Brewer[4,5], Heini M. L. Kallio[6], Gunilla Högnäs[6], Matti Annala[6], Kati Kivinummi[6], Victoria Goody[1], Calli Latimer[1], Sarah O'Meara[1], Kevin J. Dawson[1], William Isaacs[7], Michael R. Emmert-Buck[8]†, Matti Nykter[6], Christopher Foster[9], Zsofia Kote-Jarai[10], Douglas Easton[11], Hayley C. Whitaker[12], ICGC Prostate UK Group‡, David E. Neal[12,13]§, Colin S. Cooper[4,10]§, Rosalind A. Eeles[10,14]§, Tapio Visakorpi[6], Peter J. Campbell[1], Ultan McDermott[1]§*, David C. Wedge[1]* & G. Steven Bova[6]§*



A - L. humerus BM
D - Sem. vesicle
C - Prostate
E - L. adrenal

F - R. adrenal
G - Bladder
H - Pelvic LN
I - L. pelvic LN

J - R. pelvic LN
K - L. pelvic LN
L - L. media. LN

A - L. rib
C - Liver
E - Liver
G - Liver
H - Liver
D - L. adrenal
F - R. rib nod.
I - L. clavicle
J - L. iliac crest
N - GL5 EPE
Q - GL3/5

A - R. axillary LN
C - R. diaphragm
D - R. rib
E - Xiphoid
F - L. lobe liver
G - Falciform ligam.

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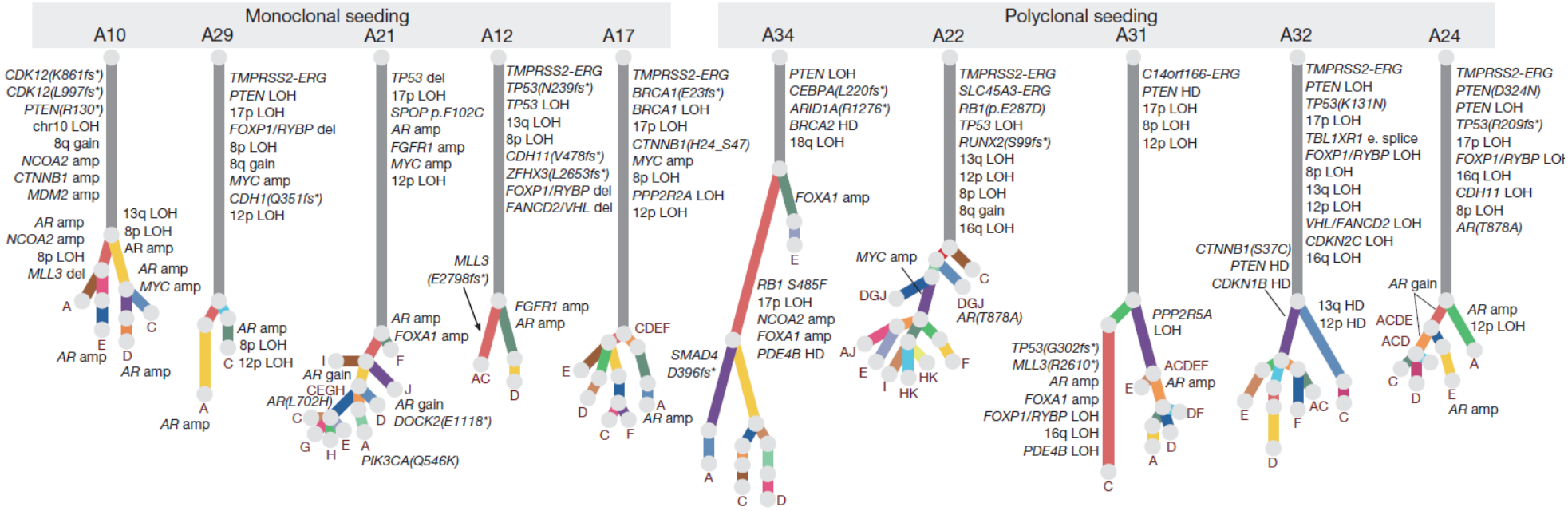
WGS reveals the cross pollination of metastatic disease (mCRPC)



Mets were often more similar to each other than the primary

Similar mets were often in geographic proximity (interclonal cooperativity)

Gundem, Nature 2015

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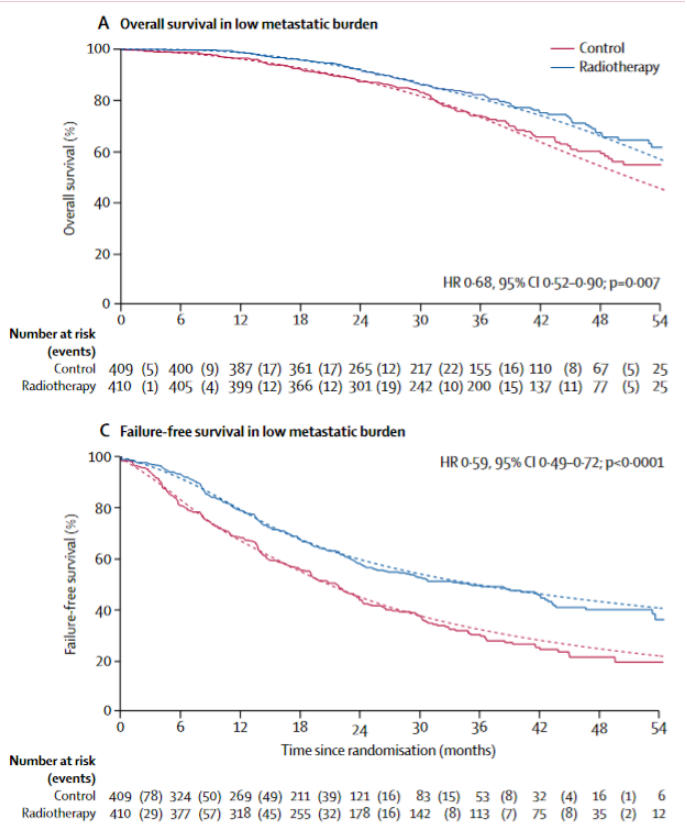
RT to the primary: STAMPEDE



Low volume: n=819 (1694)

Parker, Lancet, 2018

- Built on Horrad data (small study that only was suggestive)
- SOC +/- RT to primary
- Powered to assess low volume disease independent of the larger treatment group
- Weekly vs. daily RT schedules
- ADT was SOC (18% received doce)

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Confirmatory studies are pending

Study	N	Population	Treatment	Endpoint
PEACE-1 NCT01957436	1156	De Novo M1, all comers	Comparator: SOC (ADT +/- doce) SOC + AAP SOC + RT SOC + AAP/RT	OS
SWOG 1802 NCT03678025	1273	De novo, all comers	SOC +/- RP or EBRT	OS
TRoMbone ISRCTN15704862	50	1-3 osseous lesions (standard), no visceral	SOC +/- RP	Feasibility
G-RAMPP NCT02454543	452	1-4 osseous mets, no PET, no visceral	SOC +/- RP	Cancer specific survival

Metastasis directed therapy vs. none

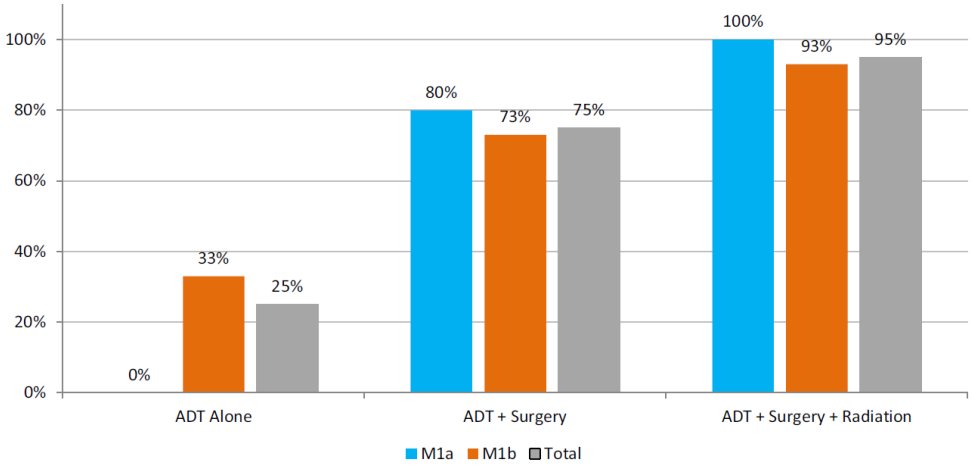

Table 3. Clinical response and primary end point

	Total N = 20	M1a N = 5	M1b N = 15
Time of follow-up (mo) median (range)	40 (17-89)	34 (18-40)	47 (17-89)
Time off ADT (mo) median (range)	9 (0-54)	6 (0-15)	9 (0-54)
PSA ≤.05 ng/mL at 12 months			
Castrate	10 (50%)	3 (60%)	7 (47%)
Non-castrate*	2 (10%)	0 (0%)	2 (13%)†
PSA ≤.05 ng/mL at 20 months			
Castrate	6 (30%)	2 (50%)†	4 (27%)†
Non-castrate*	4 (20%)	0 (0%)†	4 (27%)†

Abbreviations as in Table 1.
* Non-castrate defined as >150 mg/dL serum testosterone level.
† One patient did not have a serum testosterone assessment at the 12-month mark.
‡ One patient has not met the 20-month mark.

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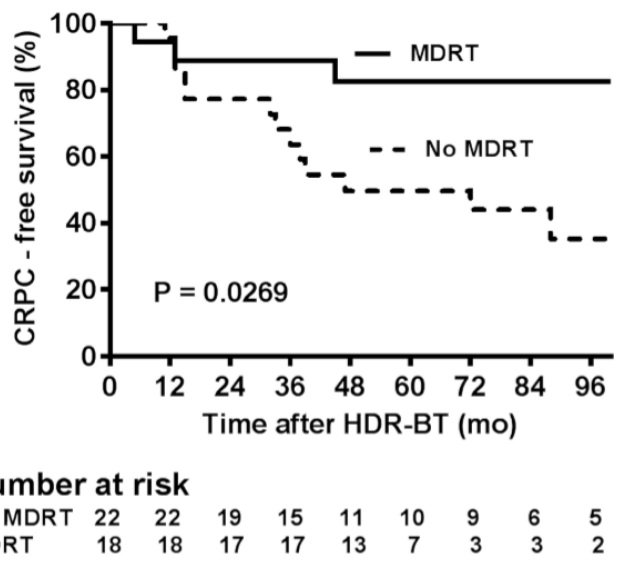

Is CRPC-free survival relevant at all?

O'Shaughnessy, J Urol 2016; Tsumura, et al, Prostate, 2018;

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Trials testing RT to metastatic sites and treating the primary with systemic therapy

Protocol	N	Population	Treatment	Endpoint
VA (USA) NCT03298087	28 (ph 2)	1-5 mets on imaging (PSMA permitted)	RP, ADT x 6 mo's, SBRT, sRT if ≥pT3a	PSA<0.05 at 6 mo's post T recovery
ARTO (Italy) NCT03449719	174 (Rand ph 2)	<3 metastatic sites	SOC local therapy, AAP +/- SBRT	PSA failure rate at 6 mo's (>50% from baseline)
PLATON Canadian NCT03784755	410 Ph 3	≤ 5 mets	SOC local/systemic therapy +/- SBRT to all disease sites	FFS
Metacure cohort B1 NCT03436654	76 Ph 2	≤3 RT isocenters	ADT/apa +/- abi, RP, SBRT, sRT	Path CR
STAMPEDE	Pending	N+M1 <5 mets (no PET)	SOC dealer's choice, surg or RT to prostate +/- pelvis, +/- SABR to mets	OS

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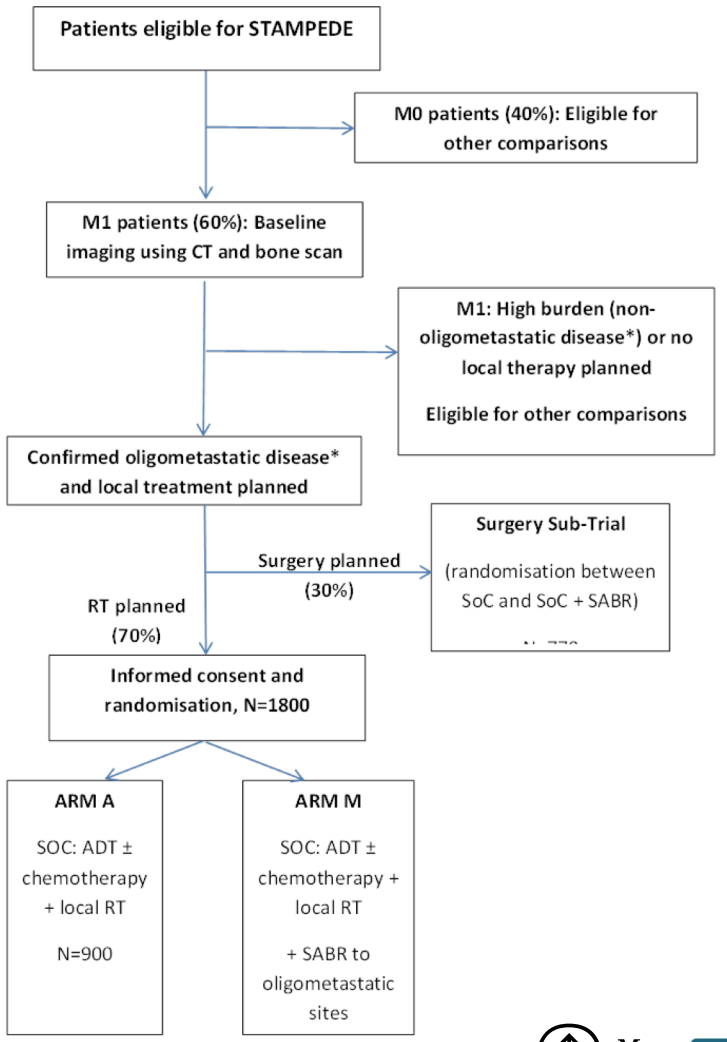
31-Aug-19

Trial schema for the oligometastatic comparison

STAMPEDE Arm M



** Oligometastatic disease defined as patients with 5 or fewer extra-pelvic metastases in lymph node, as detected on baseline CT and bone scan*

Slide courtesy of Nick James

Conclusions:

- These are a subset of M1 patients with the primary in place
- No justification for denying these patients systemic therapy – level 1 data, confirmed many times over
  - Duration of therapy remains an open question
- Rationale and data support RT to primary
  - Confirmatory studies needed and are underway
- RT to mets
  - Anecdotal. Not SOC
  - No definitive prospective data
  - Need real endpoints that we can interpret
    - Feel, function, survive or a validated interim endpoint