Hormone Sensitive Metastatic Prostate Cancer: intensification is a winning strategy, how can we do even better?

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HORMONE SENSITIVE METASTATIC PROSTATE CANCER

RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

SPEAKERS BUREAU: EXELIXIS, PROMETHEUS
CONSULTING: JANSSEN, ASTRA ZENECA

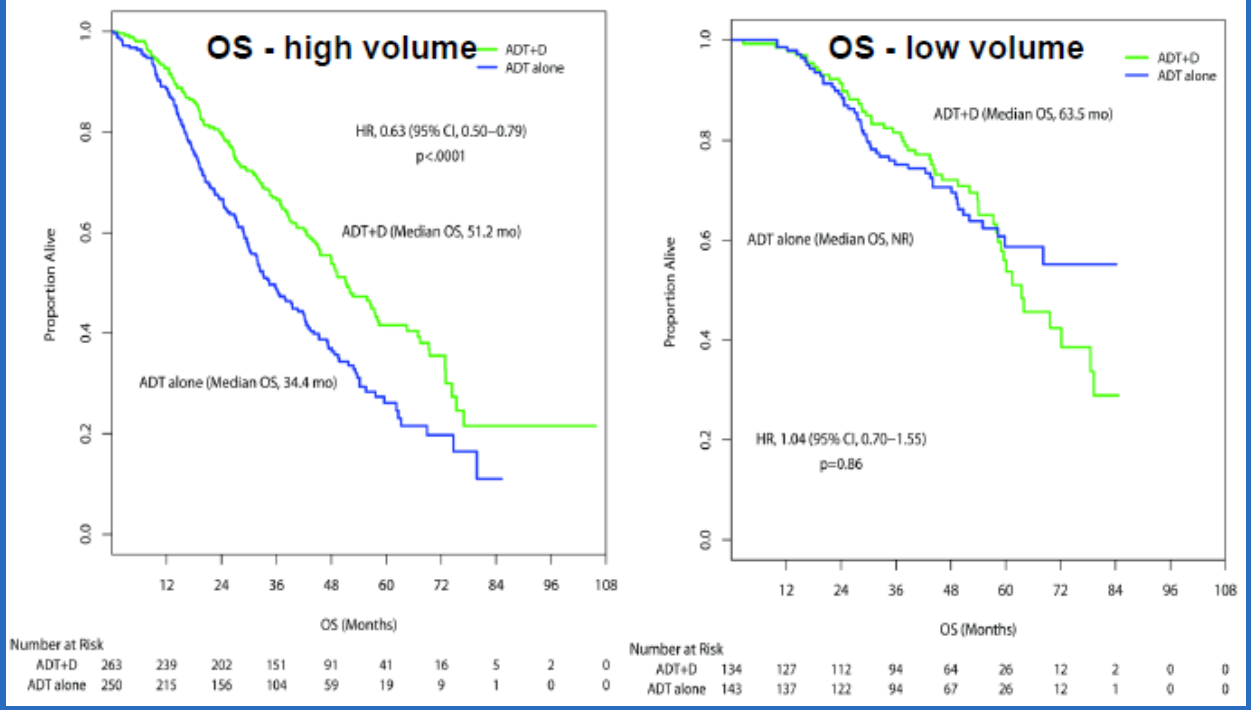
THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

Overview

- Intensified up-front therapy
  - Abiraterone: LATITUDE, STAMPEDE
  - Docetaxel: CHAARTED, STAMPEDE
- “Personalized” intensification in mHSPC; integrating genomics
- Treating the primary and/or oligo-mets with local therapy

Early chemotherapy improved survival in metastatic hormone sensitive prostate cancer (HSPC): CHAARTED

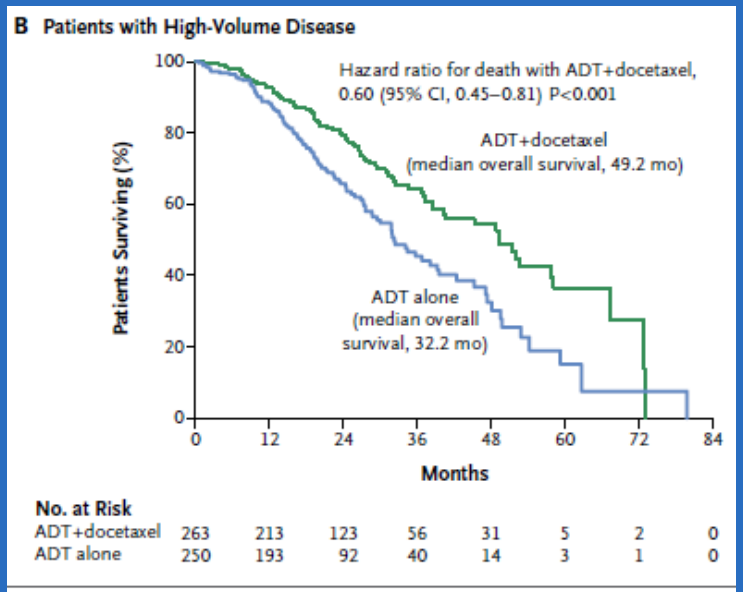
	HR (ADT+D/ADT)	95% CI	p-value
Overall	0.73	0.59 - 0.89	0.0018
High volume	0.63	0.50 - 0.79	<.0001
Low volume	1.04	0.70 - 1.55	0.86

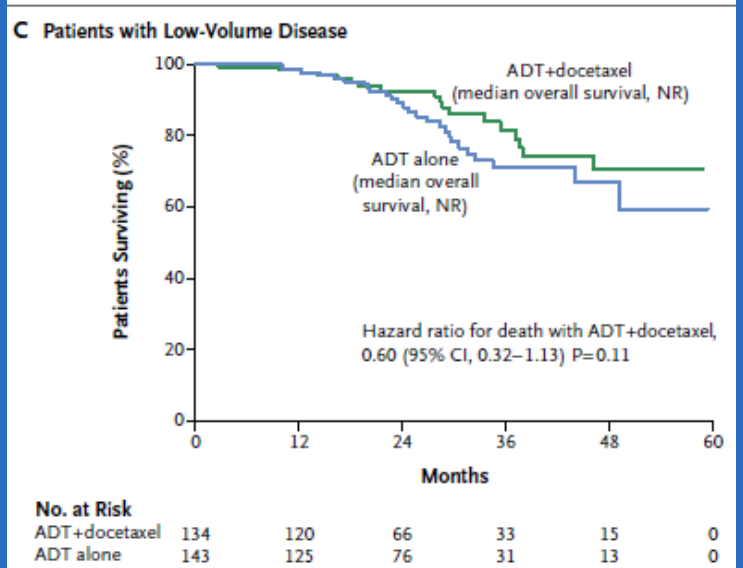


ESMO update: med f/u 57 mo, no OS benefit for low volume (aka oligomets)

Sweeney CJ et al. NEJM 2015; 373:737-46

Sweeney CJ et al, ESMO 2016; abstr 720pd





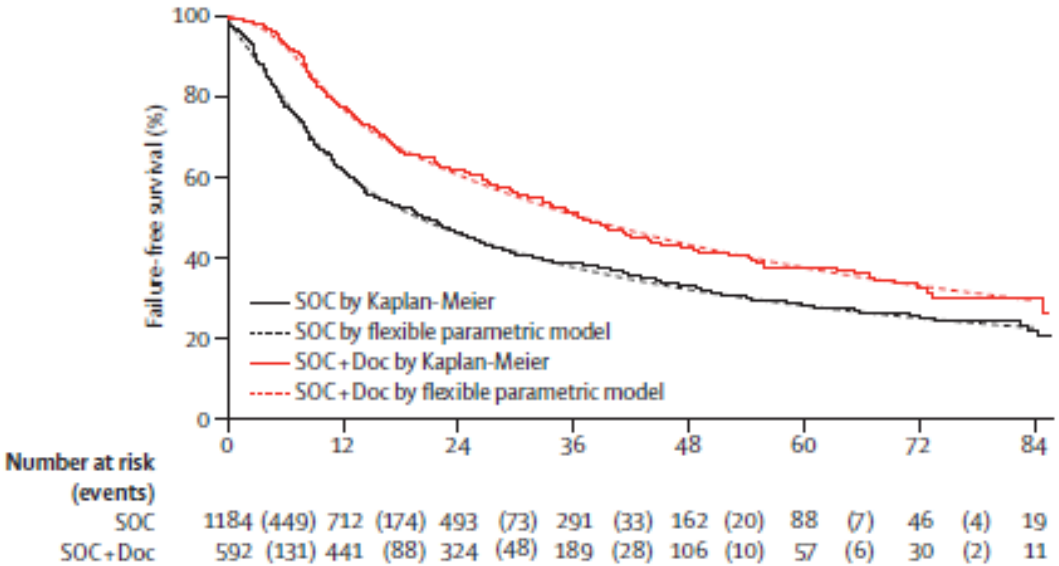
GETUG AFU-15 Study: no benefit for up-front docetaxel

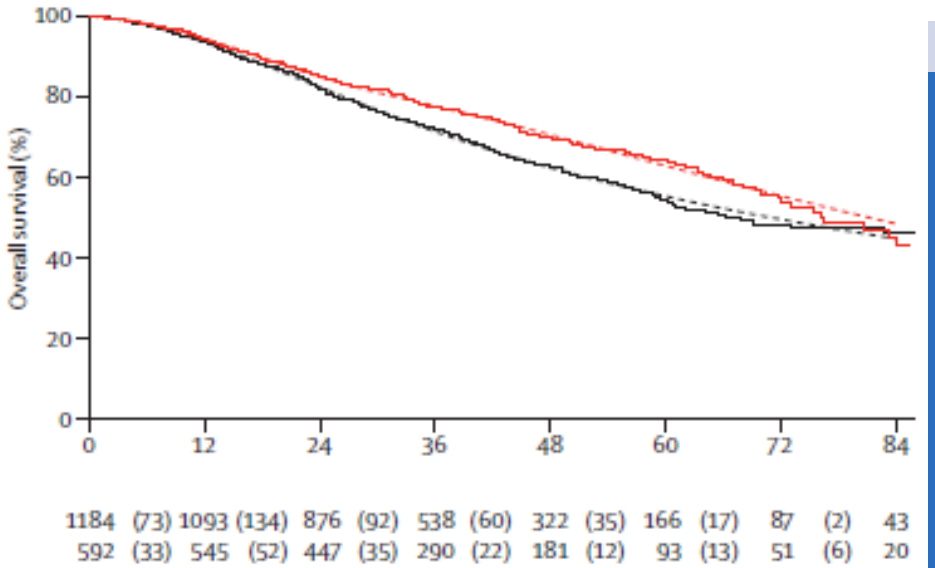
	ADT	ADT + D	p-value	Hazard ratio (95%CI)
Overall population	N = 193	N = 192		
Median OS	46.5 [39.1-60.6]	60.9 [46.1-71.4]	0.44	0.9 [0.7-1.2]
Biological PFS	12.9 [11.9-17.7]	22.9 [19.5-28.4]	0.0021	0.7 [0.6-0.9]
HVD * Pts	N = 91	N = 92		
Median OS	35.1 [29.9-44.2]	39 [28-52.6]	0.35	0.8 [0.6-1.2]
Biological PFS	9.2 [8.3-12.2]	15.2 [12-21.2]	0.0039	0.6 [0.5-0.9]
LVD Pts	N = 102	N = 100		
Median OS	NR [61.8-NR]	83.1 [69.5-NR]	0.87	1 [0.6-1.5]
Biological PFS	22.4 [16.8-37]	40.9 [28.4-62.5]	0.0533	0.7 [0.5-1]

* HVD: visceral (lung or liver) metastases and/or 4 or more bone metastases with at least 1 beyond the pelvis and the vertebral column.

Gravis G et al. 2015
ASCO GU abstr 140

STAMPEDE (Doce): James N *et al*., Lancet 2016; 387:1163





For Overall Survival:

HR 0.79, 95% CI 0.65-0.96, p=0.019 – all patients

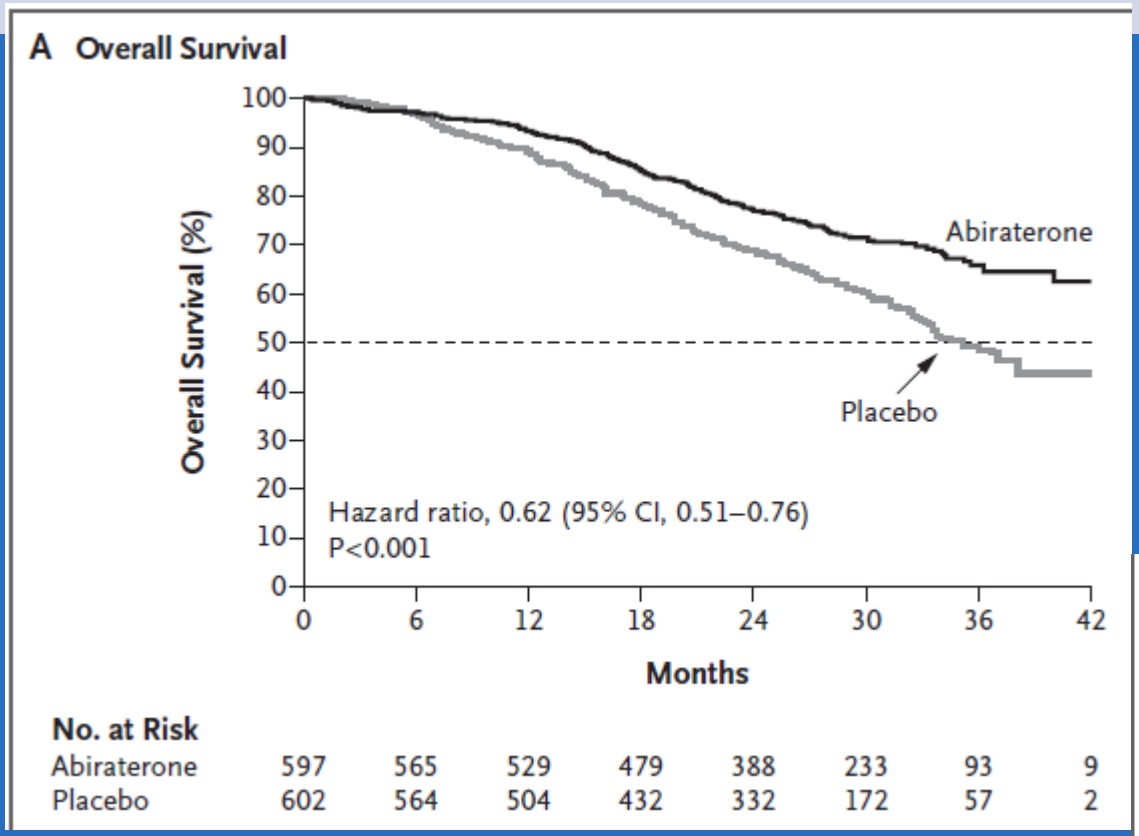
HR 0.82, 95% CI 0.48-1.4, p=0.475 – pts with mets

BUT…

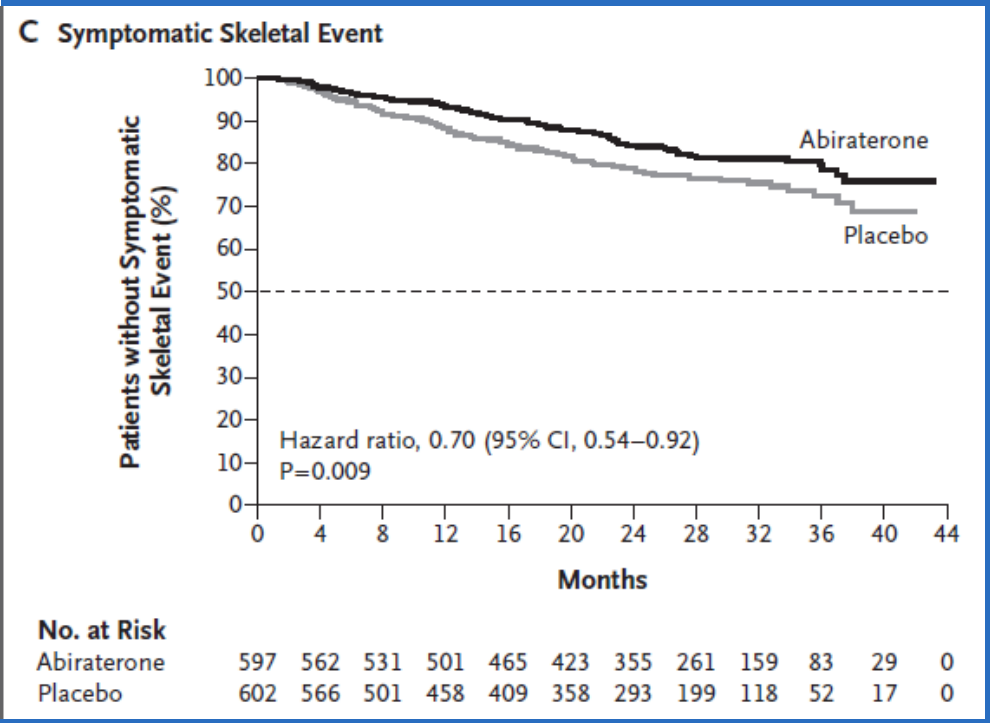
Toxicity must be considered

	Standard of care (n=1184)	Standard of care plus zoledronic acid	Standard of care plus docetaxel	Standard of care pl zoledronic acid and
ITT population				
Number of patients included in analysis†	1173	587	579	563
Grade 1–5 adverse event	1160 (99%)	583 (99%)	577 (100%)	562 (100%)
Grade 3–5 adverse event	375 (32%)	184 (31%)	298 (51%)	296 (53%)
Grade 5 adverse event	4	1	4	7

Early abiraterone improves survival in metastatic HSPC: LATITUDE



2 of 3 high risk features:
- Gleason 8-10
- 2+ bone metastases
- Visceral metastases



Fizazi K et al. NEJM 2017;
DOI:10.1056/NEJMoa1704174

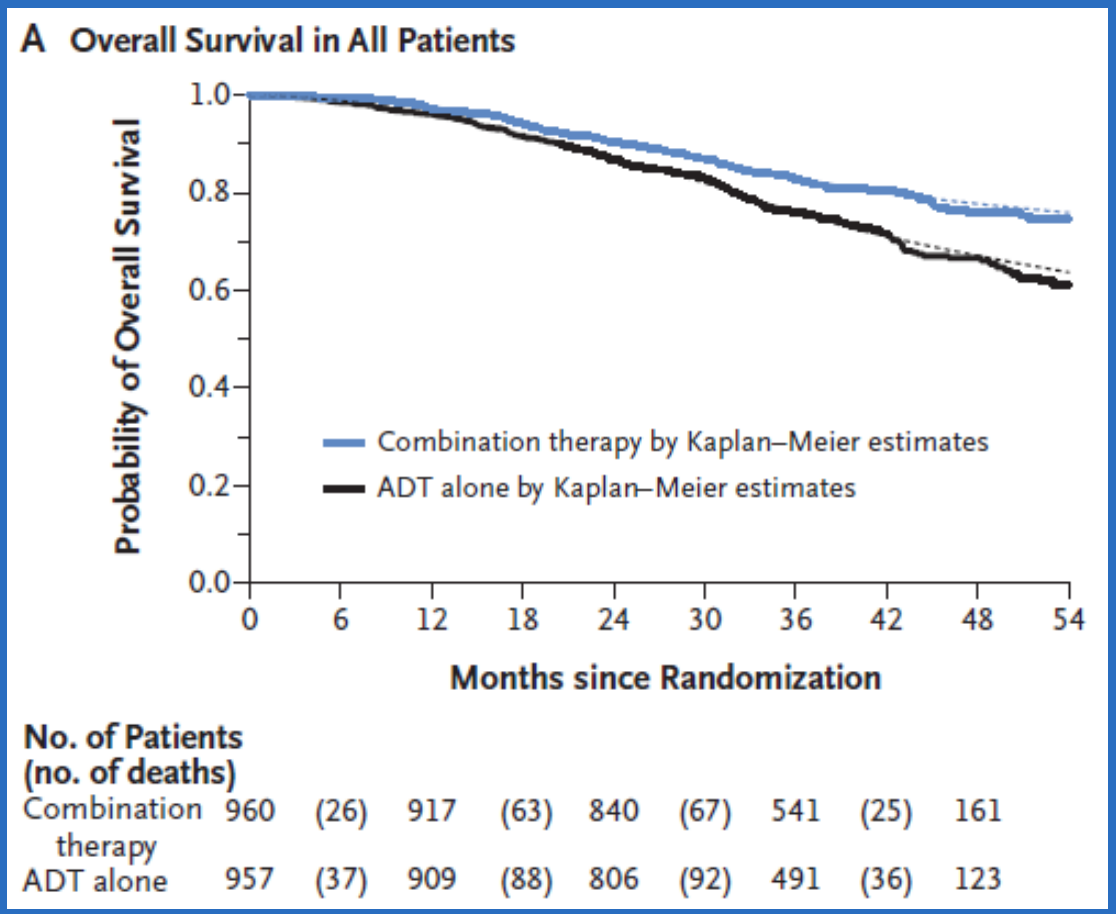
STAMPEDE: up-front abiraterone

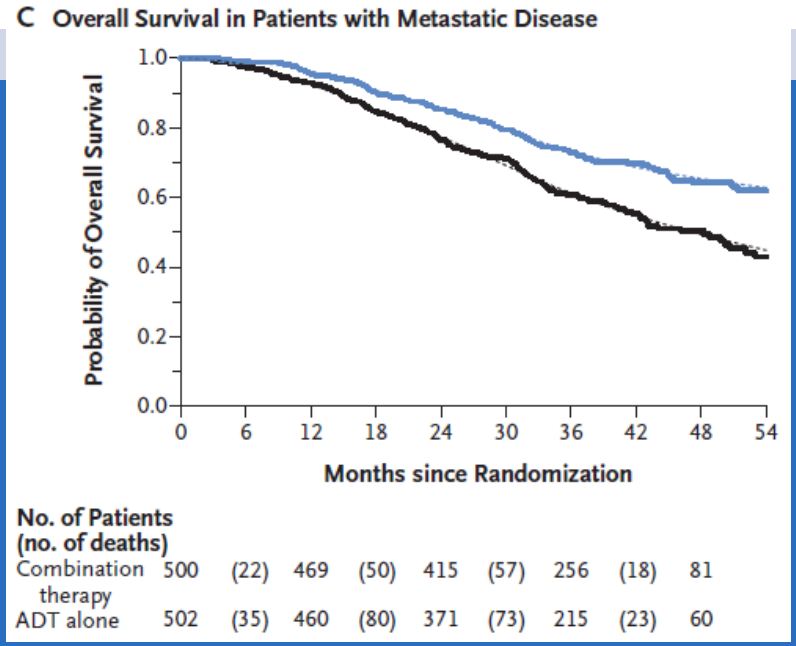
James N et al, NEJM 2017

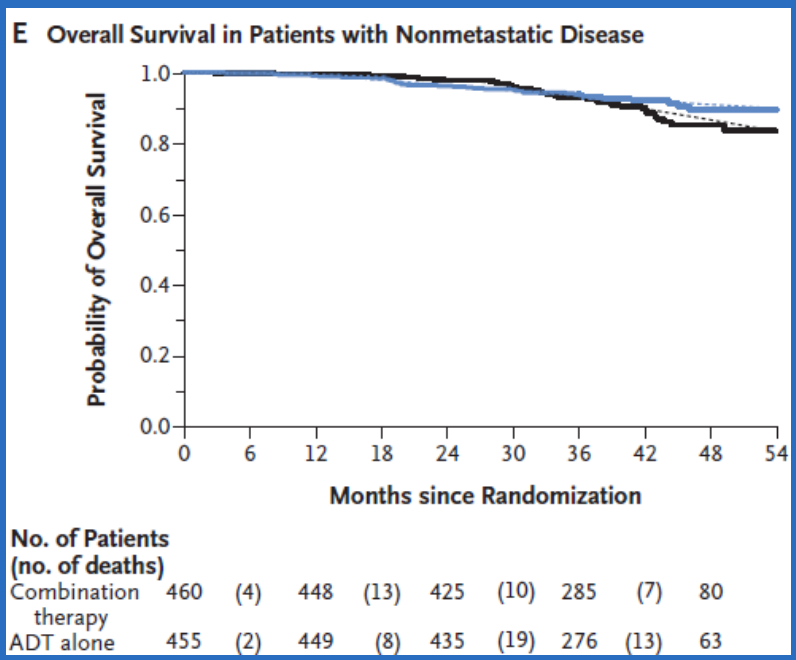
DOI10.1056/NEJMoa1702900

Hi risk local or Node+
≥2 of: Stage T3/4
PSA≥40ng/ml
Gleason 8-10

Relapsing p definitive tx
≥1 of: PSA ≥4 & PSADT <6 mo
PSA ≥20
Mets or Node +







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Should every newly diagnosed metastatic prostate cancer patient receive abiraterone or docetaxel?

Is one better than the other?

Should we give both?

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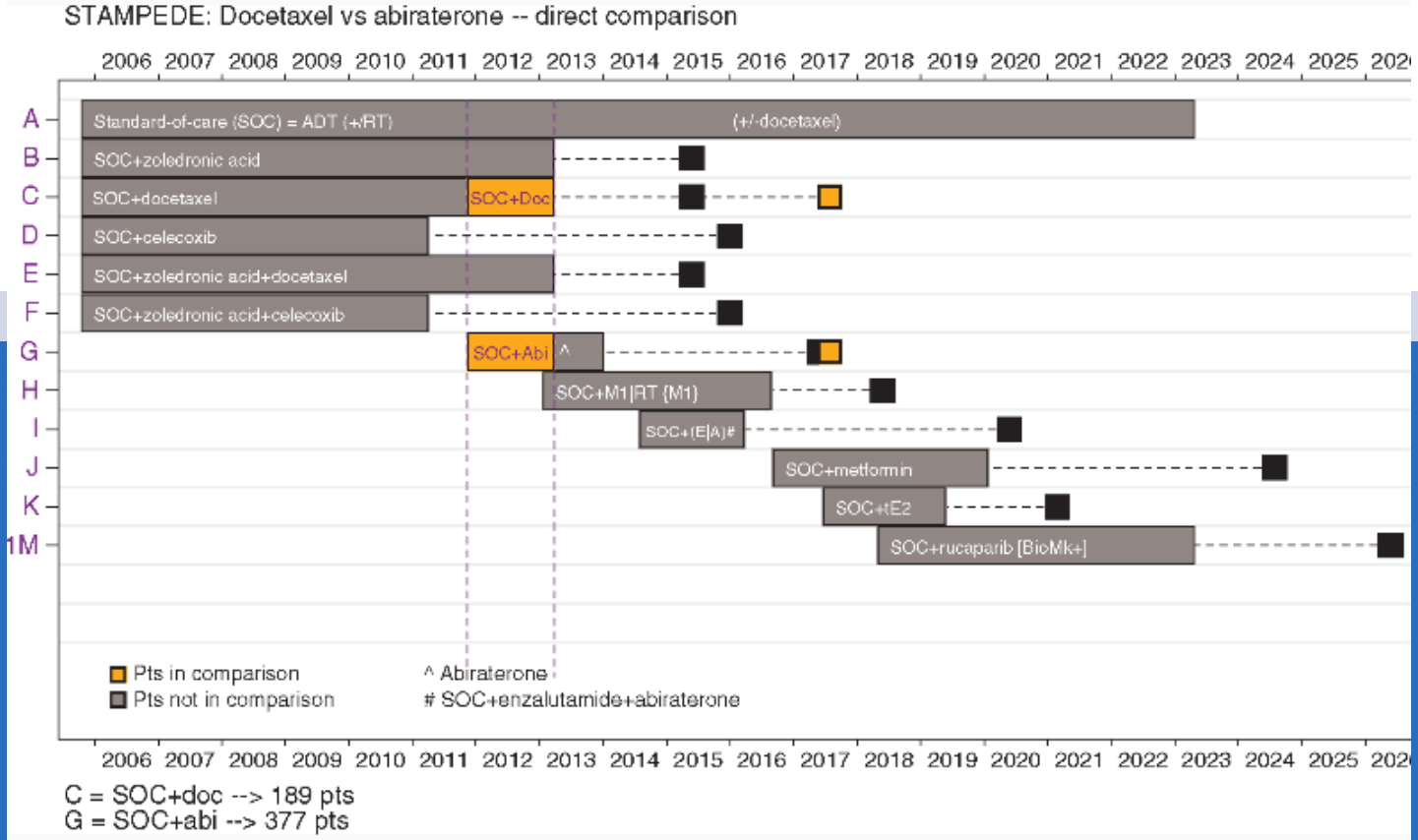
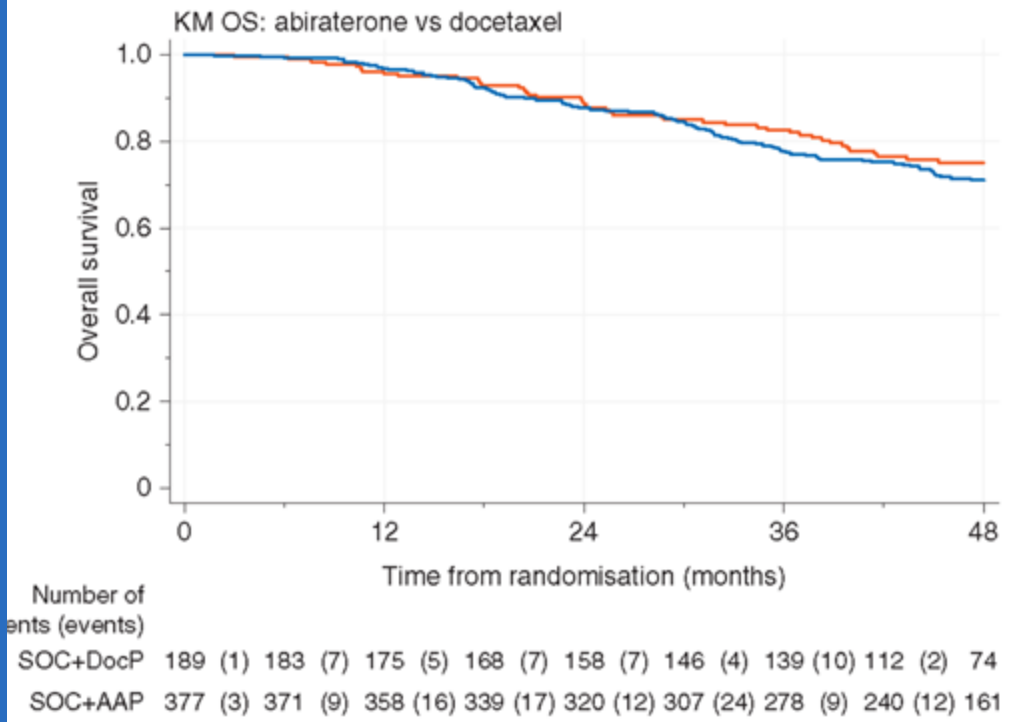
Sydes MR et al. Ann Oncol 2018; 29:1235-48
https://doi.org/10.1093/annonc/mdy072





No difference between abiraterone and docetaxel for mHSPC

Patient characteristics may impact benefit of mHSPC treatments

Bernard B, et al. Cancer 2017; 123:1536 CHAARTED analysis

TABLE 4. Proportional Hazard Models for Prostate Cancer-Specific Mortality

Covariate	Multivariable Analysis		
	HR	95% CI	*P*
Race			
White Non-Hispanic	1.00	—	Ref
White Hispanic	0.94	0.87-1.01	.094
Black	1.00	0.94-1.06	.982
Asian/Pacific Islander	0.81	0.74-0.89	< .001
American Indian/Alaska Native	1.23	0.95-1.59	.119
Marital status			
Unmarried	1.00	—	Ref
Married or domestic partner	0.89	0.86-0.93	< .001
County-wide median annual family income			
<$66,610	1.00	—	Ref
≥$66,610	1.05	0.99-1.10	.078
Percentage of adults not completing high school			
≥14.1%	1.00	—	Ref
<14.1%	0.96	0.92-1.01	.114
Age at diagnosis, y			
≤73	1.00	—	Ref
>73	1.18	1.13-1.23	< .001

Trials will answer the combination and other agents' utility for intensification questions

Study	Agent(s)	Accrual Goal	Status
ARASENS (Bayer) NCT02799602	Docetaxel ADT +/- ODM-201	1300	Completed Accrual
SWOG S1216	ADT +/- orteronel (TAK700)	1313	Completed Accrual
TITAN NCT02489318	ADT +/- apalutamide	1052	Completed Accrual

Are there genomic predictors of ADT response that could be leveraged for personalized treatment plans?

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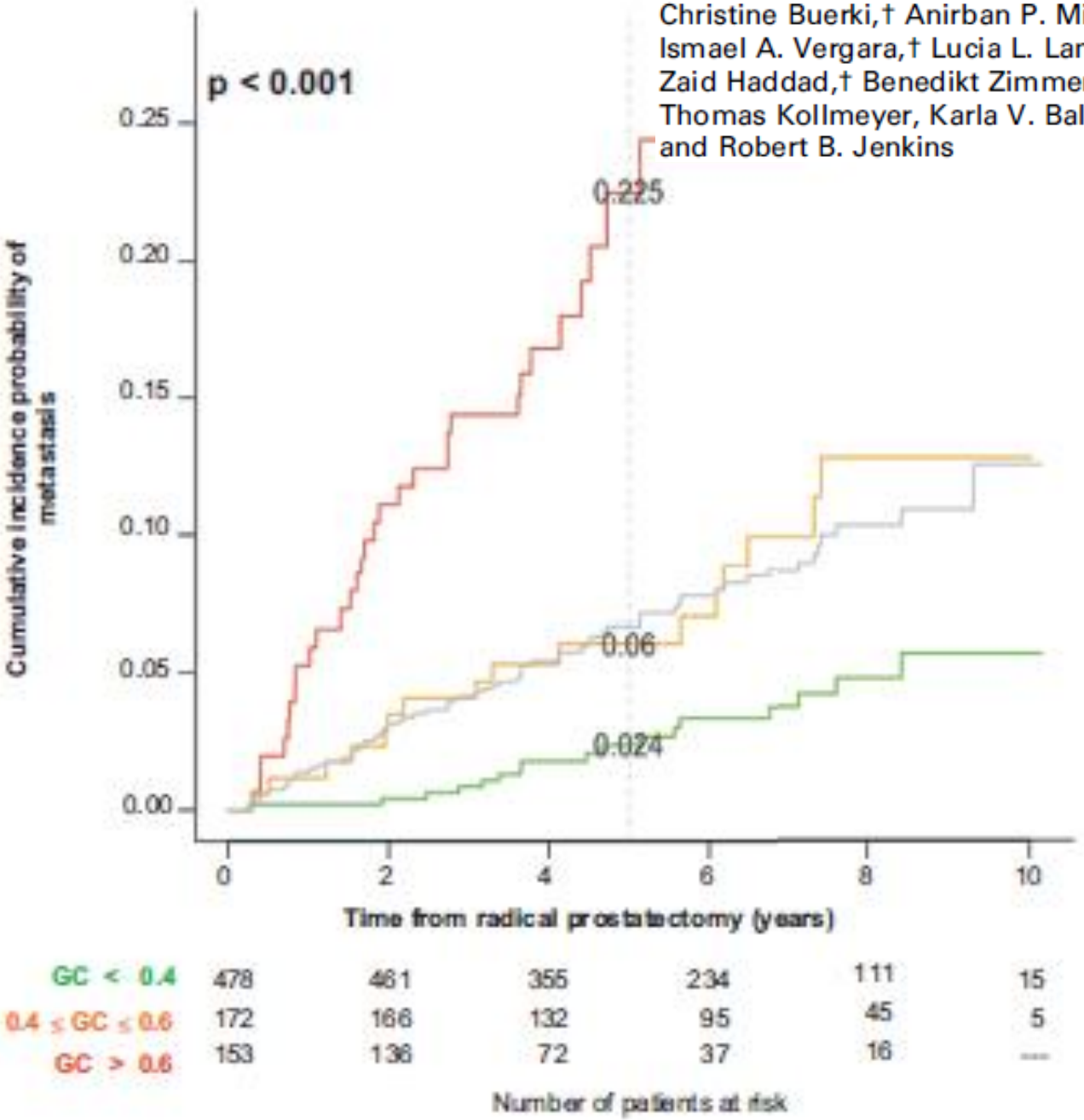
Validation of a Genomic Classifier that Predicts Metastasis Following Radical Prostatectomy in an At Risk Patient Population

R. Jeffrey Karnes,* Eric J. Bergstralh, Elai Davicioni,† Mercedeh Ghadessi,† Christine Buerki,† Anirban P. Mitra, Anamaria Crisan,† Nicholas Erho,† Ismael A. Vergara,† Lucia L. Lam,† Rachel Carlson, Darby J. S. Thompson, Zaid Haddad,† Benedikt Zimmermann,† Thomas Sierocinski,† Timothy J. Triche,‡ Thomas Kollmeyer, Karla V. Ballman,§ Peter C. Black,† George G. Klee and Robert B. Jenkins

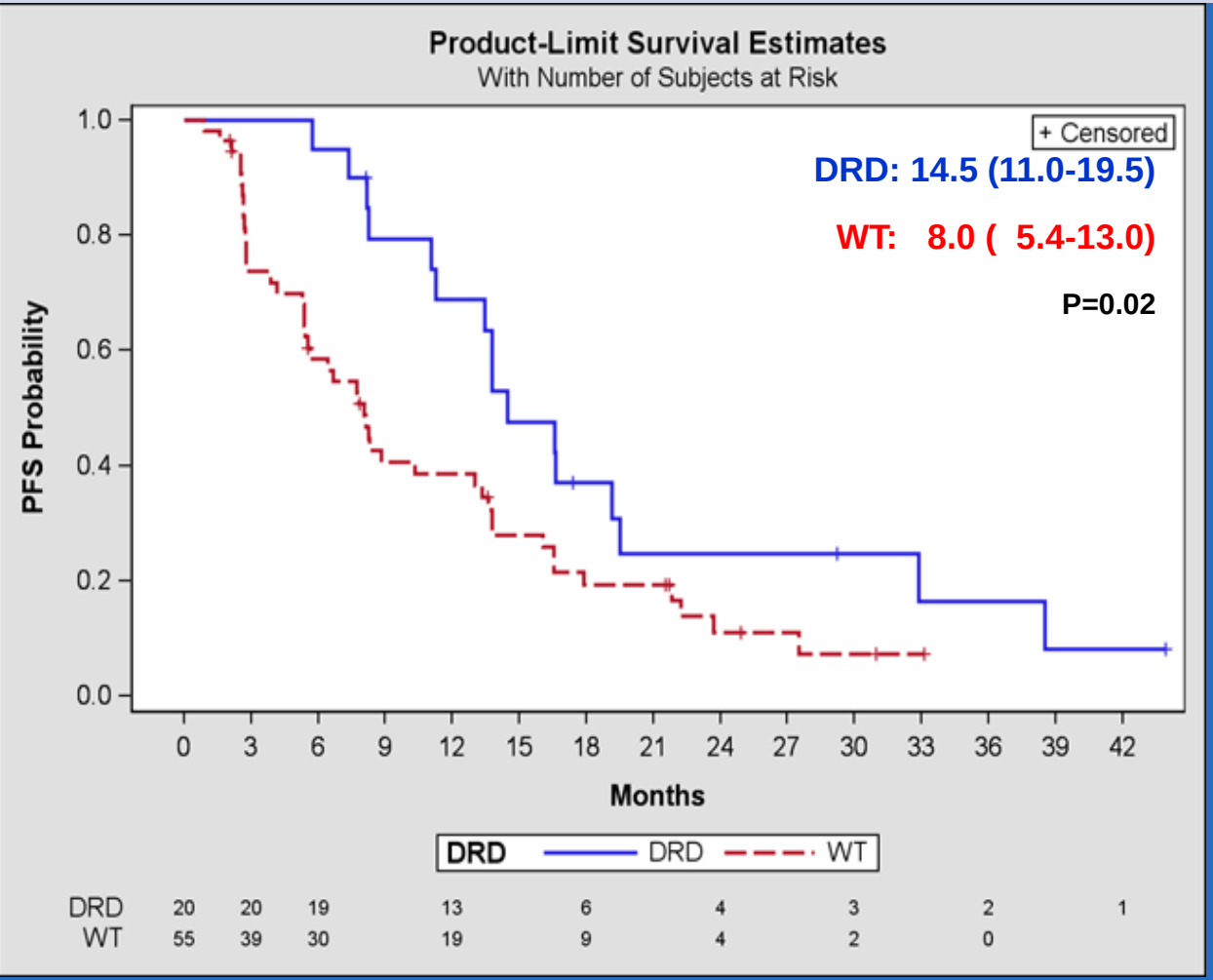


Could a genomic classifier be developed to determine who does well with ADT alone, vs who benefits from adding chemo?

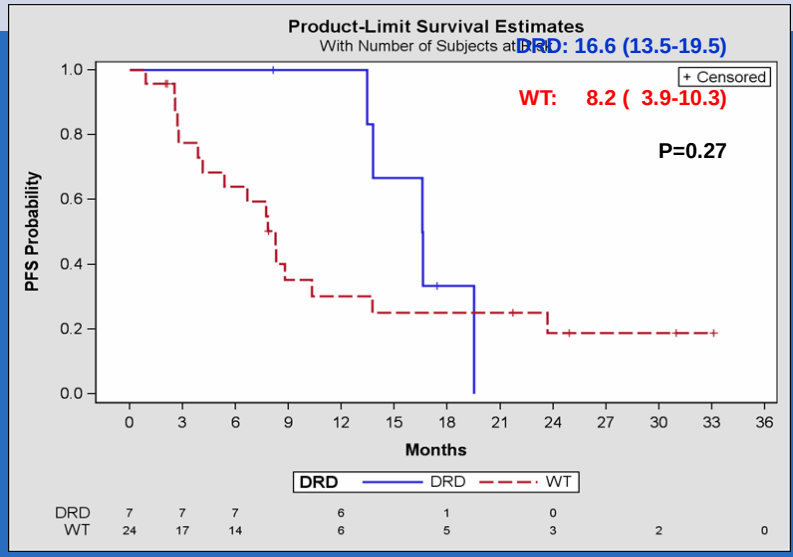
J Urol 2013, 190: 2047-53

DNA repair deficiencies may be associated with responsiveness to AR targeted therapy

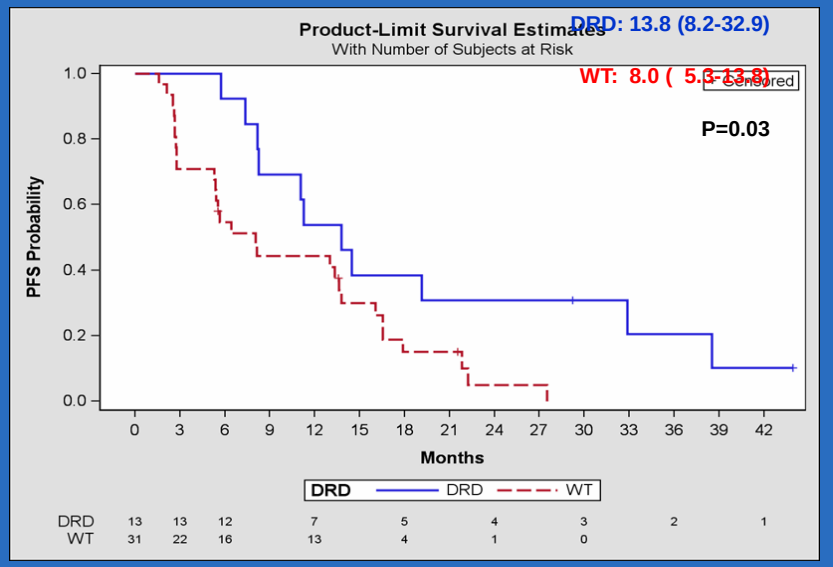
PFS by DRD status (N= 75)



Arm A: Abiraterone (N=31)

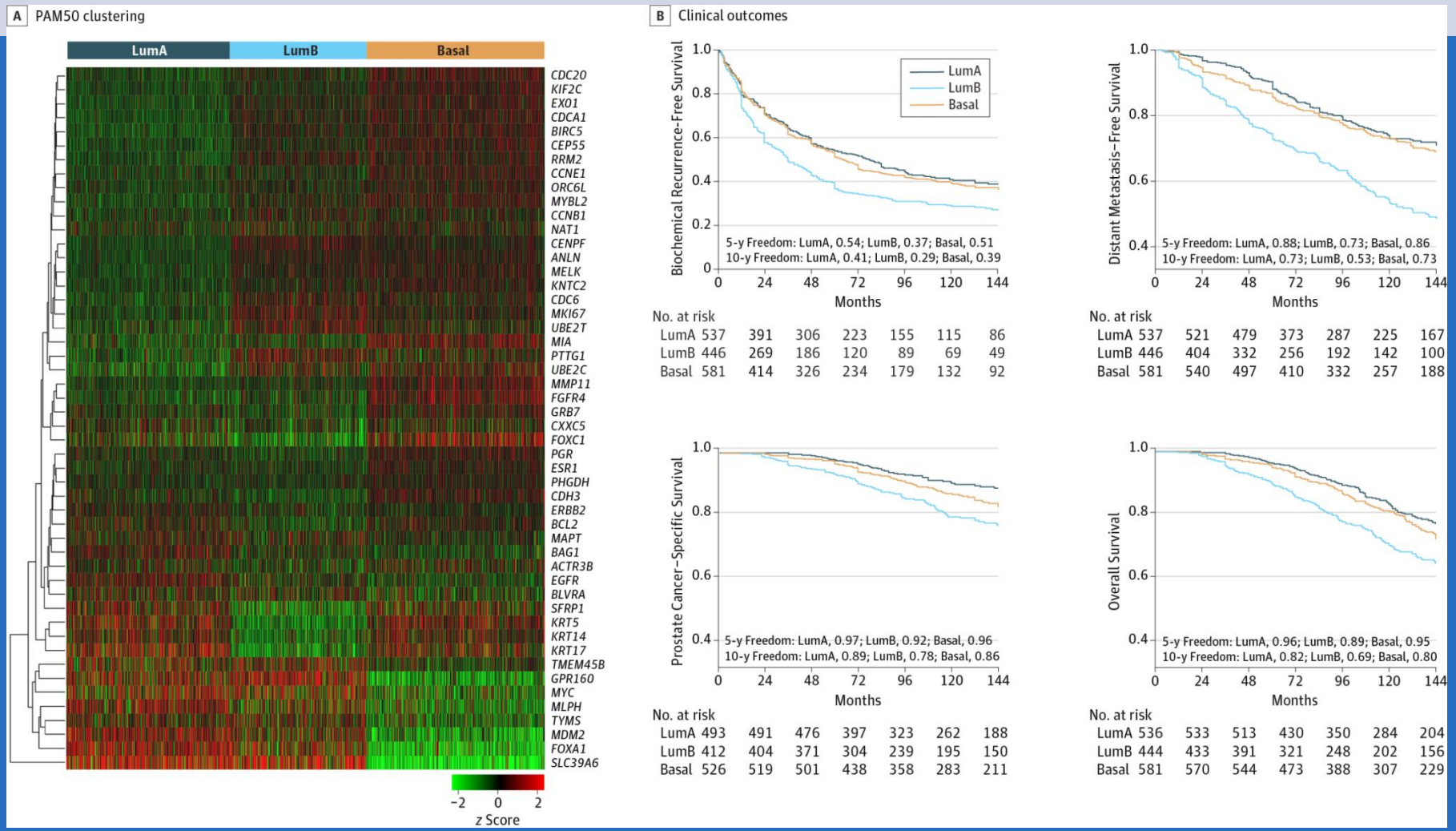


Arm B: Abiraterone + Veliparib (N=44)



Presented by: M. Hussain, MD, FACP, FASCO

Luminal and Basal Subtyping of Prostate Cancer correlates with Prognosis and response to ADT



JAMA Oncol. Published online May 11, 2017. doi:10.1001/jamaoncol.2017.0751

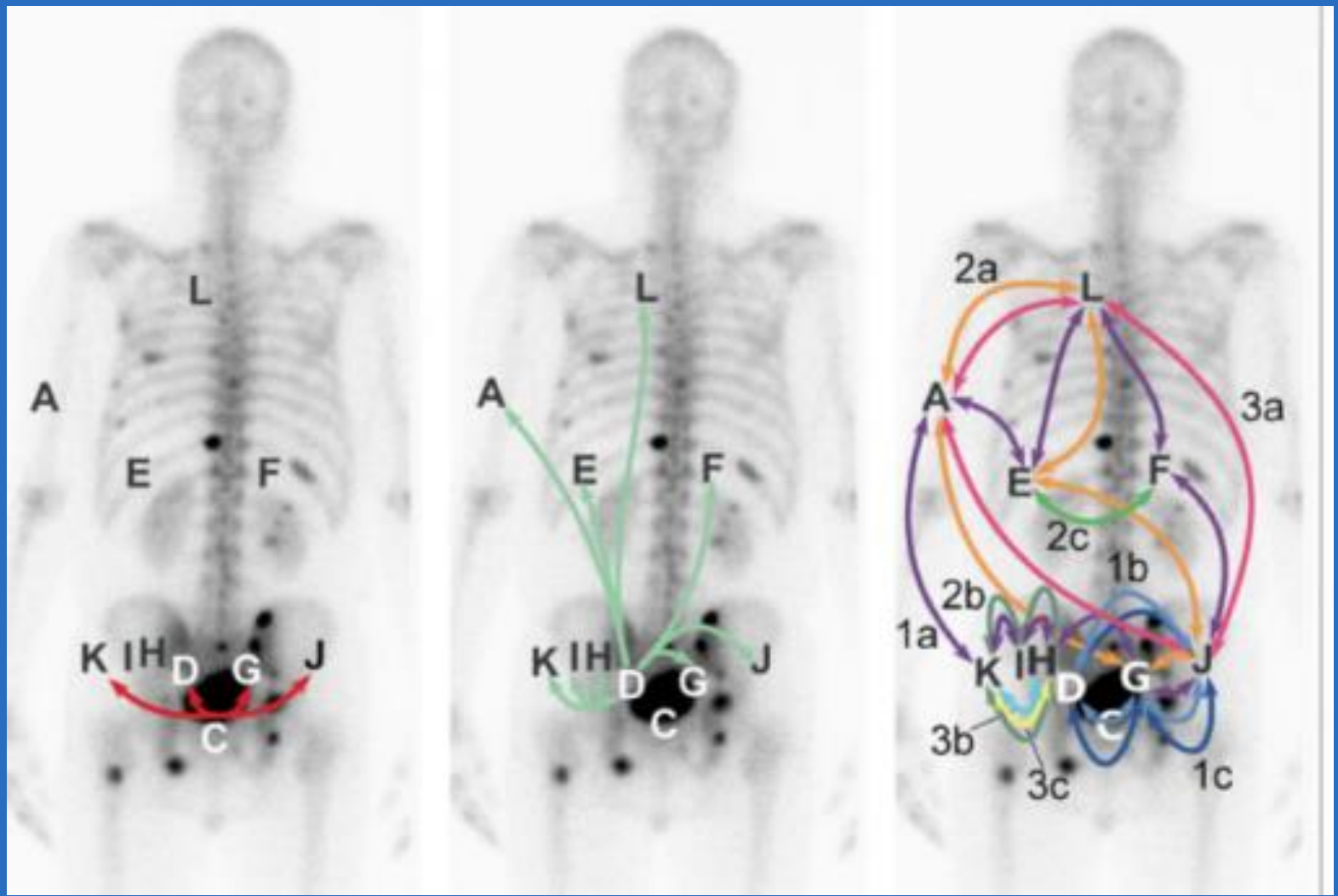
PAM50 Clustering and Clinical Outcomes in Prostate CancerA, The PAM50 genes cluster prostate cancer samples into 3 subtypes, luminal A (LumA), luminal B (LumB), and basal, in the pooled prostate cancer cohorts (Mayo Clinic I and II, Cleveland Clinic, Thomas Jefferson University, Johns Hopkins University, and Durham Veterans Affairs) using hierarchical clustering of the genes. Each column represents a patient sample, and each row represents a gene. B, Kaplan-Meier curves showing that the PAM50 clusters risk stratify biochemical recurrence-free survival, distant metastasis–free survival, prostate cancer–specific survival, and overall survival.

Genomically targeted trials are a reality! Starting to target the HSPC space

Agent	Genomic Alteration	Treatment setting	N	Status
GSK 2636771	PTEN deficient	mCRPC, prog dz on enzalutamide	64	ongoing
Ipatasertib	PTEN loss	mCRPC 1st line; abiraterone +/- ipat	850	ongoing
Palbociclib	**RB+**	**mHSPC**	**60**	**Completed accrual**
Rucaparib (TRIUMPH)	**Germline DNA repair def**	**mHSPC**	**30**	**ongoing**

Migration of Metastases

Gundem G et al. *Nature*. 2015;520(7547):353-357



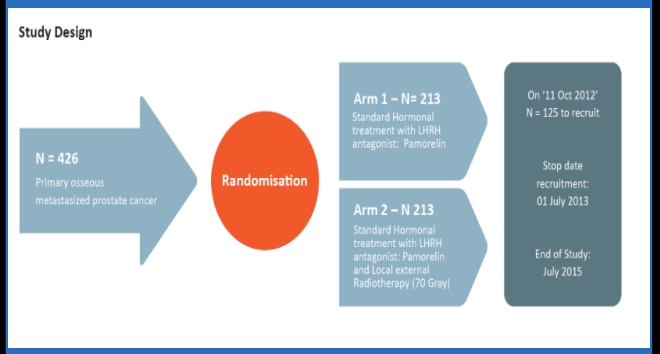
A – L humerus BM
D – Seminal vesicle
C – Prostate
E – L adrenal

F – R adrenal
G – Bladder
H – Pelvic LN
I – L pelvic LN

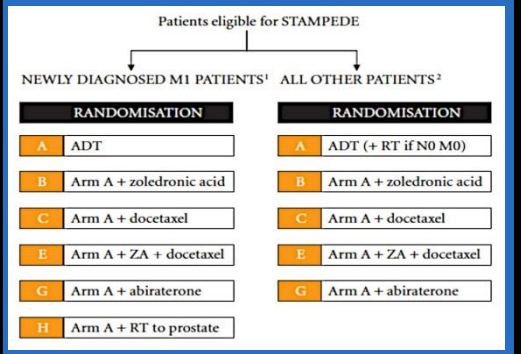
J – R pelvic LN
K – L pelvic LN
L – L media LN

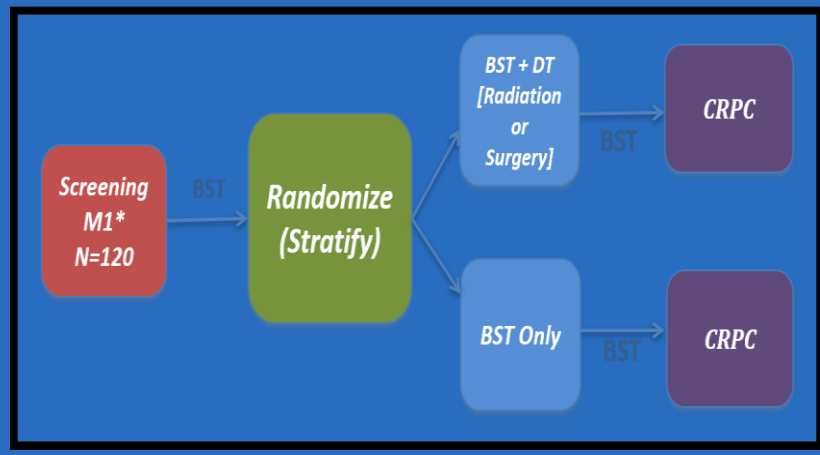
Prospective RANDOMIZED ADT +/- Local Therapy in M1 Disease

HORRAD

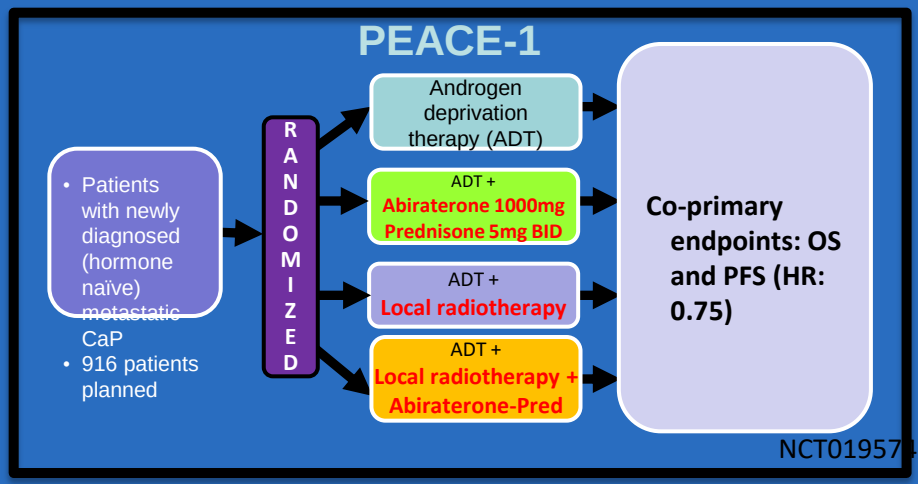


STAMPEDE





PEACE-1



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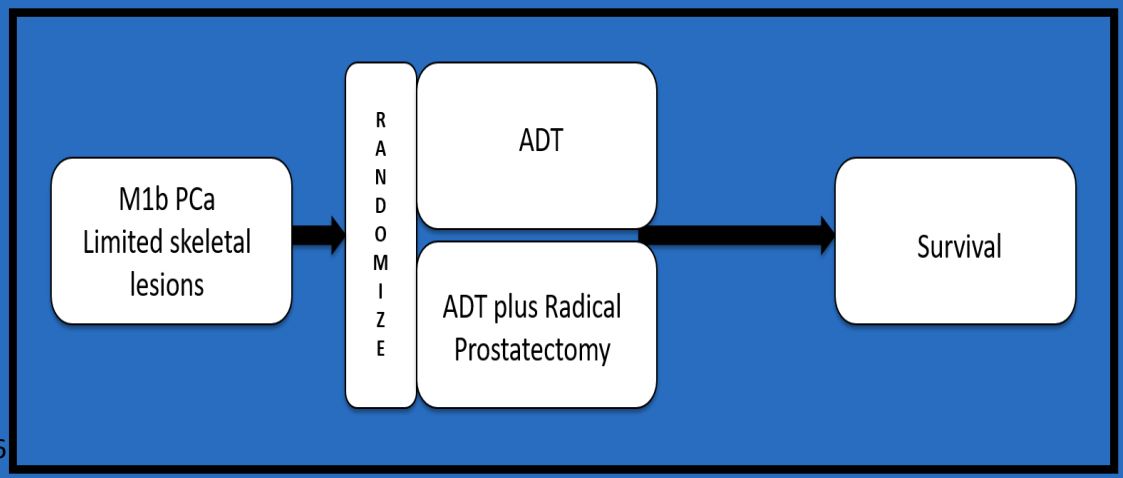
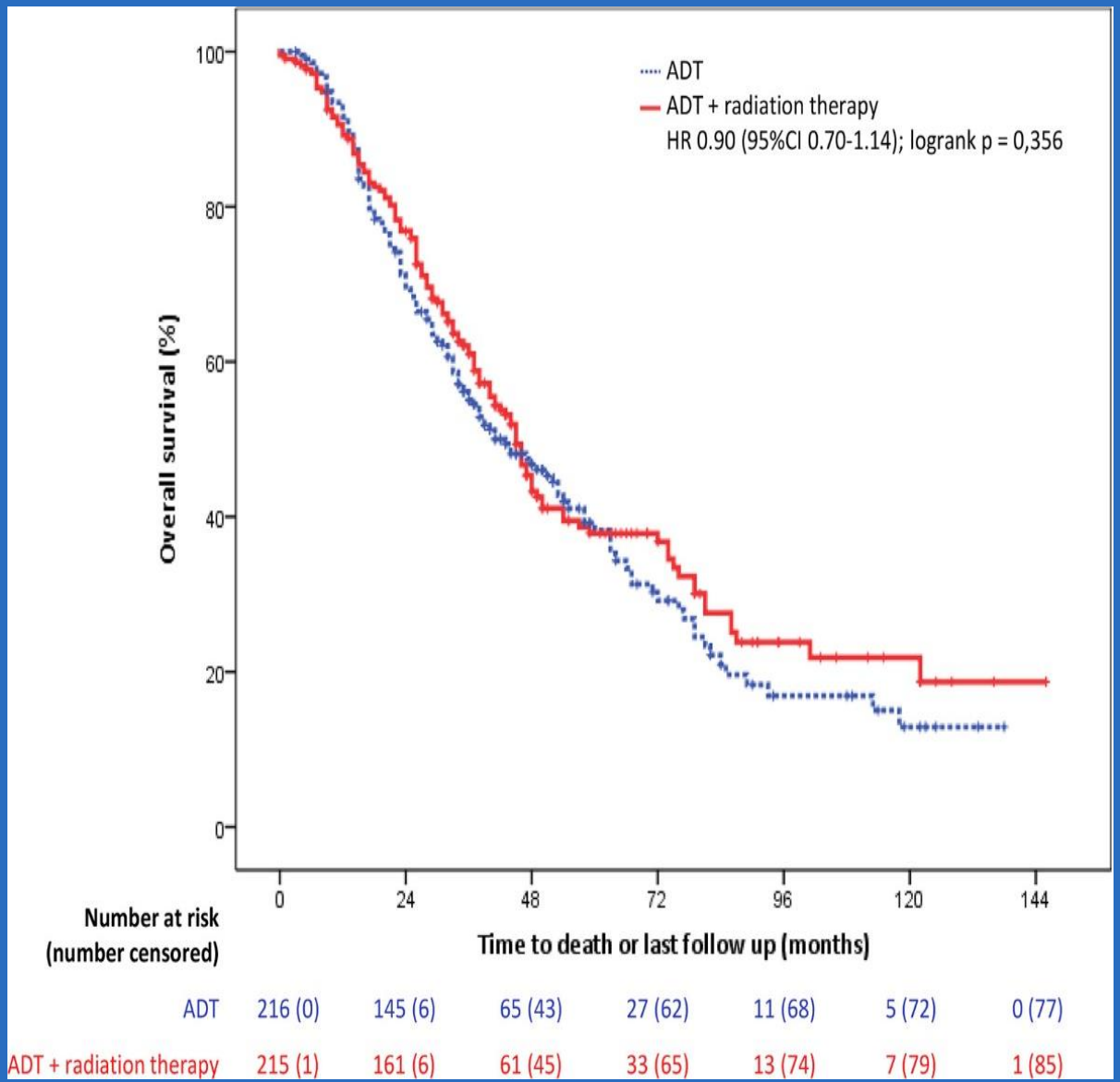


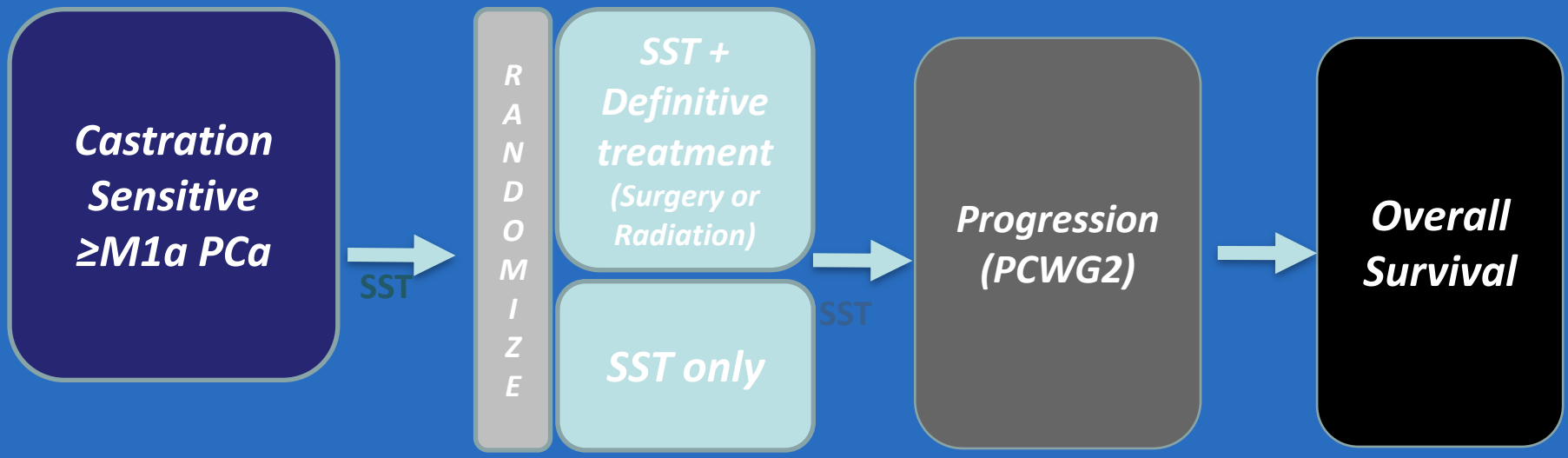
The HORRAD Study
high volume metastatic disease



Presented by: Boeve at AUA 2018

Slide courtesy of Brian Chapin, MDACC

Randomized, Phase III Trial of Standard Systemic Therapy (SST) or SST Plus Definitive Treatment of the Primary Tumor in Metastatic Prostate Cancer (S1802)

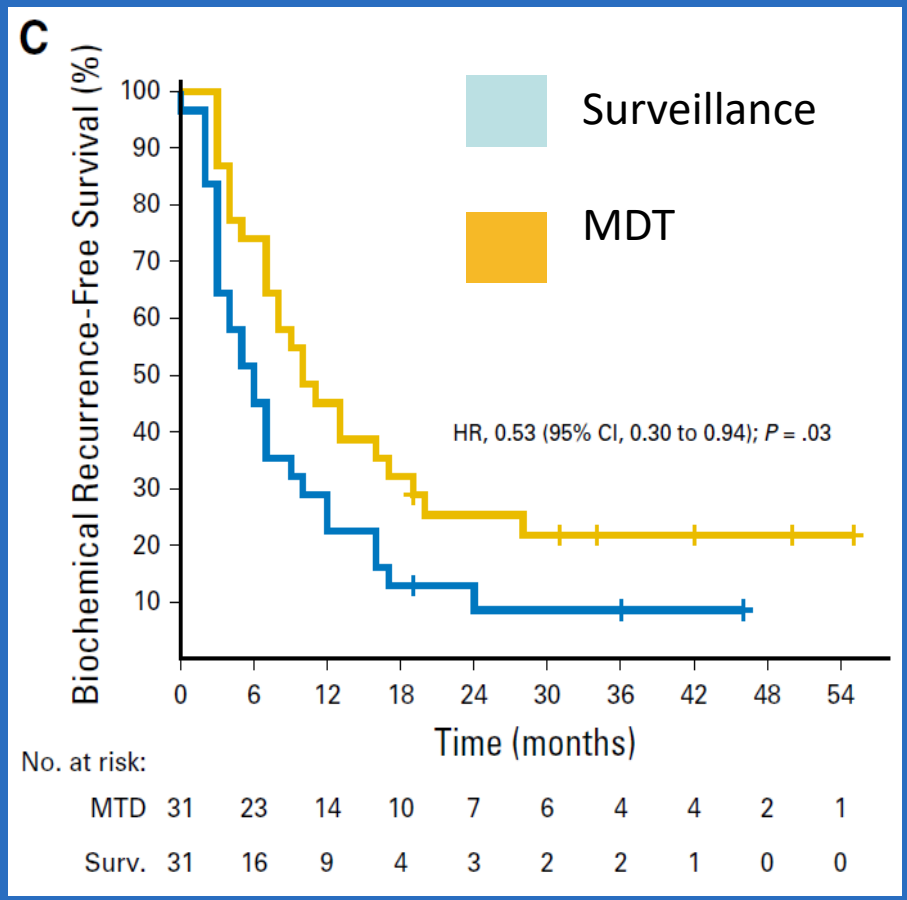


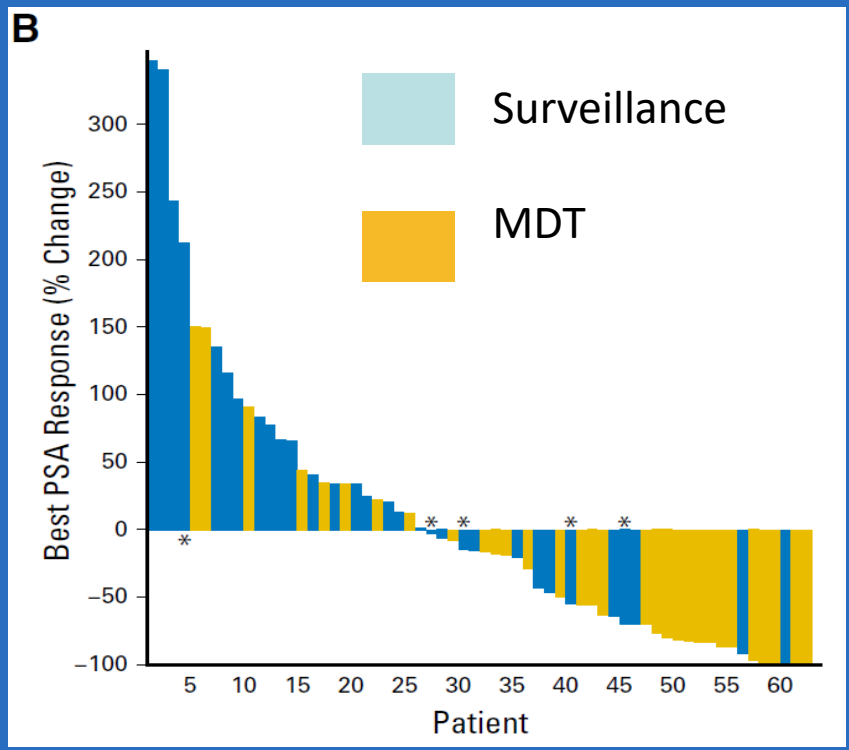
PI: Brian F Chapin, MD

SWOG : Dan Lin, David Quinn, Ana Aparicio, Cathy Tangen, Nicholas Vogelzang, Ian Thompson

Supported by: NCTN

Surveillance or Metastasis Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Phase II Trial





Ost P et al. JCO. Dec 2017

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

AR-targeted therapies and XRT to primary or (oligo)met sites: which agent?

Maryam Ghashghaei, Thierry Muanza,

DOI: 10.1158/1538-7445.AM2018-858

AACR 2018 abstr 858: radiosensitization of cell lines with abi or enza

		A		B		C	
		ENZA	ABI	ENZA	ABI	ENZA	ABI
AD	LNCaP	1.35±0.02	1.05±0.01	1.75±0.08	1.00	1.30±0.05	1.00
	PC3-AR T877A	1.30±0.03	1.00	1.65±0.01	1.00	1.35±0.06	1.05±0.02
AI	PC3	1.00	1.00	1.00	1.00	1.00	1.00
	PC3-AR V7	1.00	1.00	1.00	1.00	1.00	1.00

Conclusions

- Almost all metastatic prostate cancer patients should receive up-front intensification (Abi/Doce)
  - Future: use genomic classification to select for even more tx or de-intensification?
- Novel therapies adding to ADT in mHSPC are targeting molecular sub-populations
- Treatment of the primary and/or oligomets is best done as part of a clinical trial