Prostate Cancer Management in North Carolina: Updates for 2020

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UNC LINEBERGER UNC CANCER CARE

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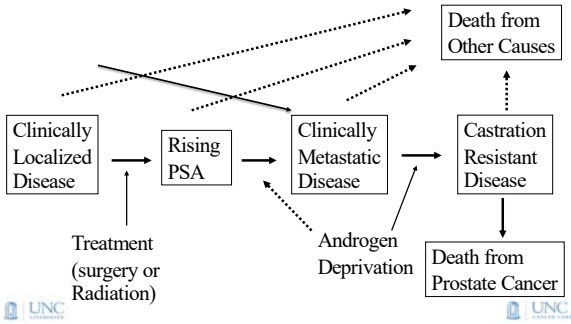
Natural History of Treated Prostate Cancer



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Case Presentation

- A 75 yo man presented with urinary symptoms. PSA 147. DRE nl.
- Prostate bx: Gleason 4+4=8, 6/12 cores positive.
- CT a/p unremarkable
- Bone scan shows 3 foci of uptake in vertebral spine
- Met volume category?

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E3805: CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

- Newly diagnosed met prostate CA
  - High volume – visceral met or 4+ bone mets (1 outside of spine/pelvis)

  vs
  - Low volume (all others)

ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

NEJM 2015; 373:737

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E3805: CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

- Newly diagnosed met prostate CA
  - High volume vs Low volume
- Prior ADT <120 days
- No prior docetaxel
- Randomized between docetaxel for 6 cycles vs no chemo

ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

NEJM 2015; 373:737

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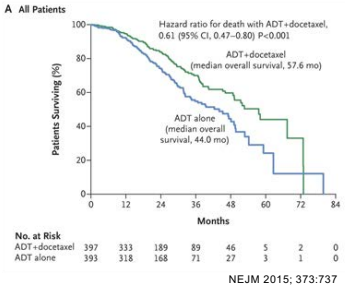
Increased Survival by 13.6 months in Patients Getting Docetaxel Chemo



NEJM 2015; 373:737

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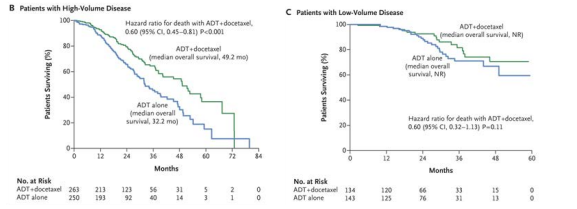
High Volume vs Low Volume



NEJM 2015; 373:737

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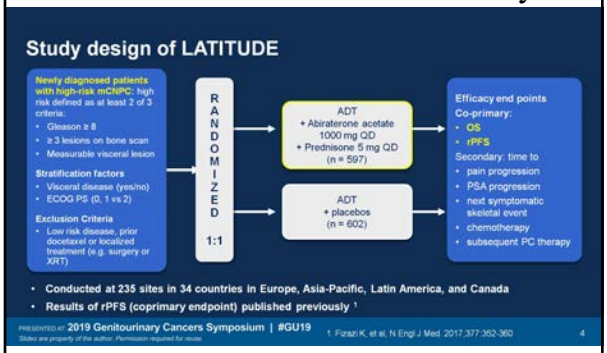
Abiraterone in Hormone Sensitive Prostate Cancer: LATITUDE study



Presented By Karim Fizazi at 2019 Genitourinary Cancers Symposium

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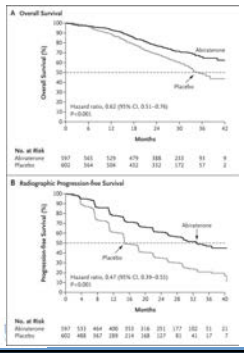
Improved Outcome with Abiraterone



- OS improved with HR of 0.62 (NR vs 34.7 mo)
- rPFS (HR 0.47, 33 mo vs 14.8 mo)
- Expected toxicity
  - HTN, hypokalemia
  - LFT abnormalities
  - Cardiac (any, 12% vs 8%)

NEJM 2017; 377:352

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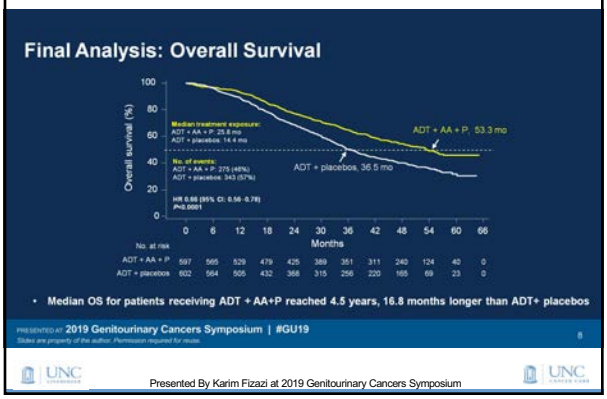
OS Improved with Abiraterone



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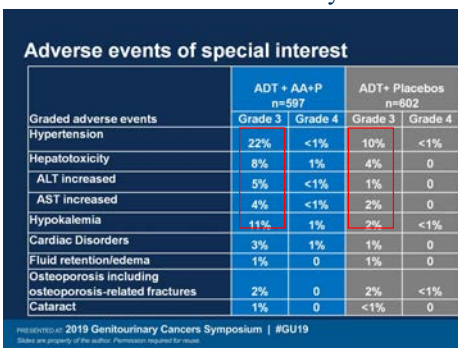
Adverse Events: Hepatotoxicity and Mineralicorticoid Excess Syndrome



Graded adverse events	ADT + AA+P n=597		ADT+ Placebos n=602	
	Grade 3	Grade 4	Grade 3	Grade 4
Hypertension	22%	<1%	10%	<1%
Hepatotoxicity	8%	1%	4%	0
ALT increased	5%	<1%	1%	0
AST increased	4%	<1%	2%	0
Hypokalemia	11%	1%	2%	<1%
Cardiac Disorders	3%	1%	1%	0
Fluid retention/edema	1%	0	1%	0
Osteoporosis including osteoporosis-related fractures	2%	0	2%	<1%
Cataract	1%	0	<1%	0

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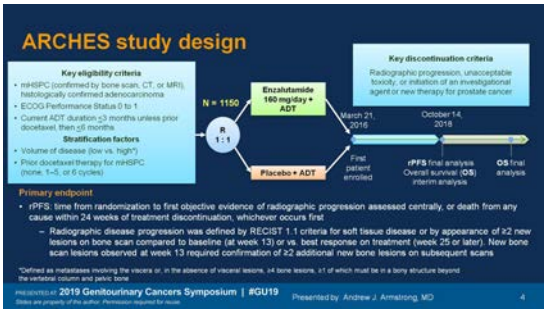
ARCHES: Phase 3 study of androgen deprivation with enzalutamide or placebo in mHSPC



Presented By Andrew Armstrong at 2019 Genitourinary Cancers Symposium

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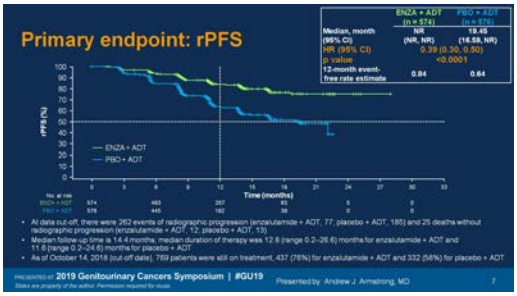
Improved radiographic progression free survival with enzalutamide



J Clin Oncol 2019; 37:2974

Presented By Andrew Armstrong at 2019 Genitourinary Cancers Symposium

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AEs of special interest

Event, n (%)	Enzalutamide + ADT (n = 872)		Placebo + ADT (n = 574)	
Any AE of special interest*	324 (56.6)		291 (50.7)	
	All grades	Grade ≥3	All grades	Grade ≥3
Convulsion	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Hypertension	49 (8.6)	19 (3.3)	36 (6.3)	12 (2.1)
Neutrophil count decreased	5 (0.9)	2 (0.3)	4 (0.7)	2 (0.3)
Cognitive / memory impairment	26 (4.5)	4 (0.7)	12 (2.1)	0
Ischemic heart disease	10 (1.7)	3 (0.5)	8 (1.4)	6 (1.0)
Other selected cardiovascular events	13 (2.3)	6 (1.0)	9 (1.6)	5 (0.9)
Posterior reversible encephalopathy syndrome	0	0	0	0
Fatigue	138 (24.1)	10 (1.7)	112 (19.5)	9 (1.6)
Fall	21 (3.7)	2 (0.3)	15 (2.6)	1 (0.2)
Fractures	37 (6.5)	6 (1.0)	24 (4.2)	6 (1.0)
Loss of consciousness	9 (1.6)	6 (1.0)	1 (0.2)	1 (0.2)
Thrombocytopenia	3 (0.5)	0	3 (0.5)	0
Musculoskeletal events	151 (26.4)	9 (1.6)	159 (27.7)	12 (2.1)
Severe cutaneous adverse reactions	0	0	1 (0.2)	0
Angioedema	7 (1.2)	1 (0.2)	1 (0.2)	0
Rash	15 (2.6)	0	9 (1.6)	0
Second primary malignancies	11 (1.9)	9 (1.6)	11 (1.9)	7 (1.2)

Bold: AEs (all grades) that occur >2% in enzalutamide + ADT compared with placebo + ADT
*Based on pre-specified combinations of preferred terms (MedDRA 21.0) related to the AE of special interest; the only AEs of special interest that were grade 5 were in the enzalutamide + ADT group (ischemic heart disease, n=1; other selected cardiovascular events, n=1)

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J Clin Oncol 2019; 37:2974

Presented By Andrew Armstrong at 2019 Genitourinary Cancers Symposium

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Phase 3 randomized trial of standard of care therapy with or without enzalutamide for mHSPC

Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

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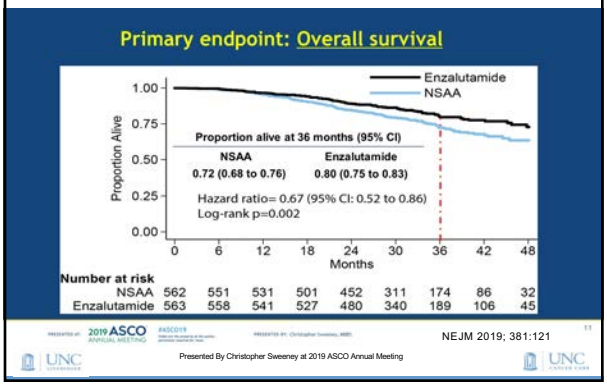
Survival improvement with enzalutamide



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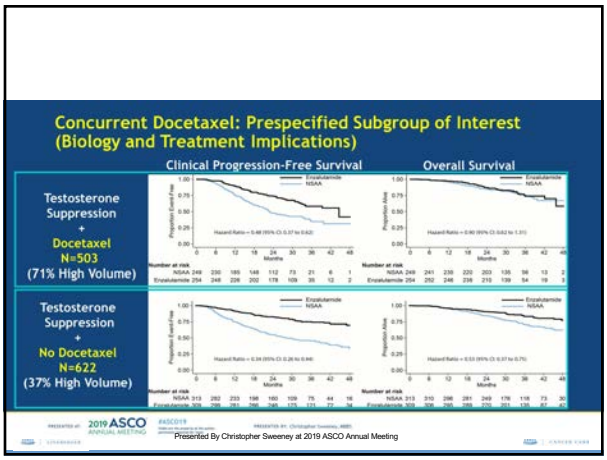

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Adverse events of enzalutamide

	TS + NSAA N=558		TS + ENZA N=563	
Serious AE rate per yr of Rx exposure	0.33	95% CI: 0.28-0.39	0.34	95% CI: 0.29-0.40
AEs of Interest	N	%	N	%
Hypertension: Gde 3	24	4%	43	8%
Gde 2	30	5%	60	11%
Fatigue: Gde 3	4	1%	31	6%
Gde 2	80	14%	142	25%
Falls: Gde 3	2	<1%	6	1%
Gde 2	8	1%	28	5%
Syncope	7	1%	20	4%
Concentration Impairment: Gde 1/2	6	1%	24	4%
Any Seizure	0	0%	7	1%

Selected adverse events (AE)*:

All patients at anytime

*worst grade AE shown

2019 ASCO
NEJM 2019; 381:121
Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

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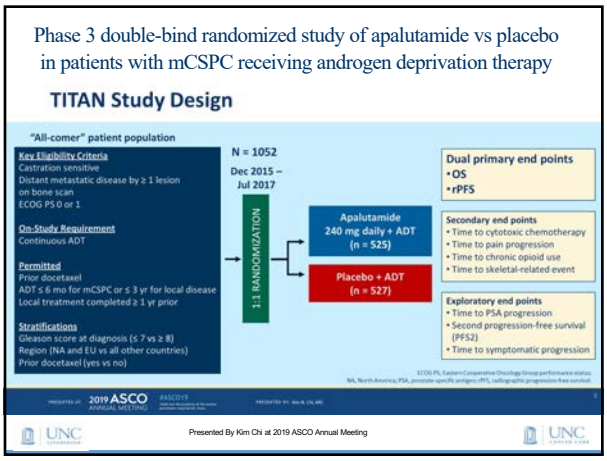
Phase 3 double-bind randomized study of apalutamide vs placebo in patients with mCSPC receiving androgen deprivation therapy



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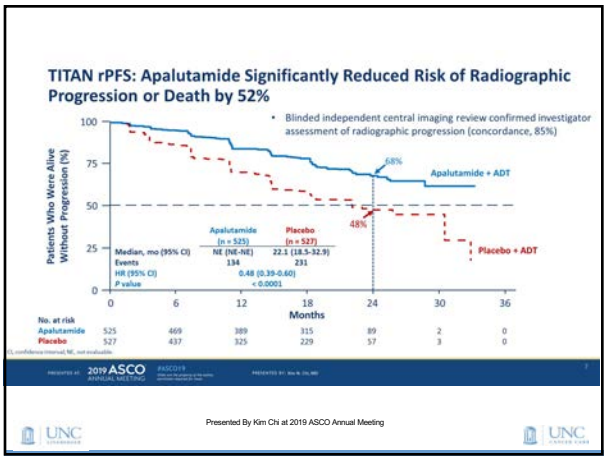

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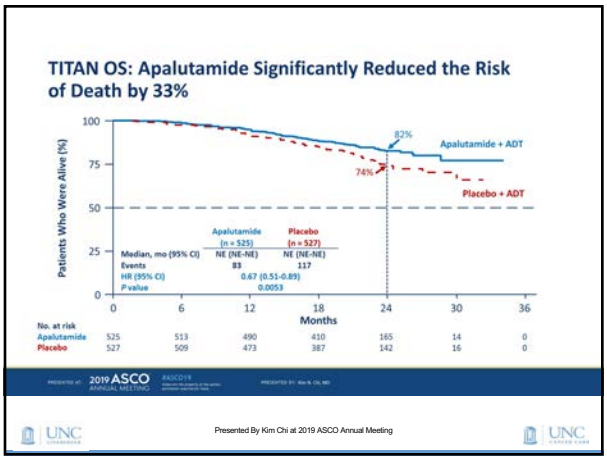

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Summary of data for intensification of mHSPC therapy

Trial	Drug	Outcome
CHAARTED and STAMPEDE	Docetaxel	OS improvement (high volume disease)
LATITUDE and STAMPEDE	Abiraterone	OS improvement
ARCHES and ENZAMET	Enzalutamide	PFS/OS improvement
TITAN	Apalutamide	OS improvement

- Benefit vs Toxicity
- Cost
- Patient comorbidities and preferences

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My personal approach for mHSPC therapy

- For some (poor PS, comorbities, age, etc), ADT only reasonable
- Consider docetaxel for healthy young pts, high vol disease, visceral mets
- Unless contraindicated (eg, CHF), I prefer abiraterone/prednisone
- Enzalutamide (or apalutamide) is a reasonable alternative.

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Castration resistant prostate cancer

- Definition: castrate testosterone and two consecutive PSA rise or scans progressing
- FDA-approved agents
  - Cytotoxic chemo (docetaxel, cabazitaxel)
  - Androgen receptor signaling inihbitors
    - Abiraterone, enzalutamide, apalutamide, darolutamide
  - Radium 223, alpha-emitter radiopharmaceutical
  - Sipuleucel-T, cellular immunotherapy

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Case presentation

- A 75 yo man was diagnosed with met prostate cancer.
  - PSA 150 ng/ml.
  - Bx Gleason 4+4=8.
  - Bone scan showed 10 foci of uptake.
- The patient is otherwise healthy and no other medical history.
- The family history is negative for prostate cancer or any other history of cancer.

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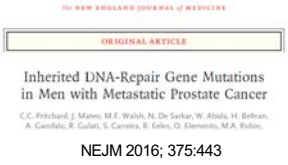
Genetics of met PC

- Sequencing of 20 DNA-repair genes in germline DNA from 692 mPC patients demonstrated 11.8% had mutation in DNA-repair gene
  - BRCA2 – 5.3%
  - ATM – 1.6%
  - CHEK2 – 1.9%
  - BRCA1 – 0.9%
  - Long tail
- No impact of fam history or age


ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

NEJM 2016; 375:443

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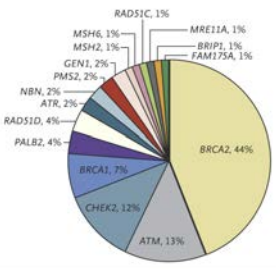
Distribution of germline mutations



Pritchard CC et al. N Engl J Med 2016;375:443-453.

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Germline testing in prostate cancer

- NCCN recommends germline testing of all patients with metastatic prostate cancer
  - Also, if tumor sequencing positive.
- Genetic counselor should provide post-test counseling for those testing positive, for "cascade" testing of relatives

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Treatment of mCRPC with DNA-repair mutation

- ~30% of mCRPC may have a mutation in DNA repair genes (germline or somatic)
- Treatment with Olaparib, a PARP inhibitor, led to a high response rate

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson,

NEJM 2015: 373:1697

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PROfound: Phase 3 study of olaparib vs enzalutamide or abiraterone for mCRPC with homologous recomb repair gene alterations

- 245 mCRPC patients with tumor mutation in BRCA2/1, ATM were randomized to olaparib vs physician choice (enza or abi)
- Olaparib led to improved rPFS (7.4 vs 3.6 mo), response rate (33.3 vs 2.3%), trend for OS (18.5 vs 15.1 mo)

Annals of Oncology, 2019; 30: suppl_5, LBA12_PR

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References

- Sartor & de Bono, Metastatic prostate cancer, NEJM, 2018, 378:645-57
  - Great overview of current therapeutics

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