Advances in Non-Hormonal Therapy for Advanced Prostate Cancer

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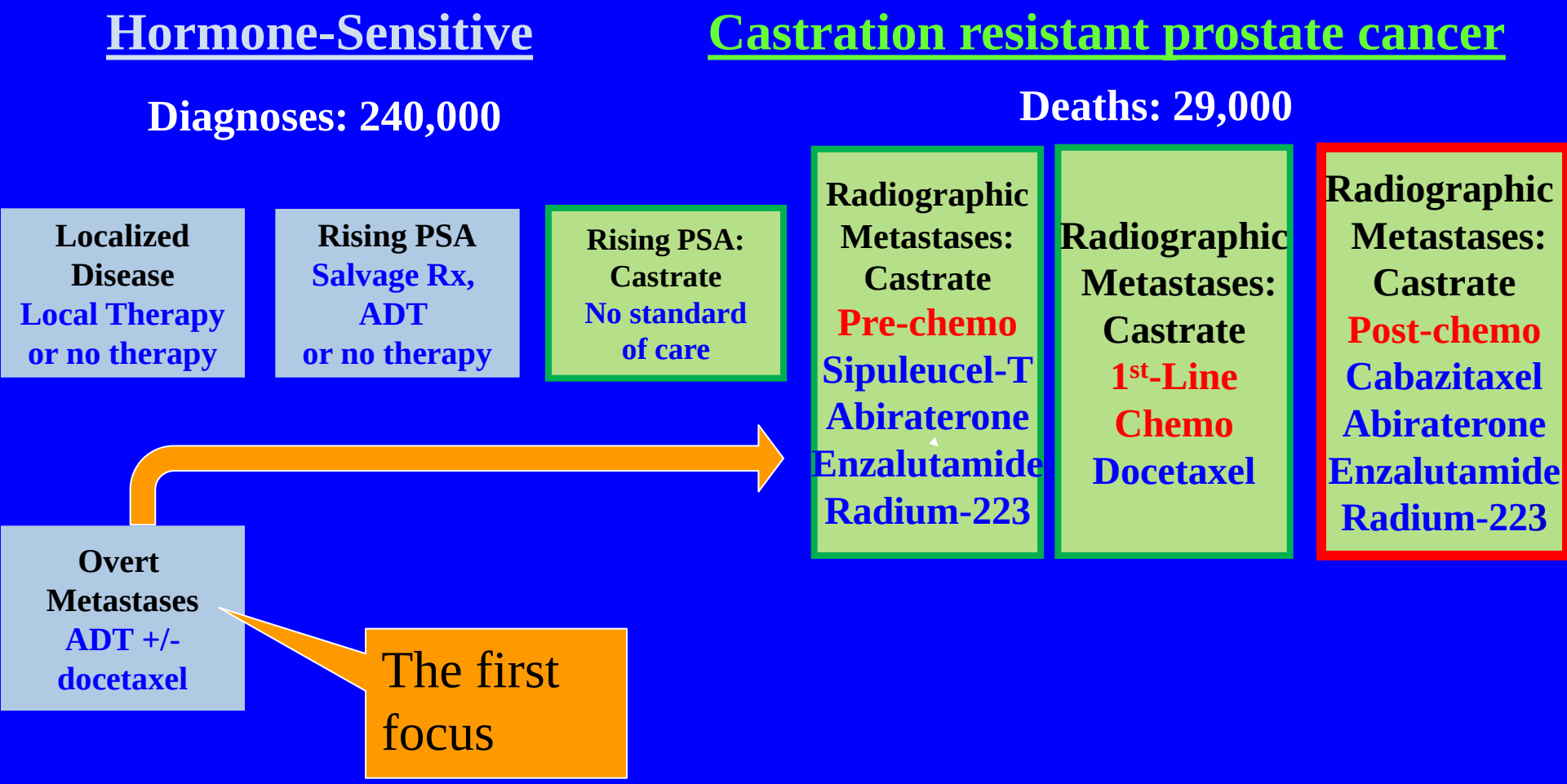
Prostate Cancer Clinical States



Charles B. Huggins: Nobel Prize 1966

For discoveries related to the treatment of prostate cancer in 1941

The NEW ENGLAND JOURNAL of MEDICINE

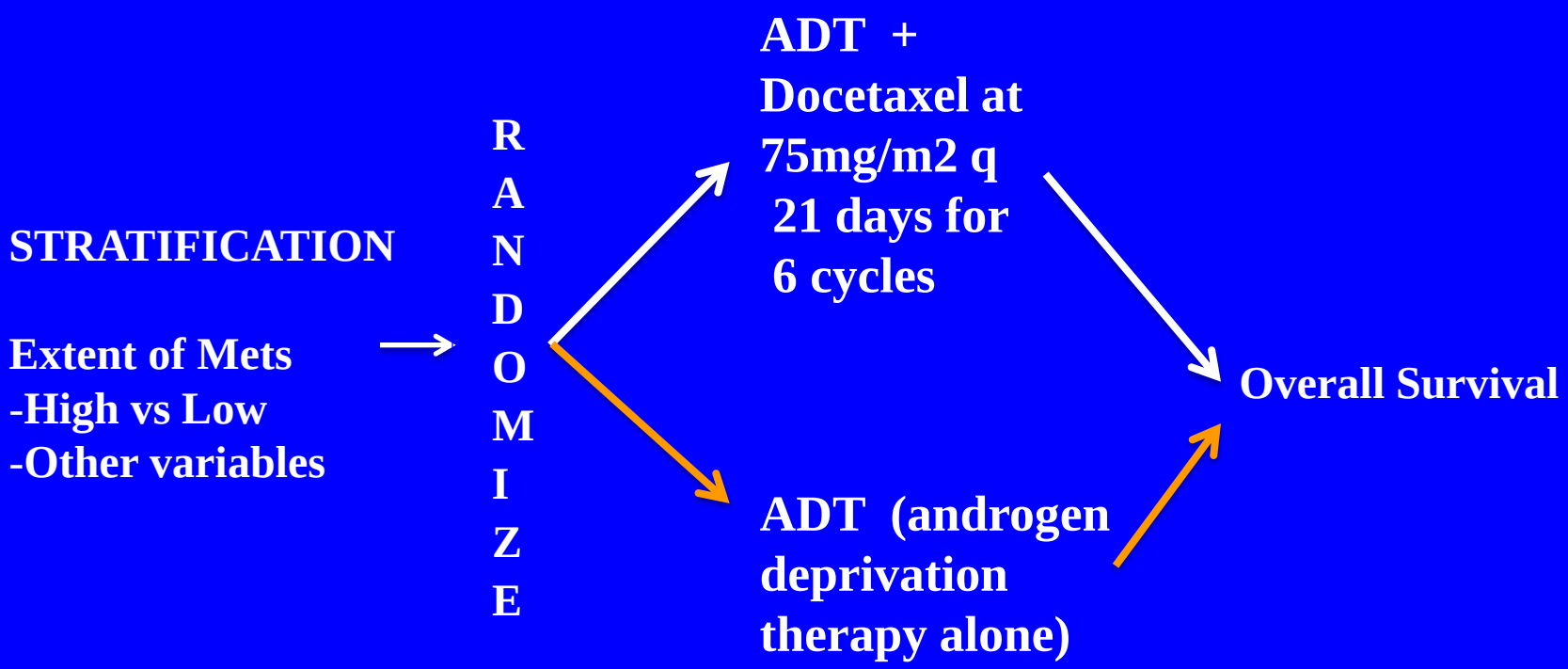
ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

August 5, 2015

CHAARTED Treatment for Metastatic Hormone Sensitive Prostate Cancer



- ADT allowed up to 120 days prior to randomization
- Standard dexamethasone premed but no daily prednisone

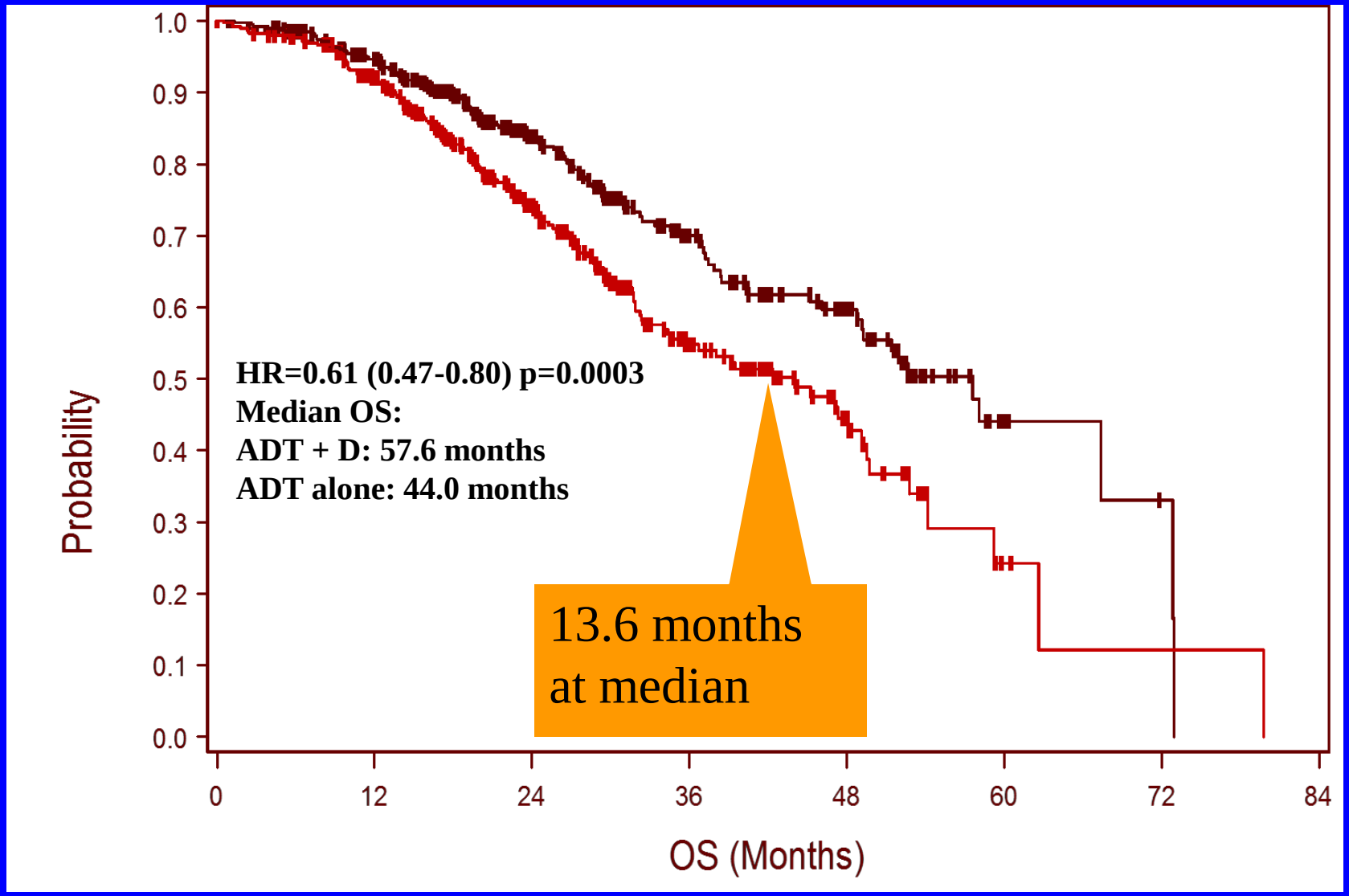
E3805 Definition of High Volume

- **High volume:**
  - **visceral metastases**

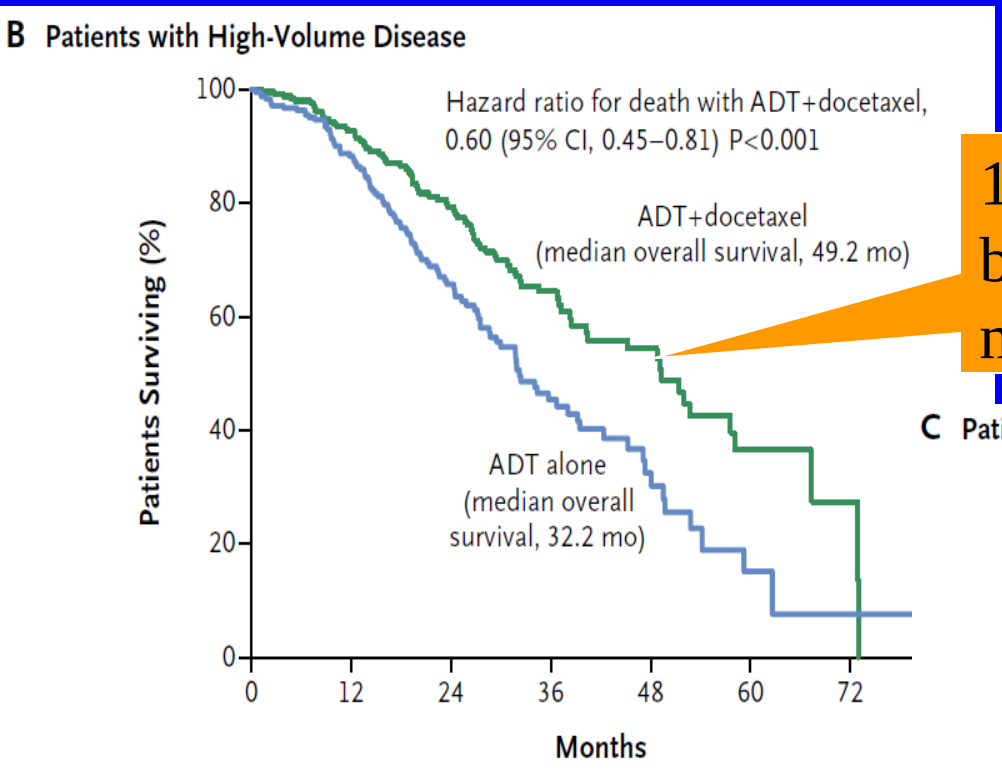
    and/or
  - **4 or more bone metastases with at least 1 beyond pelvis and vertebral column**

- **At inception, only patients with high volume disease were to be accrued**

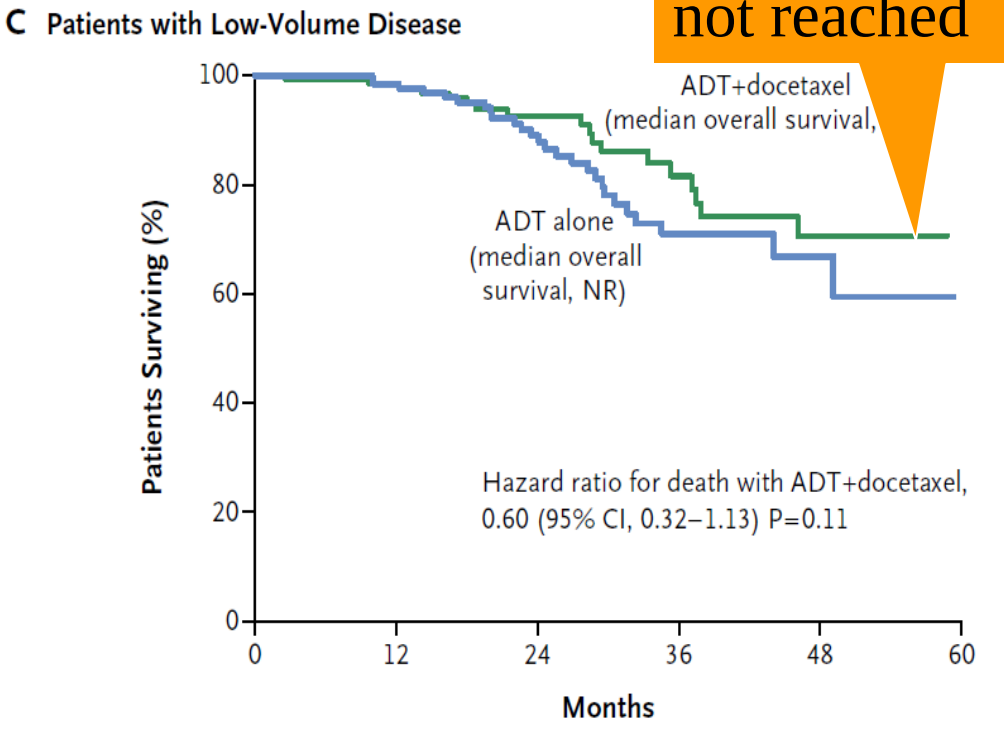
CHAARTED Primary endpoint: Overall survival



CHAARTED:
Survival by extent of metastatic disease



17 months better at median



Median OS not reached

Hematologic Toxicity (%)

	ADT + Docetaxel (N=397)		
Grade	**3**	**4**	**5**
Anemia	1	<1	-
Thrombocytopenia	-	<1	-
Neutropenia	3	9	
Febrile neutropenia	4	2	
Infection with neutropenia	1	1	
Worst grade heme and non-heme toxicity per patient	16%	12%	1 patient

8% Grade 3-4 neutropenia with fever or infection

CHAARTED Conclusion

- High volume metastases, but not low volume, benefit from the addition of docetaxel to conventional ADT for metastatic disease

- Low volume patients may benefit but event rates are inconclusive at this time

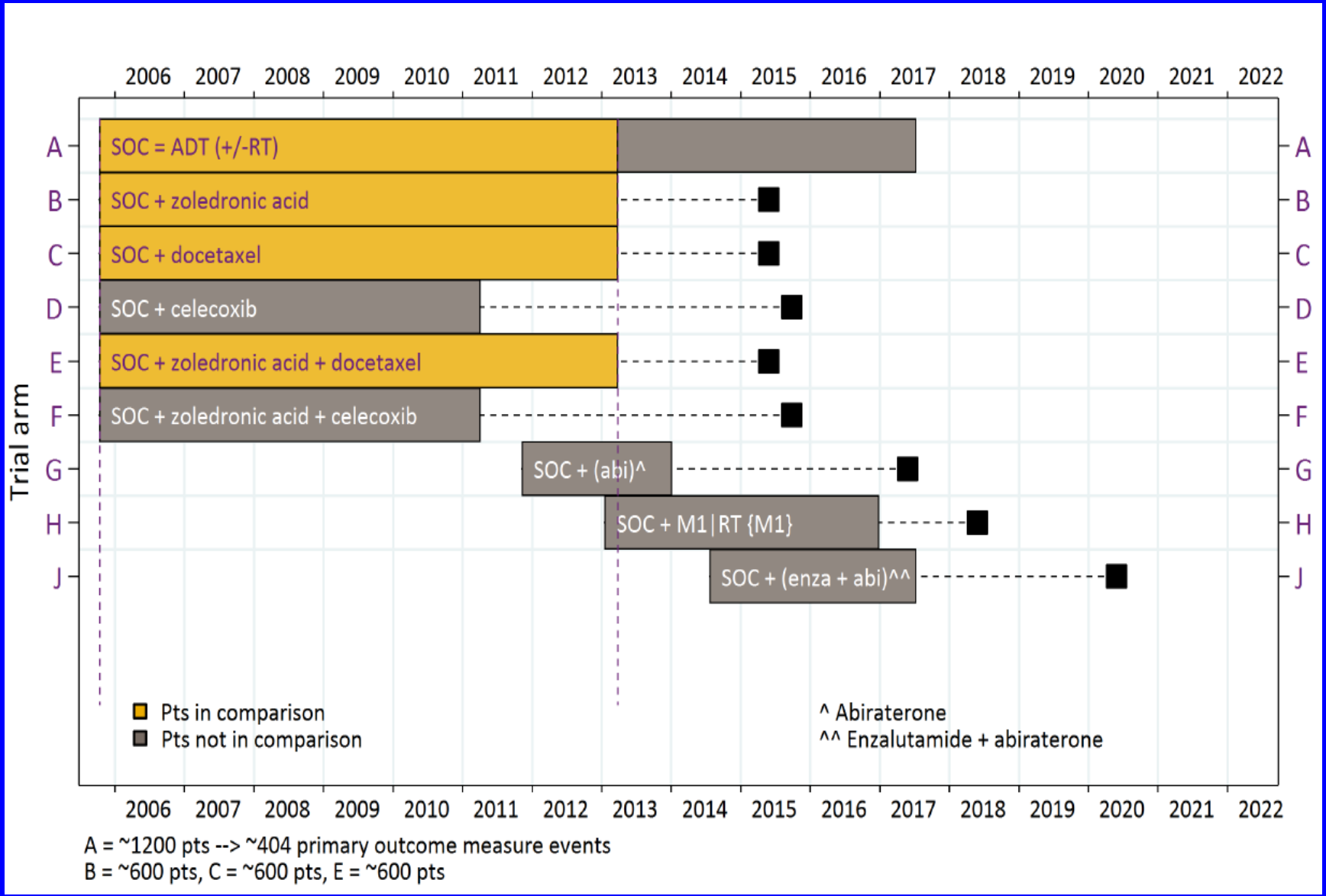
Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First survival results from STAMPEDE

Nicholas James
University of Warwick and Queen Elizabeth Hospital Birmingham
on behalf of

Matthew Sydes, Malcolm Mason, Noel Clarke, David Dearnaley, Melissa Spears, Robin Millman, Chris Parker, Alastair Ritchie, J. Martin Russell, John Staffurth, Robert Jones, Shaun Tolan, John Wagstaff, Andrew Protheroe, Rajaguru Srinivasan, Alison Birtle, Joe O'Sullivan, Richard Cathomas, Mahesh Parmar and the STAMPEDE Investigators

ASCO 2015 oral presentation

The Amazing STAMPEDE Trial: How do they do that?



Patient characteristics

1%	WHO PS 2	[s]
21%	WHO PS 1	[s]
65yr	Median age (min 40, max 84)	[s]
61%	Metastatic (85% Bony mets)	[s]
15%	N+M0	
24%	N0M0	

Accrual

Comparison

Open: Oct-2005

Closed: Mar-2013

Accrual: 2962

Number of patients

1184 **A** Standard-of-care (SOC)

593 **B** SOC + zoledronic acid

592 **C** SOC + docetaxel

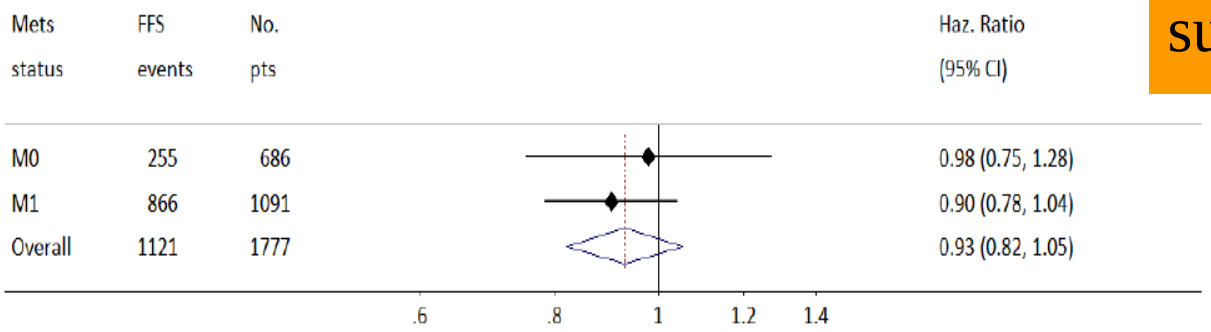
593 **E** SOC + zoledronic acid + docetaxel

Treatment effect by metastatic status: FFS

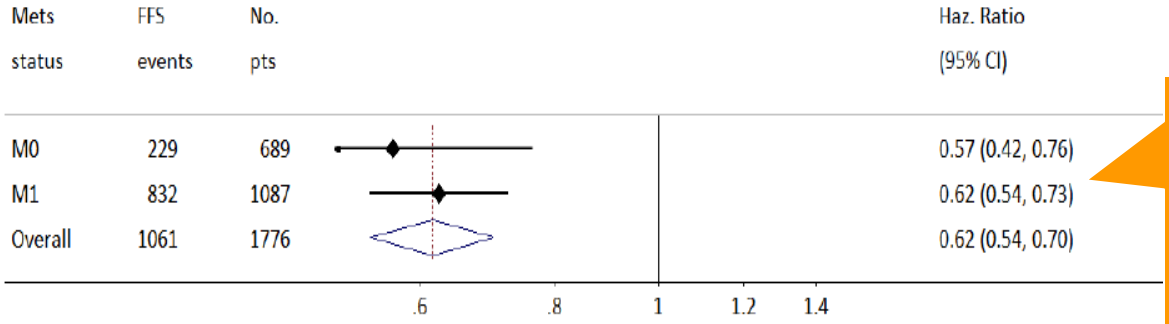
Pre-planned analysis

Failure-free survival

+ZA

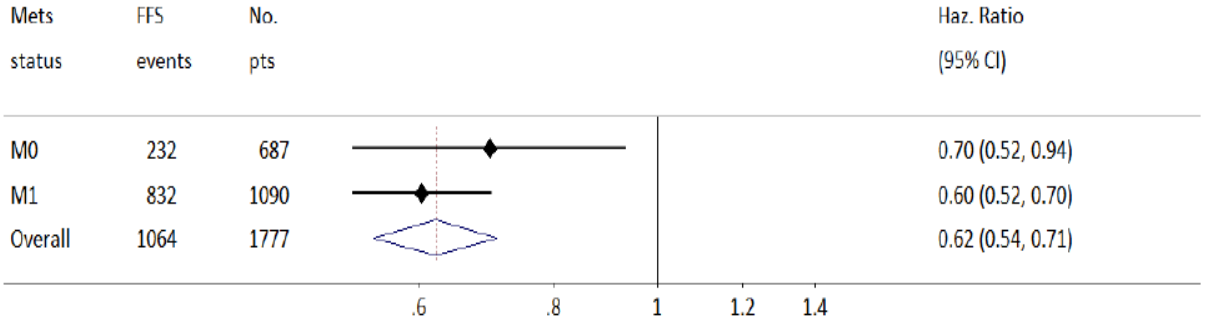


+Doc



HR=0.57 for M0 and 0.62 for M1

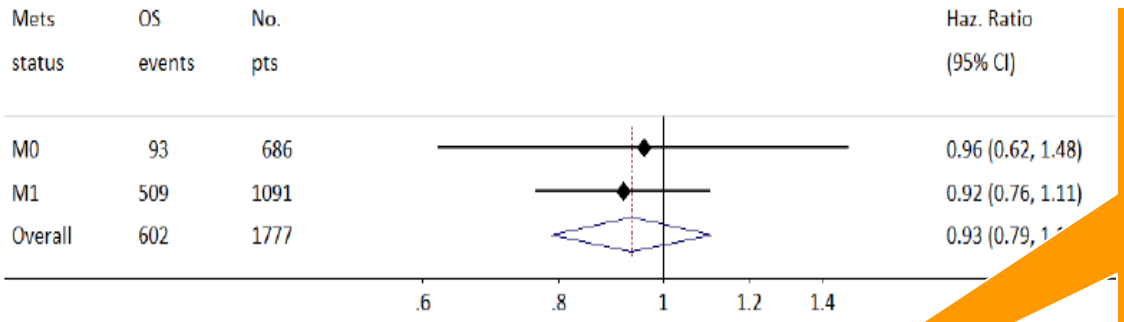
+ZA+Doc



Treatment effect by metastatic status: Overall survival

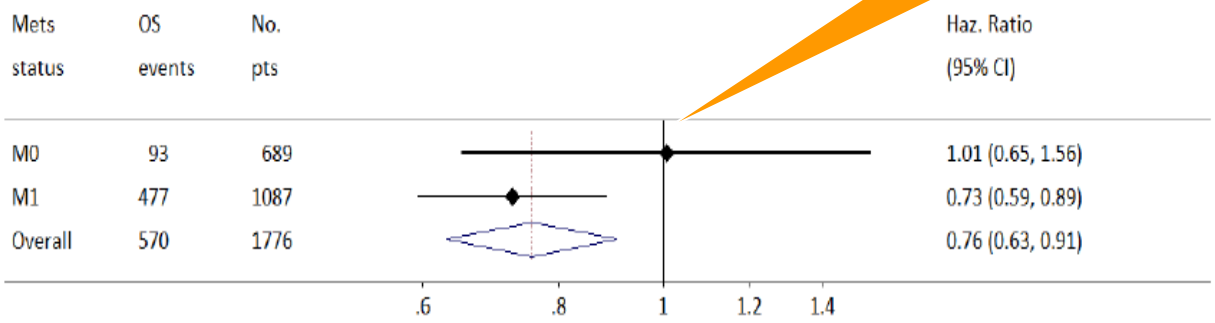
Pre-planned analysis

+ZA

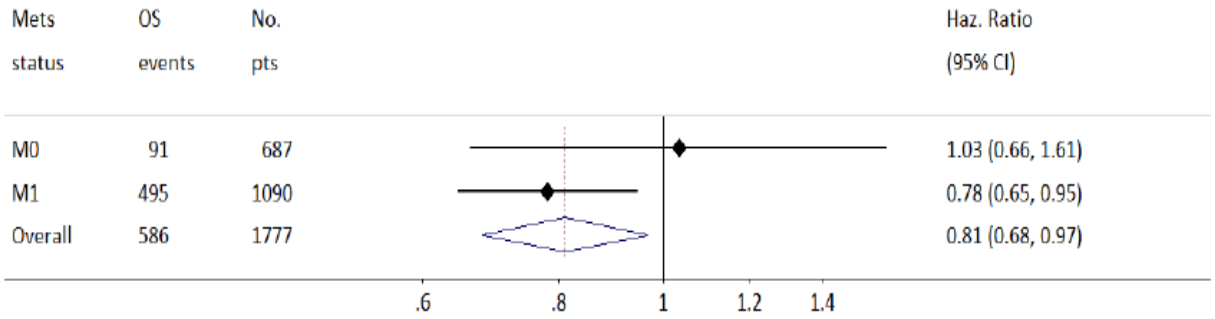


HR=1.01 for M0 disease but 0.73 for M1

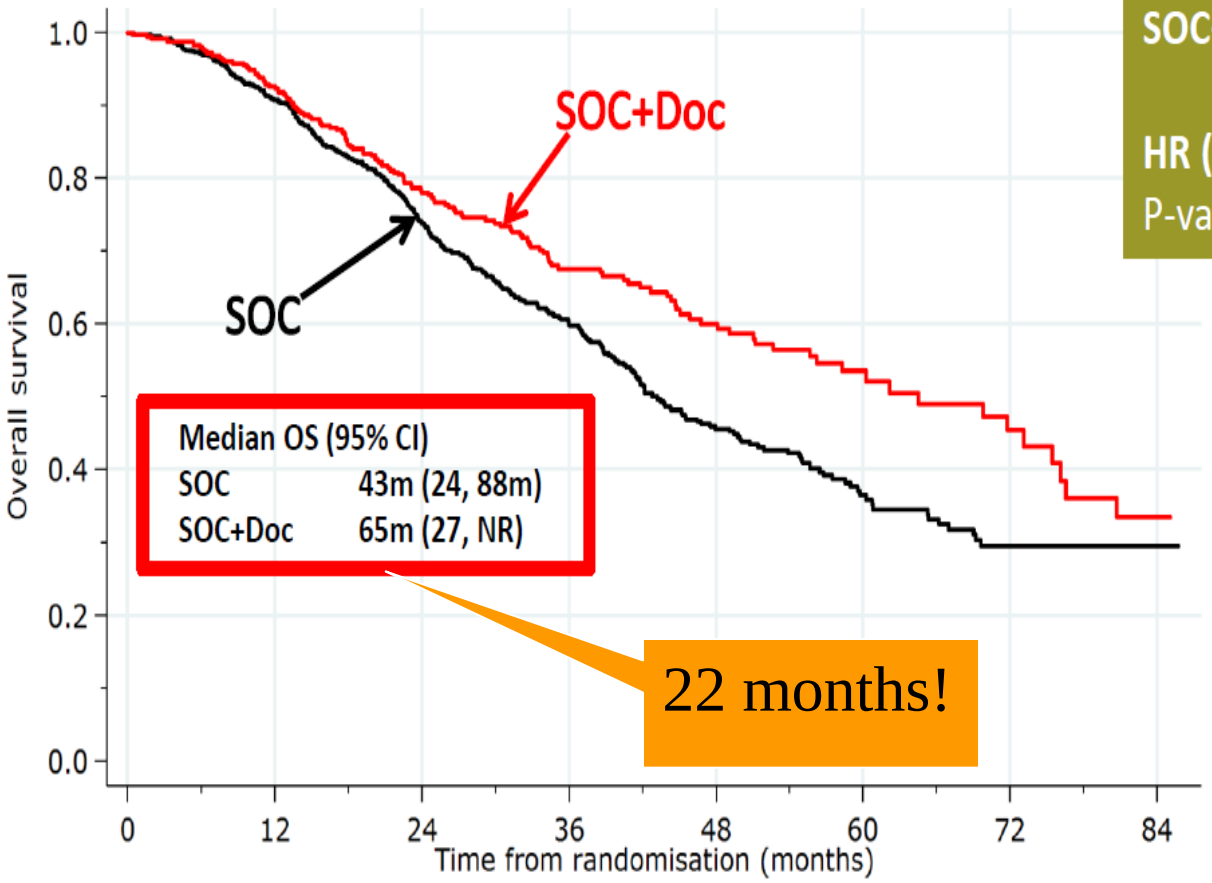
+Doc



+ZA+Doc



Docetaxel: Survival – M1 Patients



Group														
At risk (events)														
SOC	725	(66)	645	(117)	469	(75)	254	(52)	134	(21)	58	(10)	24	(0)	10
SOC+Doc	362	(27)	326	(49)	242	(27)	151	(13)	91	(8)	37	(5)	24	(5)	9

SOC	**343 deaths**
SOC+Doc	**134 deaths**
HR (95%CI)	**0.73** (0.59, 0.89)
P-value	**0.002**

Non-PH p-value 0.23

Restricted mean OS time

SOC	49.3m
SOC+Doc	56.1m
Diff (95%CI)	6.8m (2.8, 11.0m)

Grade 3+ adverse events ever reported

		A *SOC*	B *SOC+ZA*	C *SOC+Doc*	E *SOC+ZA+Doc*
Patients randomised		1184	593	592	593
Patients with adverse event data		1174	587	579	564
Grade 3-5 AE (G5)	N	363 (3)	185 (1)	291 (3)	294 (7)
	%	31%	31%	51%	52%
Endocrine disorder		12%	12%	10%	12%
Blood and lymphatic *(febrile neutropenia)*		1%	2%	12%	12%
Blood/bone marrow *(neutrophils)*		1%	1%	12%	11%
General disorder		4%	5%	8%	11%
Musculo-skeletal		5%	5%	6%	
Gastrointestinal disorder		3%	3%	7%	
Renal		5%	4%	4%	6%

12% notable

Upfront Chemotherapy for Hormone-Sensitive Metastatic Prostate Cancer

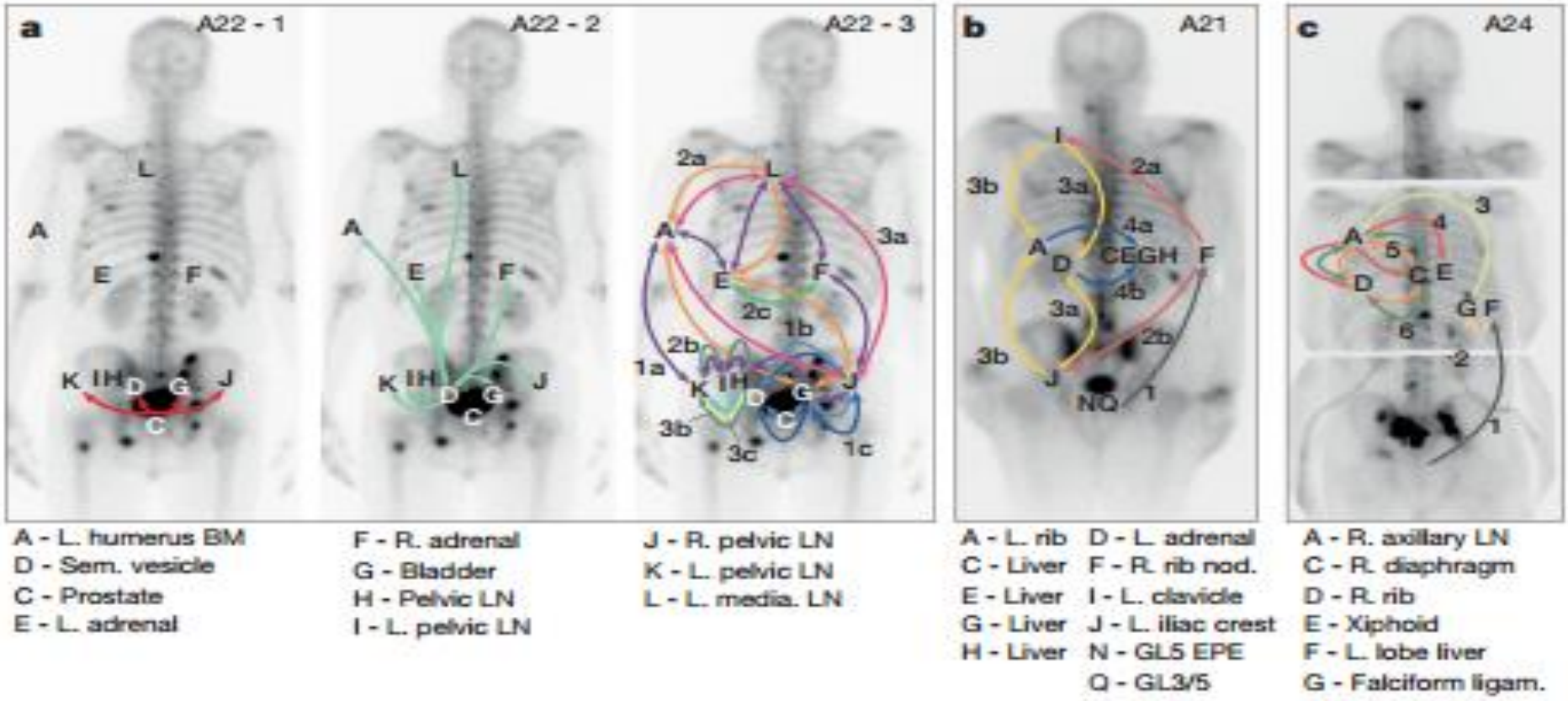
- ADT + docetaxel is the new standard of care for men with hormone-sensitive metastatic prostate cancer
- The Brits did not address the high risk disease versus low risk disease issue
- Low risk disease in CHAARTED is too premature to comment
- Non-metastatic in STAMPEDE is too premature to comment but FFS clearly better

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]§*



If metastases are the source of additional metastases, then attempts to eradicate early metastatic disease makes sense

If one eradicates visible metastases, should the primary be ignored?

Oligometastatic Disease

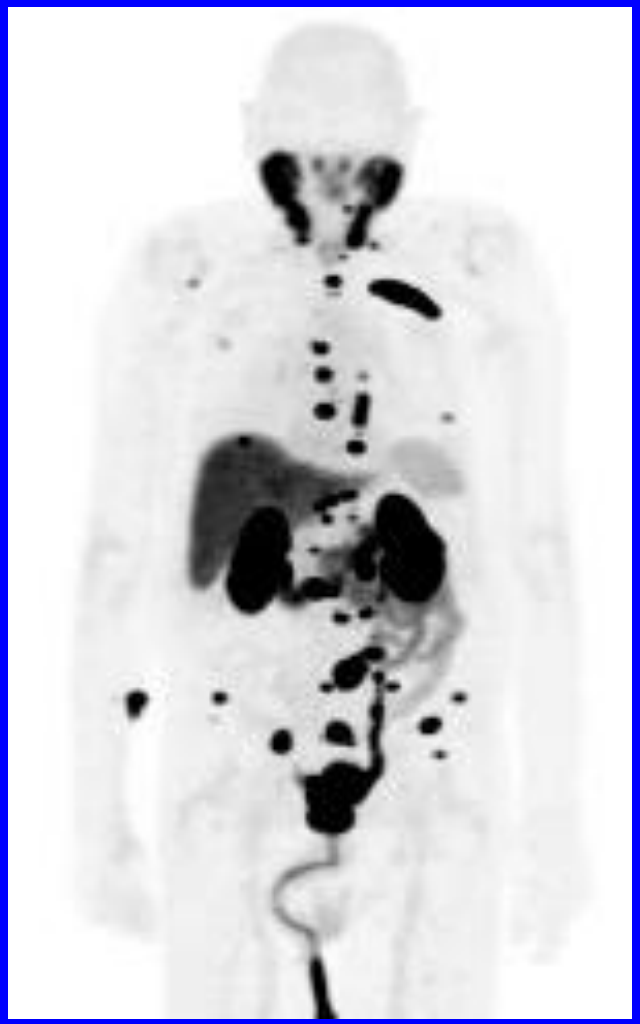
- How do we define?
  - Less than 3 mets? Less than 5 mets?
- Imaging is key
  - Old versus new imaging
  - What we see depends on how we look!

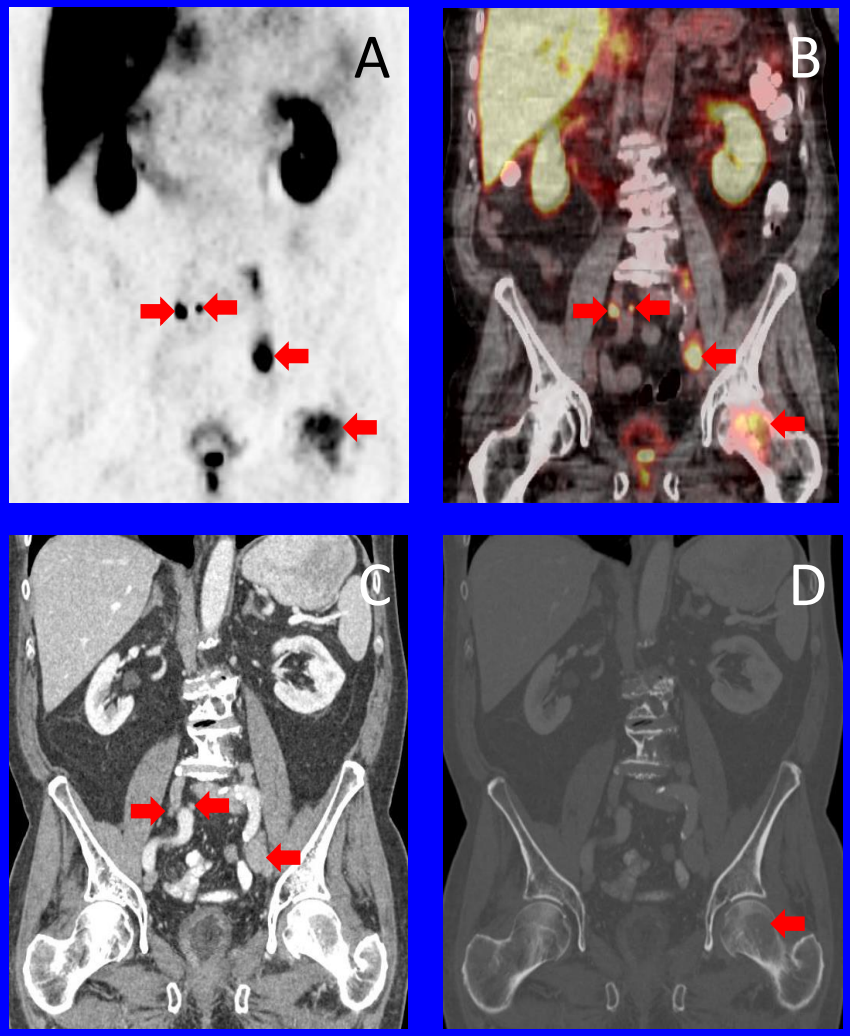
The Critical Role of Imaging

- How much you find depends on how you look
- If one contemplates eradication of the metastatic disease, one must image better
  - Micro-metastases will never be imaged
- Bone scan and CT scans <u>are not up to the task</u>
  - NaF PET
  - PSMA PET
  - Choline PET
  - MRI
    - DWI
    - Combidex

2nd Generation PSMA PET Imaging of Metastatic Prostate Cancer (^{18}F-DCFPyL)

Improved Sensitivity for Detection of Nodal and Bone Metastatic PCa





Courtesy of Steve Y. Cho (UW) and Martin G. Pomper (JHU)

High dose radiation (SBRT)to oligo-mets in prostate cancer: Is it worthwhile?

From Reyes and Pienta, Oncotarget 6:8491-8524, 2015

Decaestecker, 2014 [144]	3iii/B	R	50	≤3 metachronous asymptomatic mets	SBRT (2 RT schedules used) +/– HT	Median PFS- 19mo; median ADT-FS- 25 month; 2-, 5yr PCSS- 96%, 90%
Berkovic, 2013 [146]	3iii/Di	R	24	Biochemical recurrence after curative treatment to primary (RP, RT, or both), then ≤3 synchronous asymptomatic mets	SBRT	Androgen deprivation therapy-free survival (ADT-FS)- 1-, 2yr- 82%, 54%; clinical progression free survival- 1-, 2yr- 72% and 42%
Ahmed, 2013 [145]	3iii/B	R	17	≤5 met lesions	SBRT	Local control-100% at 6mo; cancer specific survival (CSS)-6- and 12mo- 100%; freedom from distant progression (FFDP)- 6- and 12mo- 74%, 40%

Approach to Oligo-Mets Today
Treatment of the Primary +/- with surgery or radiation

- ADT + docetaxel + radiation (SBRT) to mets
- ADT + radiation to mets
- ADT + docetaxel
- ADT
- Radiation to mets and avoidance of ADT
- Observation
- Something for everyone…a true “dealer’s choice”

<u>But no data on what is best!</u>

Prostate Cancer Clinical States

Now CRPC focus

Hormone-Sensitive

Diagnoses: 240,000

Localized Disease
Local Therapy or no therapy

Rising PSA
Salvage Rx, ADT or no therapy

Rising PSA: Castrate
No standard of care

Overt Metastases
ADT +/- docetaxel

Castration resistant prostate cancer

Deaths: 29,000

Radiographic Metastases: Castrate
Pre-chemo
Sipuleucel-T
Abiraterone
Enzalutamide
Radium-223

Radiographic Metastases: Castrate
1st-Line Chemo
Docetaxel

Radiographic Metastases: Castrate
Post-chemo
Cabazitaxel
Abiraterone
Enzalutamide
Radium-223

TRIAL	PRE-DOCETAXEL	HR	Survival (months)
TAX 327	Docetaxel/prednisone vs mitoxantrone/prednisone	0.79	19.3 vs 16.3*
IMPACT	Sipuleucel-T vs Control	0.78	25.8 vs 21.7
COU-AA-302	Abiraterone/prednisone vs Placebo/prednisone	0.79	34.7 vs. 30.3*
PREVAIL	Enzalutamide vs Placebo	0.71	35.3 vs. 30.3*
	POST-DOCETAXEL		
TROPIC	Cabazitaxel/prednisone vs mitoxantrone/prednisone	0.70	15.1 vs 12.7
COU-AA- 301	Abiraterone/prednisone vs Placebo/prednisone	0.74	15.8 vs 11.2*
AFFIRM	Enzalutamide vs Placebo	0.63	18.4 vs 13.6
	PRE- and POST-DOCETAXEL		
ALSYMPCA	Radium-223/supportive care vs placebo/BSC	0.70	14.9 vs 11.3*

*updated analysis

How could we be smarter in choosing the right agent for the mCRPC patient?

- What discriminates patients from one another?
- Why do some people respond to agent X and others to agent Y?
- How can we better stratify people to increase their chances of responding?
- Biomarkers are the great hope
  - What do we test for that predicts therapeutic benefit????

Two Types of Biomarkers: Tumor and Host

Tumor Related

- Various proteins and isoforms: PSA, AR, and LDH
- DNA mutations, deletions, CNV, translocations, methylation, etc.
- RNA expression and/or alterations (big ones, little ones, coding, and non-coding)
- CTCs, oncosomes, exosomes, and all their contents
- Imaging galore

Host related

- Pain
- Performance status
- Weight loss
- Alkaline phosphatase
- Albumin
- Tc-99 MDP bone scans
- Immune cell analysis
- Hematopoetic cell function: hemoglobin, NLR, platelets, etc.

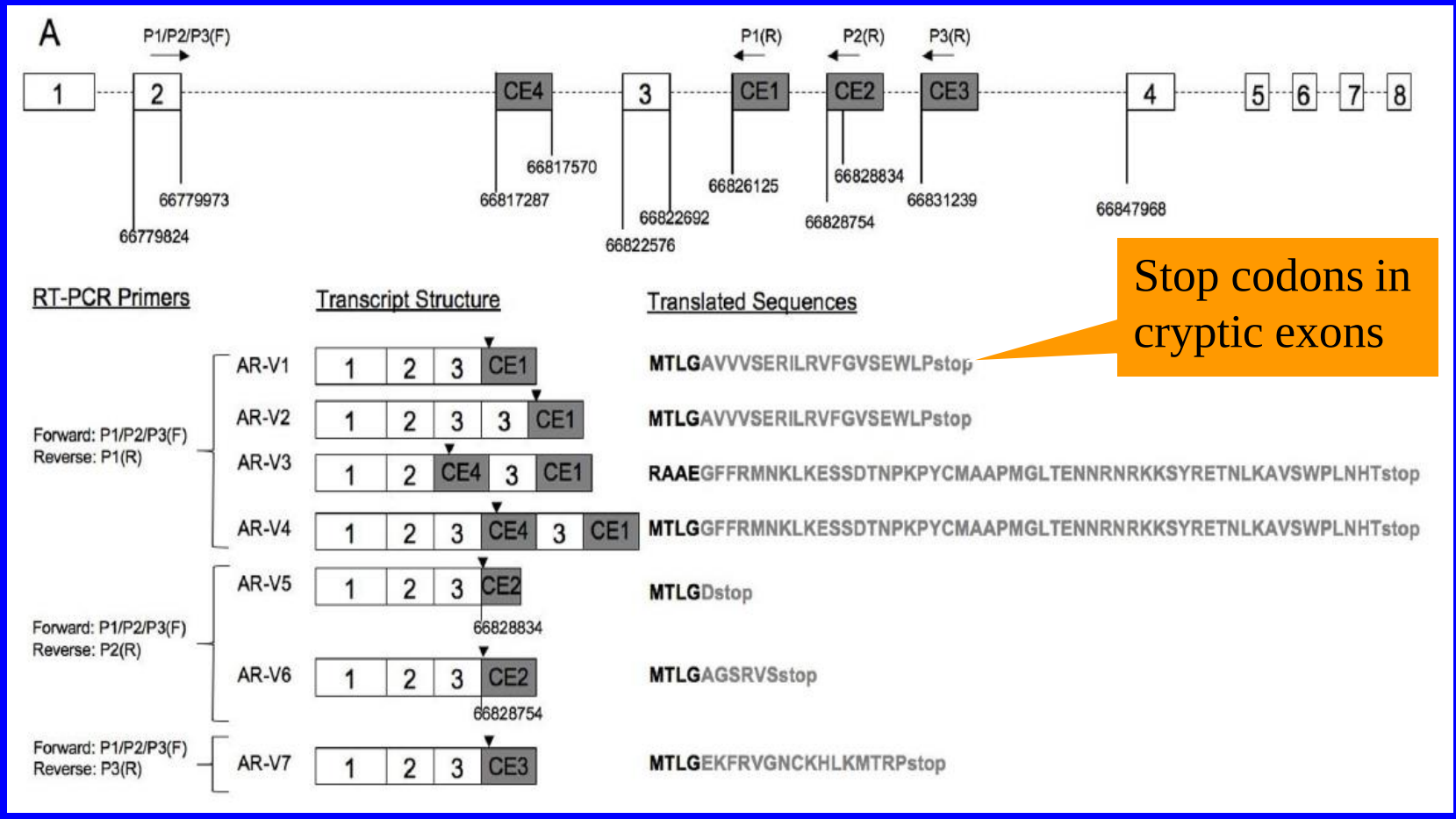
Prognostic and Predictive Biomarkers

- Prognostic biomarkers
  - Associates with various endpoints including survival
  - i.e. LDH, Alk Phos, Hgb, PSA, NLT, extent of disease, site of metastases (liver), PS, pain, weight loss, etc.
- Predictive biomarkers
  - Predict response or resistance to therapy
  - AR Variant 7 in CTC RNA assays for abiraterone and enzalutamide but validation pending
  - AR copy number/mutations (L702H, T878A) for abiraterone
  - DNA repair defects and response to PARP inhibition or platinum are quite interesting!

Predictive Biomarkers: Focus on V7 and DNA Repair Defects

Ligand-Independent AR Variants Derived from Splicing of Cryptic Exons Are Clearly Described in Tumors and CTCs

Hu et al. Cancer Research 69:16-22, 2009



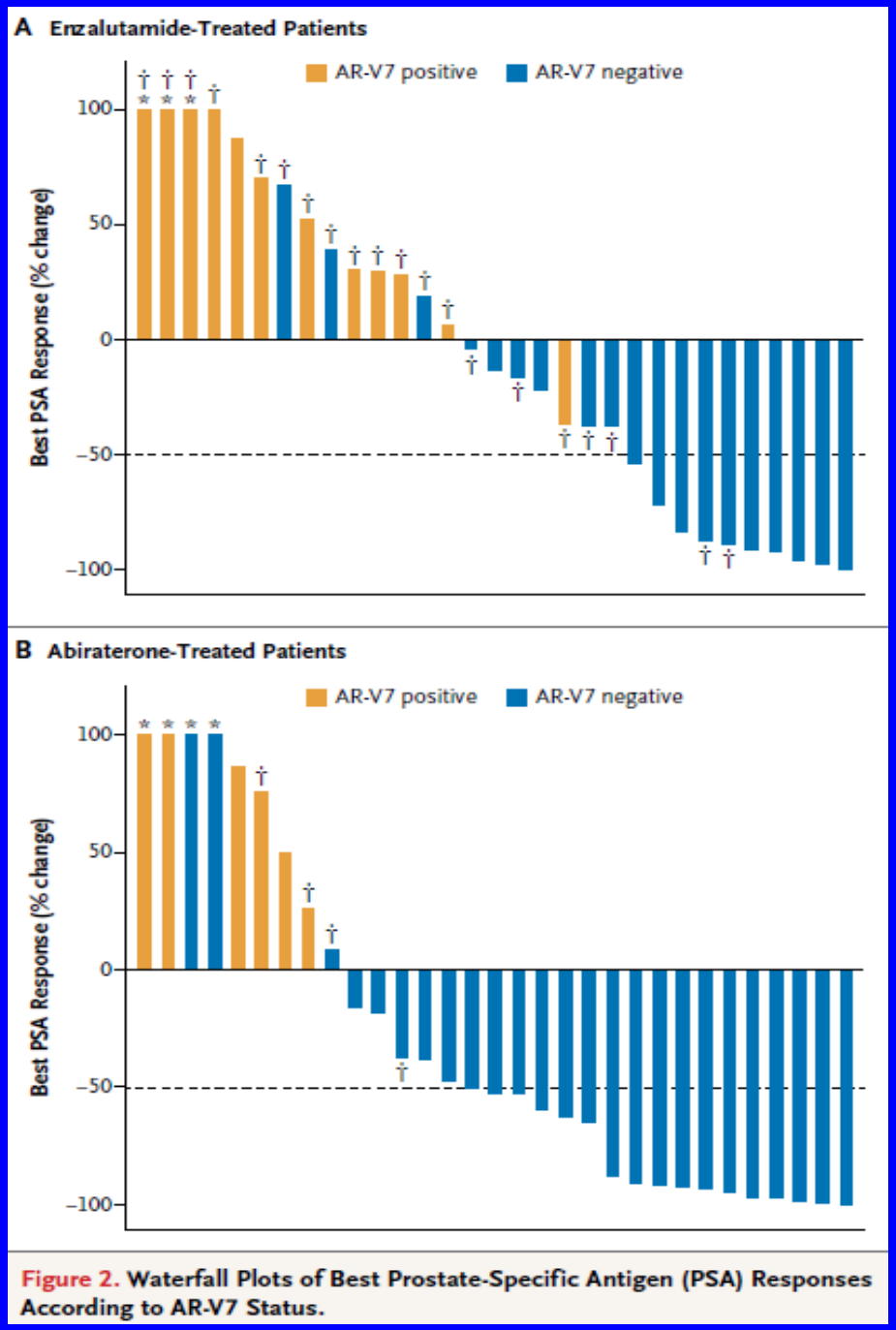


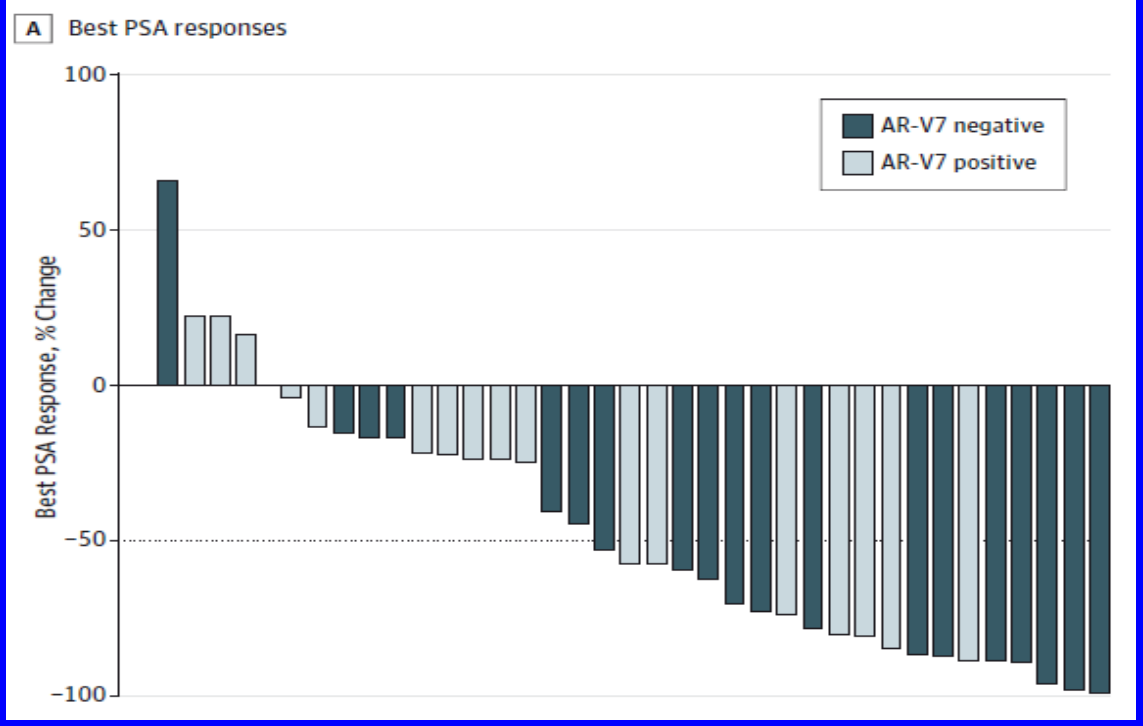
Figure 2. Waterfall Plots of Best Prostate-Specific Antigen (PSA) Responses According to AR-V7 Status.

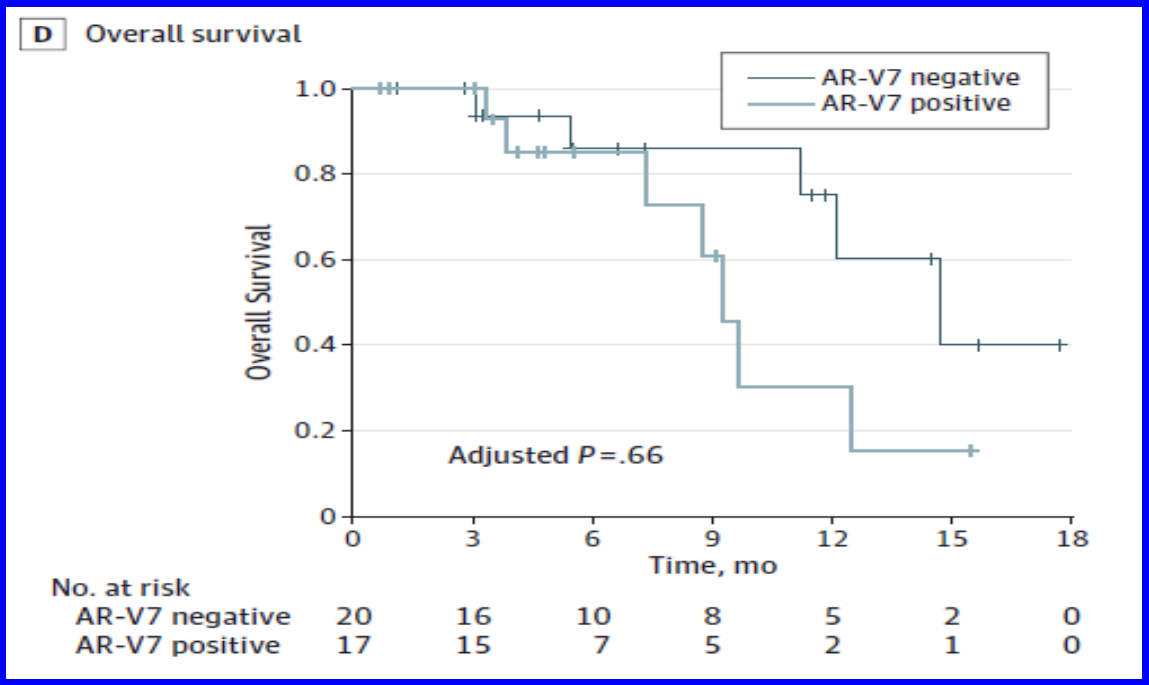
PSA responses in Abi/Enza Treated Patients Stratified by AR-V7 Status in CTCs

Antonarakis et al, NEJM 371:1028, 2014

Experimental Concepts: Can we make AR-V7 irrelevant or simply go away?

- Hormonal agents that bind to ligand site in AR
  - Galeterone
  - High dose testosterone
- Non-hormonal agents
  - PSMA targeted concepts
  - N-Terminal AR targeted agents (Epi-506)
  - Niclosamide
  - Bromodomain inhibitors
  - Taxanes (new concepts)
  - Radiation (including Radium-223)
  - Immunotherapy



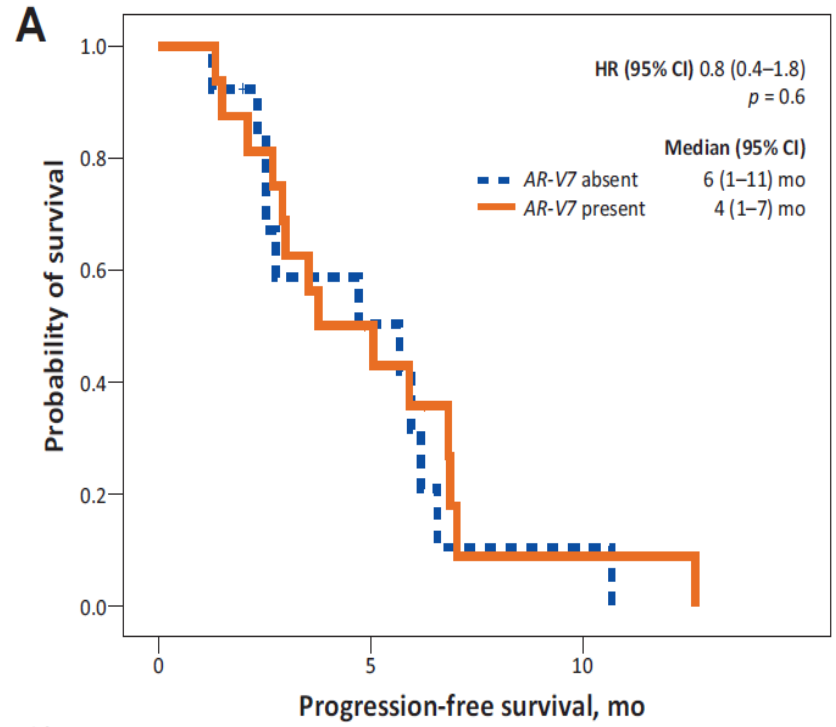


PSA Responses and Survival in Taxane Treated Patients Stratified by AR-V7 Status in CTCs

Antonarakis et al, JAMA Oncology, 1:582-591,2015

Cabazitaxel activity is independent of AR-V7 expression

Onstenk et al. Eur Urol August, 2015 epub



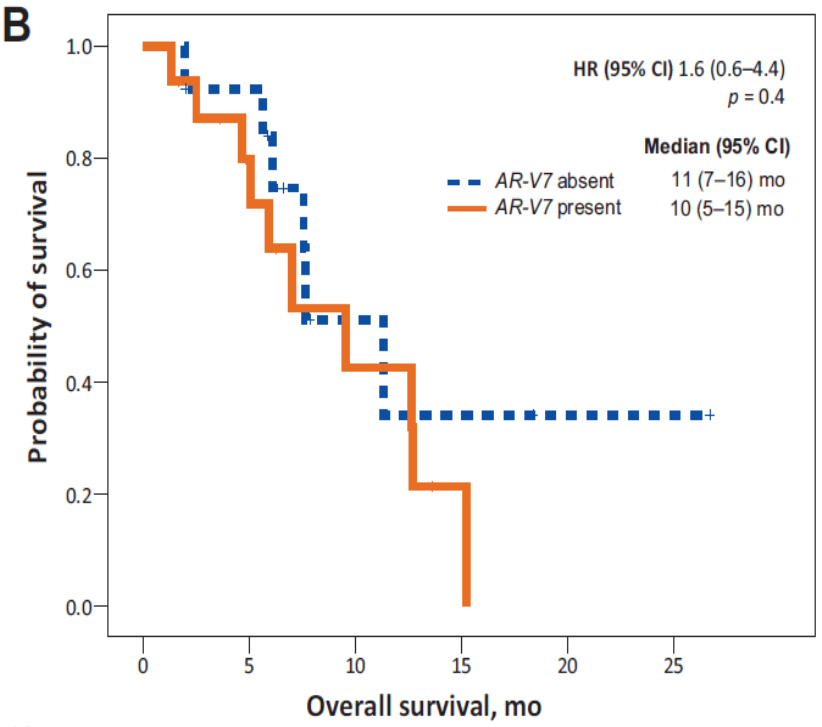
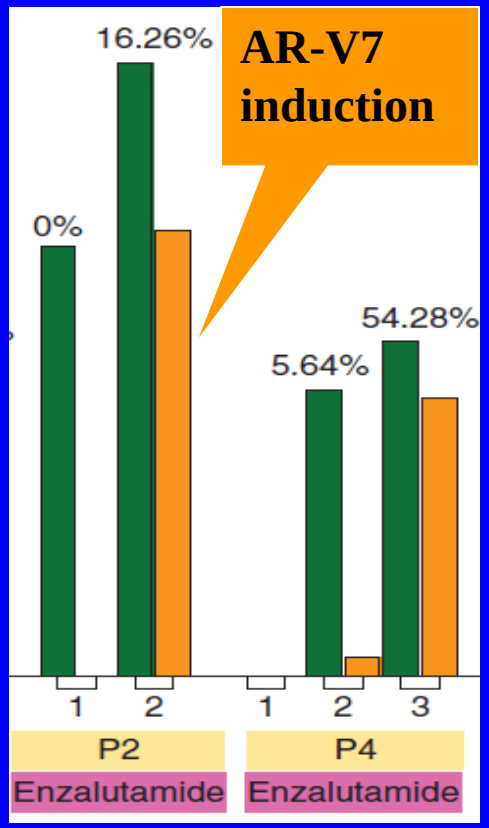


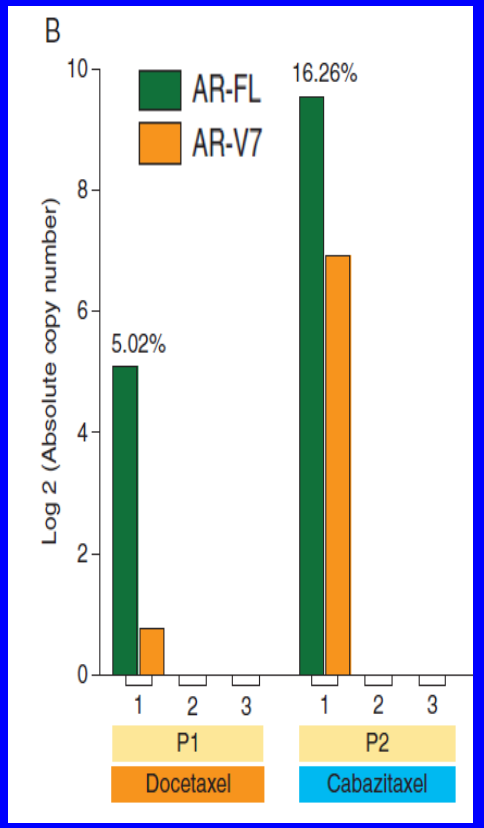
Fig. 3 – (A) Progression-free survival and (B) overall survival as a function of *AR-V7* in circulating tumor cells at baseline. The reported *p* value is from a log-rank test.

Converting AR-V7 CTCs from positive to negative with taxanes but not abiraterone/enzalutamide

Nakazawa et al. Annals of Oncology epub July 27, 2015

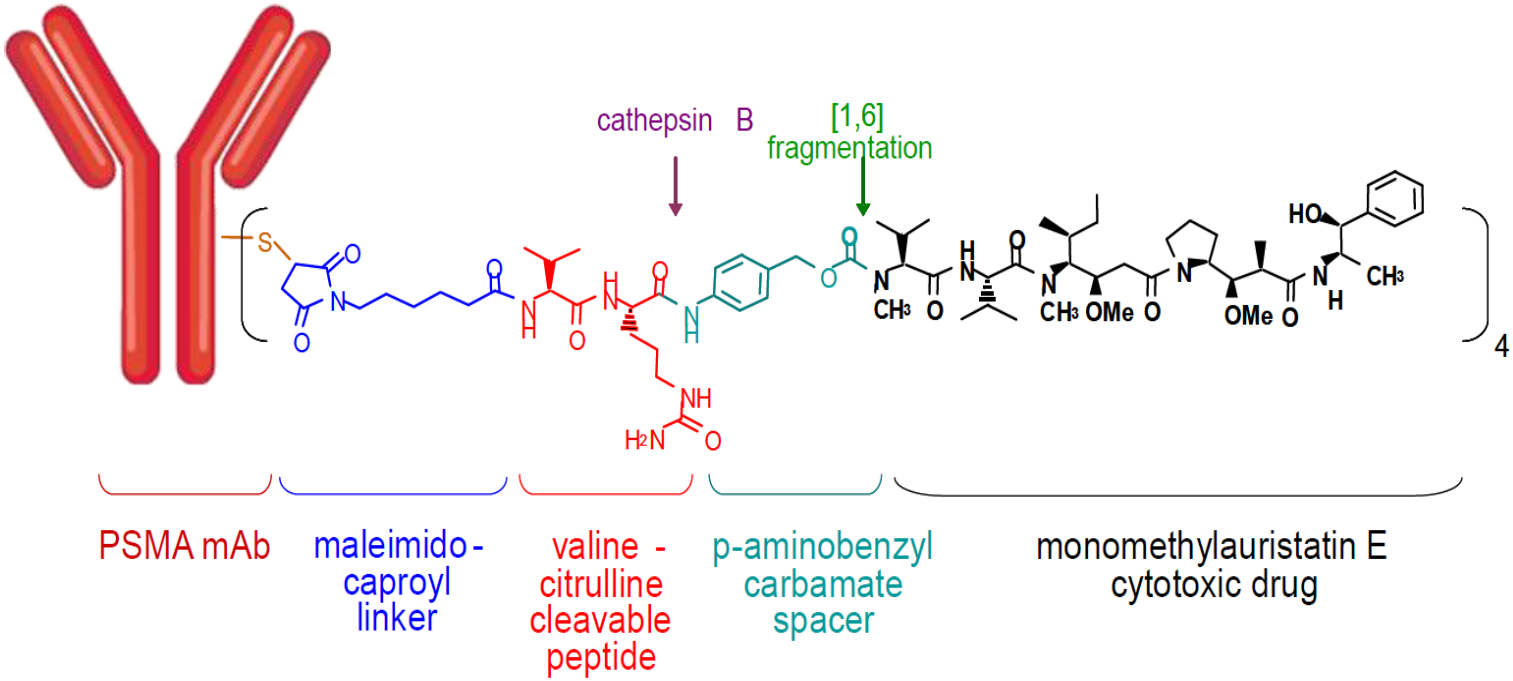


Treatment	Remained AR-V7 positive	'Reversions' to AR-V7 negative	Unknown[a]
First-line ADT ($n = 0$)	0	0	0
Abiraterone ($n = 5$)	4	0	1
Enzalutamide ($n = 4$)	4	0	0
Docetaxel ($n = 9$)	4	5	0
Cabazitaxel ($n = 4$)	1	1	2
Total ($n = 22$)	13	6	3



PSMA Targeted Therapy: i.e. Antibody Drug Conjugates (and others)

PSMA: Target for ADC Therapy

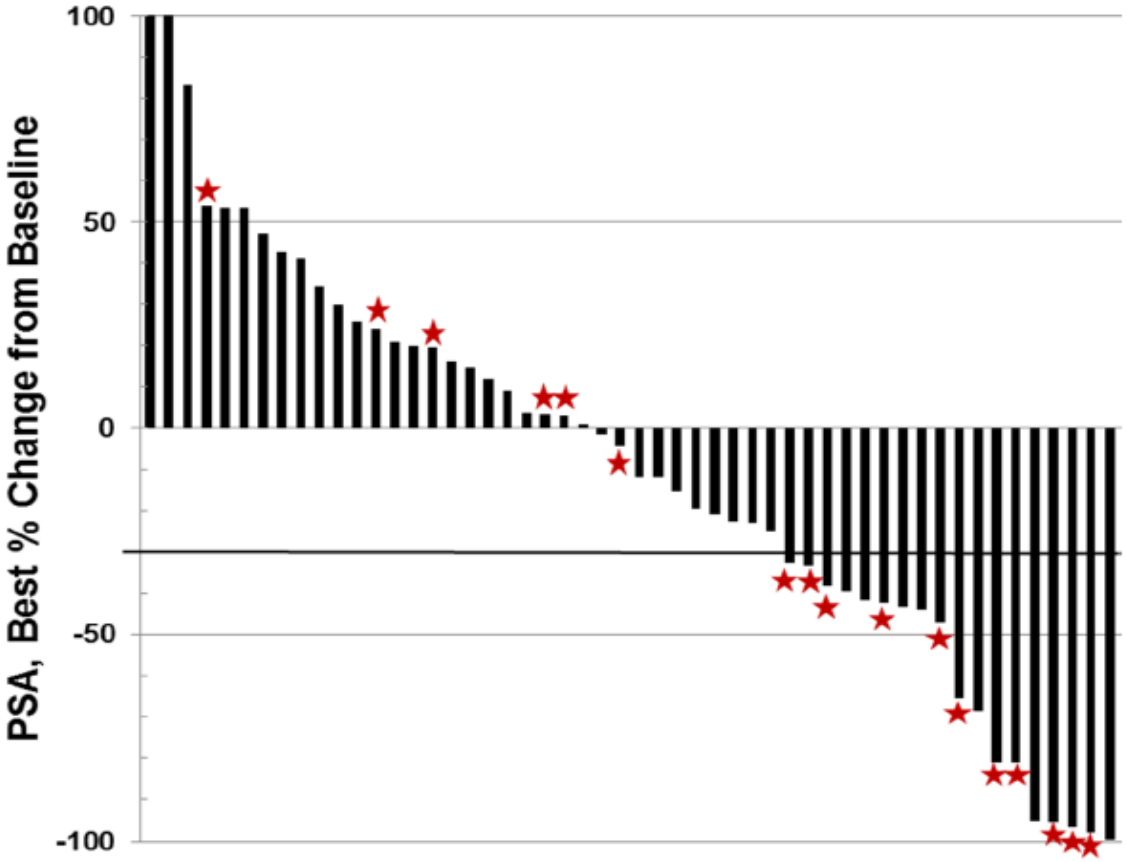


Note: PSMA upregulated in enzalutamide resistance

Unpublished Progenics

Study 2301

AR-V7 status does not confer resistance to PSMA ADC



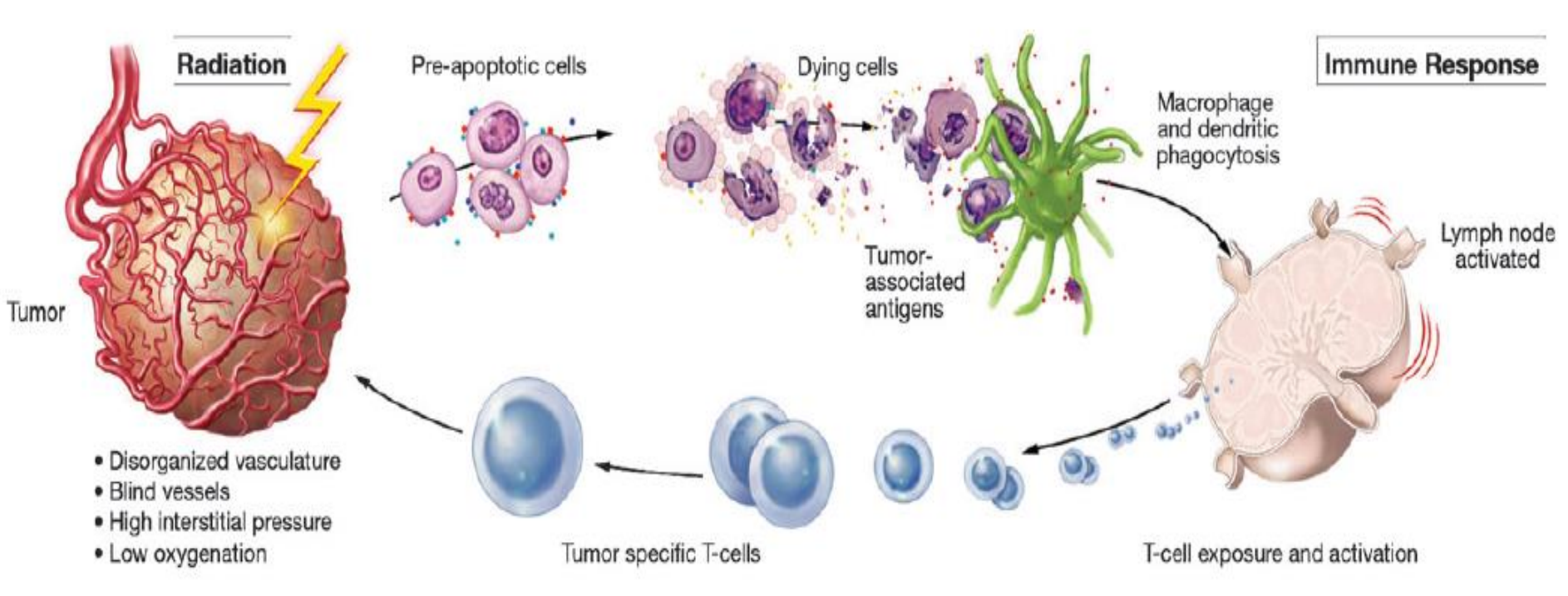
- A total of 52 samples were analyzed for AR-V7
- 17/52 tested positive for N-term AR = AR+
- 35/52 were negative for N-term AR = AR-
- 17 proceeded to be tested for C-term AR
- All 17 had C-term loss to various degree, thus AR-V7+ (★)
- 11/17 responded to PSMA ADC (65%)

PSMA ADC can be effective in reducing PSA regardless of AR-V7 status

Immunotherapy is not V7 Dependent

Antigen Release from Dying Tumor Cells Activate Immune Responses:

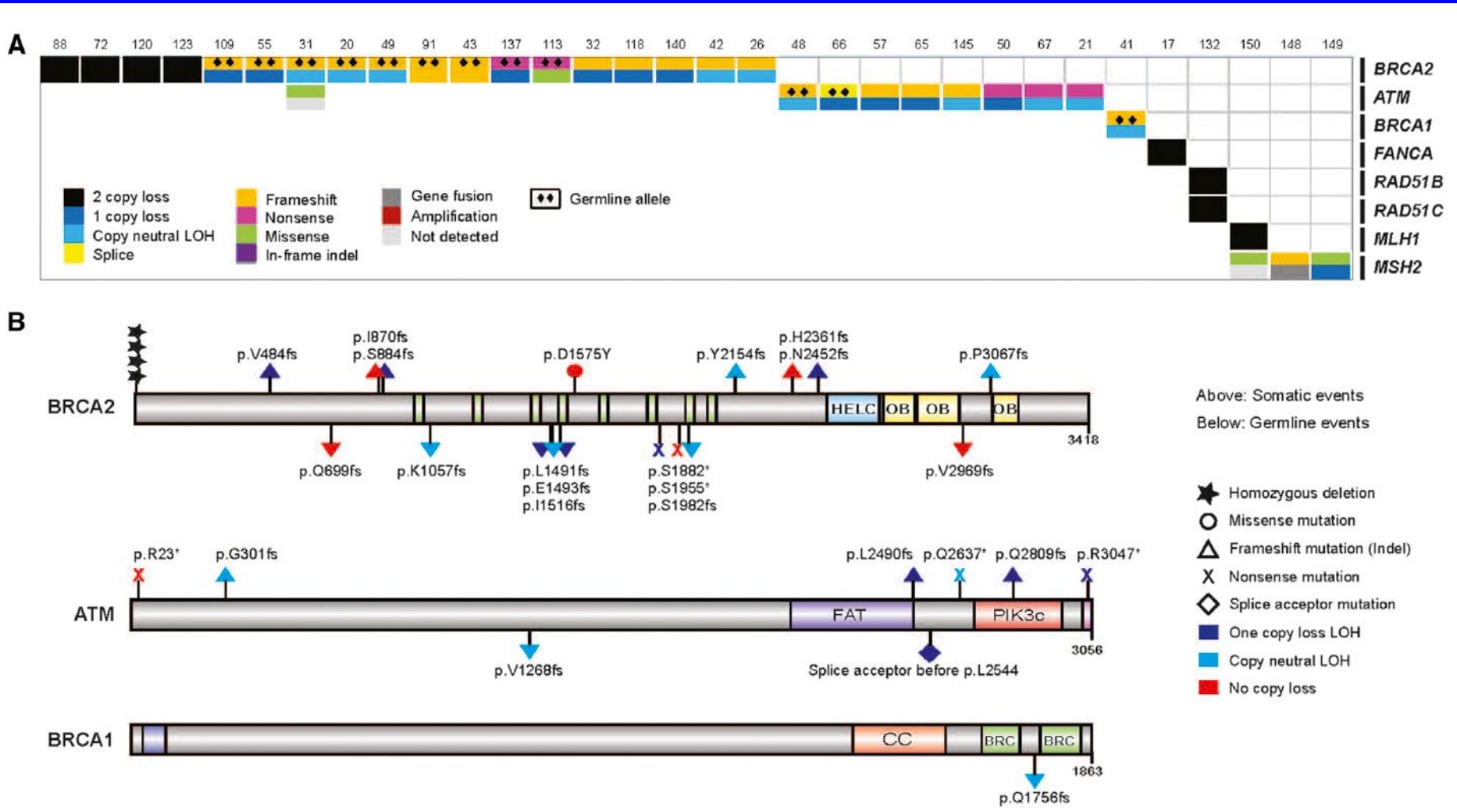
Radiation Induces Death of Cancer Cells



Radium-223 + anti-PDL1 concept: Studies soon

A new predictive biomarker: DNA repair defects are more common than appreciated

Robinson et al. Cell 161:1215. 2015



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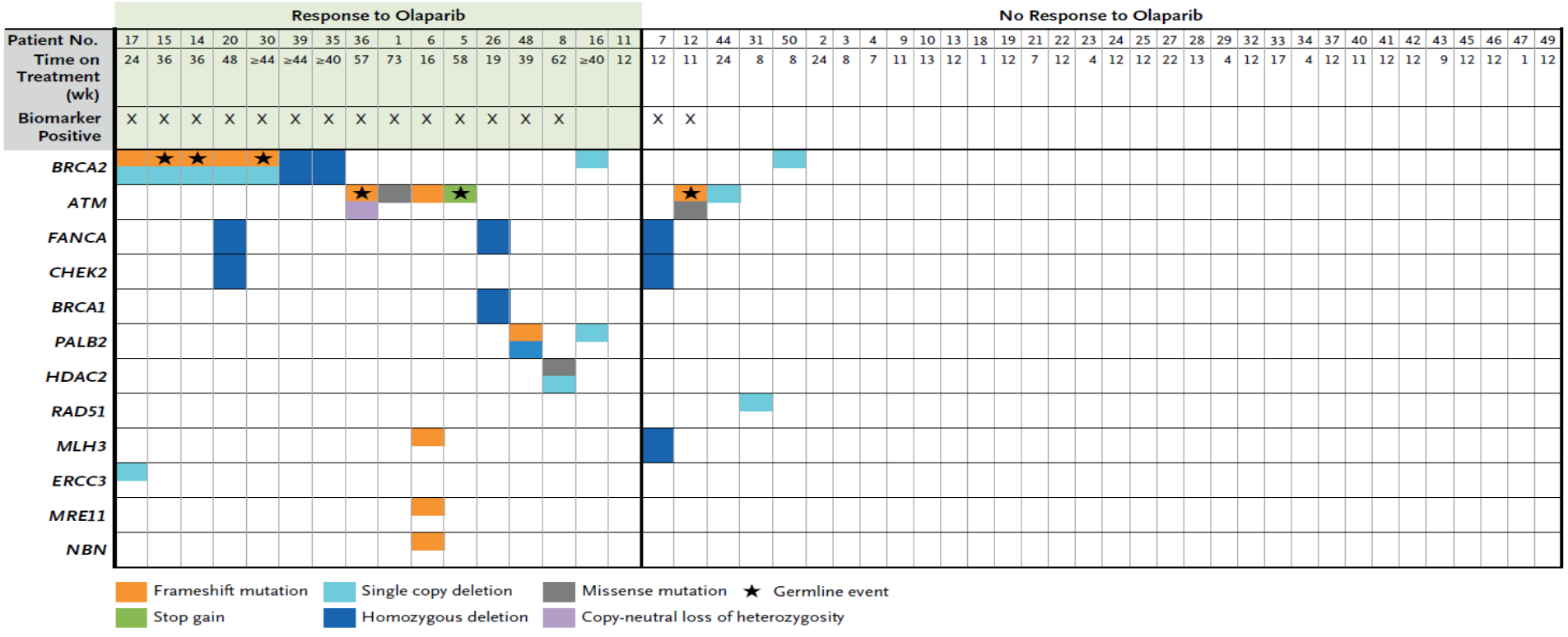

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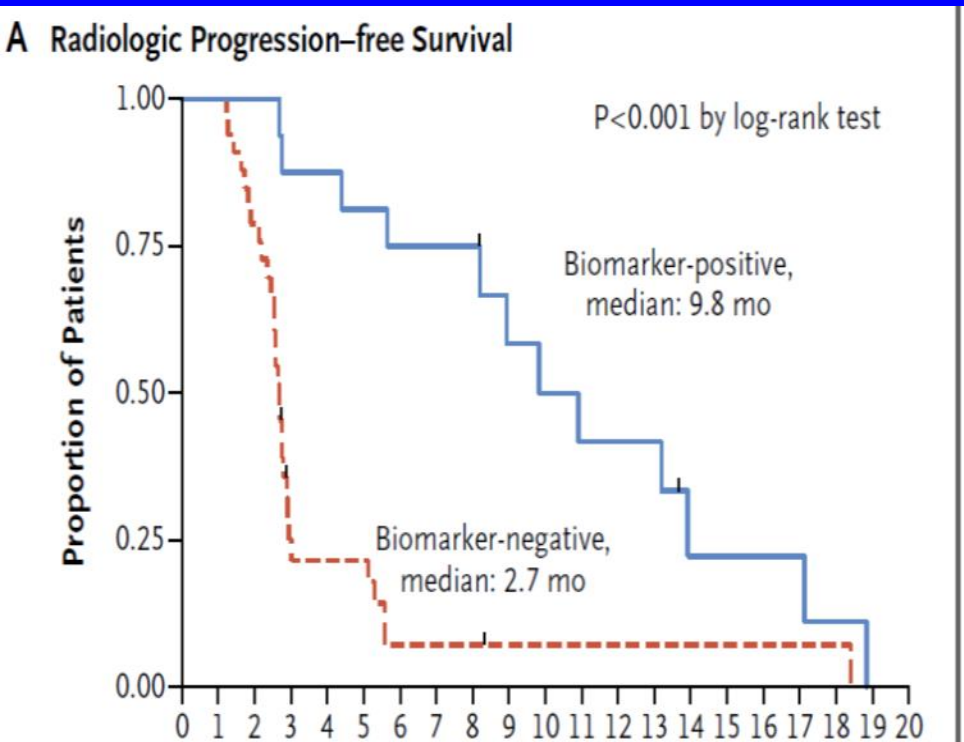

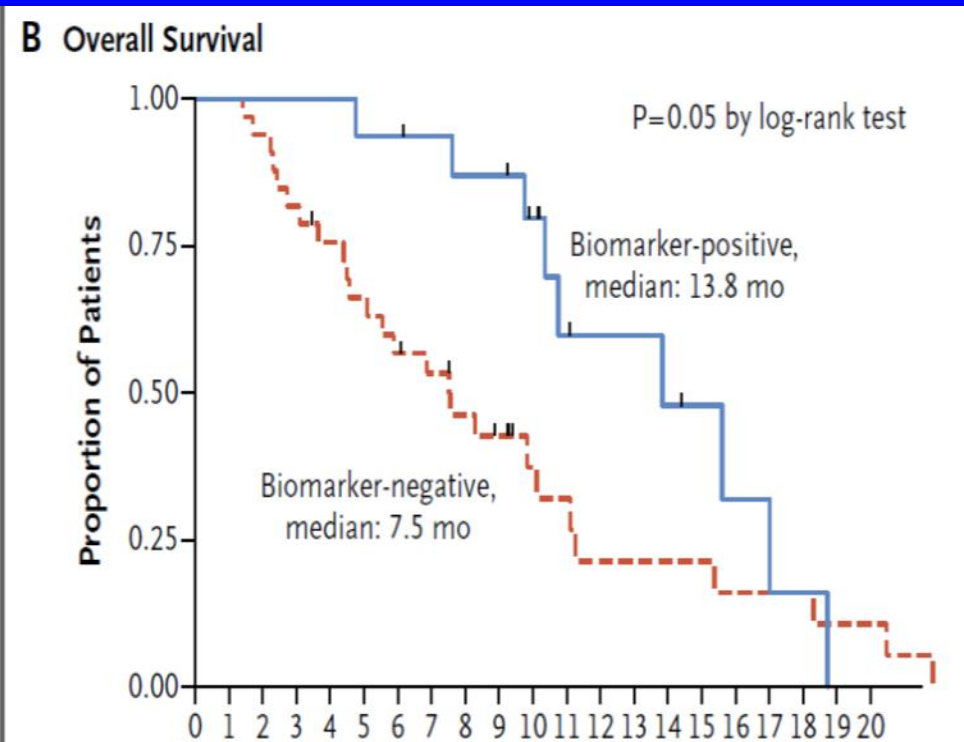

Multiple new concepts exploitable with DNA repair defects

- PARP inhibition has been shown in patients with no prior platinum exposure
- Various forms of radiation including radium-223
- Platinum and other DNA damaging patients
  - Extreme responder analysis by Beltran et al indicated that DNA repair defects may be involved
- Combinations of all the above

Summary

- The role of chemotherapy expands to the hormone-sensitive metastatic setting
- New concepts and new imaging provide new opportunities in oligo-metastatic disease
- Newer concepts in immunotherapy are worthy of exploration given success in other diseases
- New predictive biomarkers, especially DNA repair defects, are clinically exploitable in an important subset of patients