Therapeutic Advances in Prostate Cancer

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THE ANNUAL APSHO MEETING

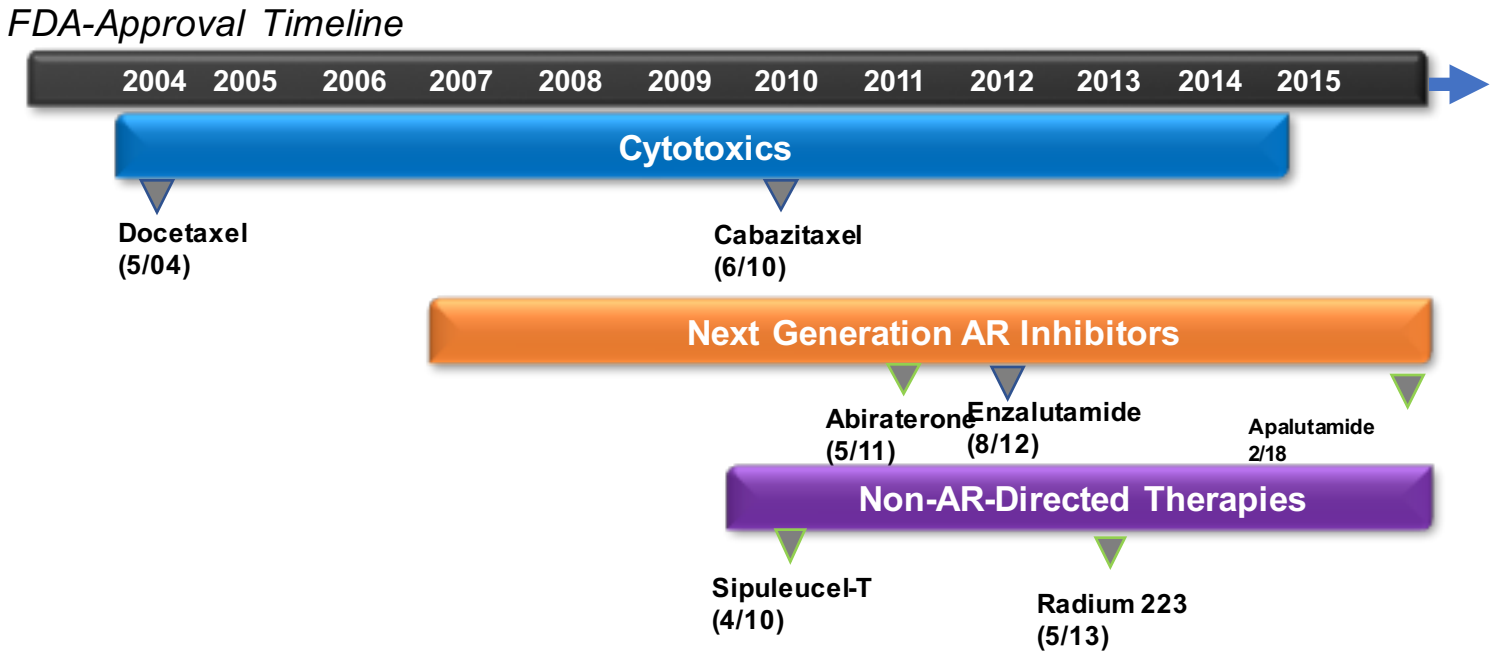
Learning Objectives

1. Identify clinical data of emerging and current agents for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) for rapidly rising prostate specific antigen (PSA) levels
2. Evaluate the role of docetaxel and abiraterone in newly diagnosed metastatic prostate cancer
3. Interpret emerging data regarding the role of genomics in metastatic castration-sensitive and -resistant prostate cancer
4. Devise strategies to manage toxicities of current and emerging treatments for advanced prostate cancer

Financial Disclosure

- Dr. Dreicer has acted as a consultant for Astellas, AstraZeneca, Genentech/Roche, Incyte, and Pfizer.
- Dr. Diven has nothing to disclose.

Relative FDA Approval Timeline of Agents Used in Metastatic Castration-Resistant Prostate Cancer



AR = androgen receptor.

Challenges in Managing Patients With PSA-Only Disease

- Moving the patient (and some of his docs) away from a curative mindset
- Recognition of limitations of therapy
  - "Really early ADT"
- Using PSADT to inform timing of evaluation/intervention

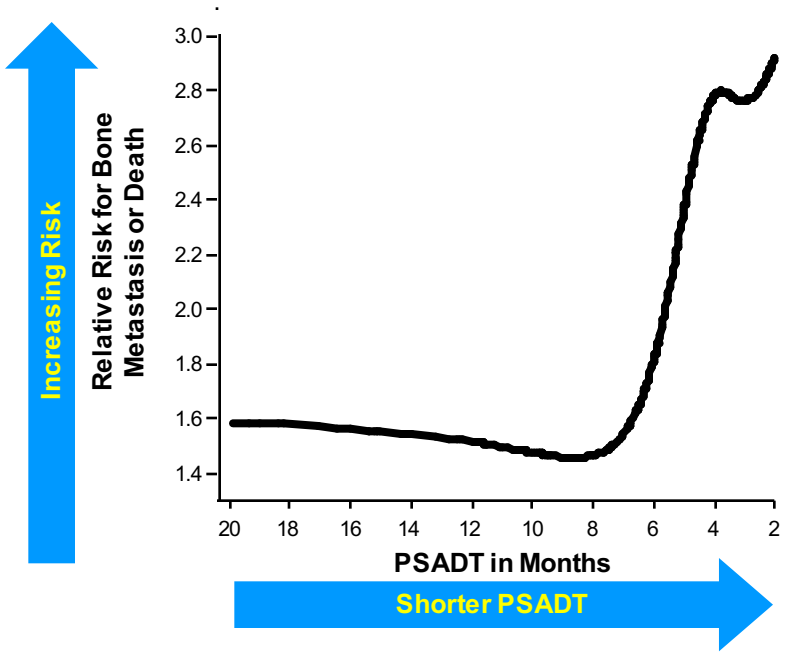
ADT = androgen deprivation therapy; PSADT = prostate-specific antigen doubling time.

Castration-Resistant PSA-Only Disease: Metaphysics

- New disease subsets followed introduction of PSA into clinical practice in the late 1980s
  - PSA or biochemical failure followed rapidly by PSA progression in the castrate state
- Use of ADT broadly used (primarily in the US) to "reduce PSA"
- Presumption of "undetectable" metastatic disease
- Impact of advanced imaging
- Most patients with PSA only disease do not die of prostate cancer
  - But some do

Relationship Between PSADT and Risk for Bone Metastasis or Death

- Placebo arm of effect of denosumab on prolonging bone metastasis-free survival in men with non-metastatic castration-resistant prostate cancer



Smith MR, et al J Clin Oncol 2013;31:3800-06.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

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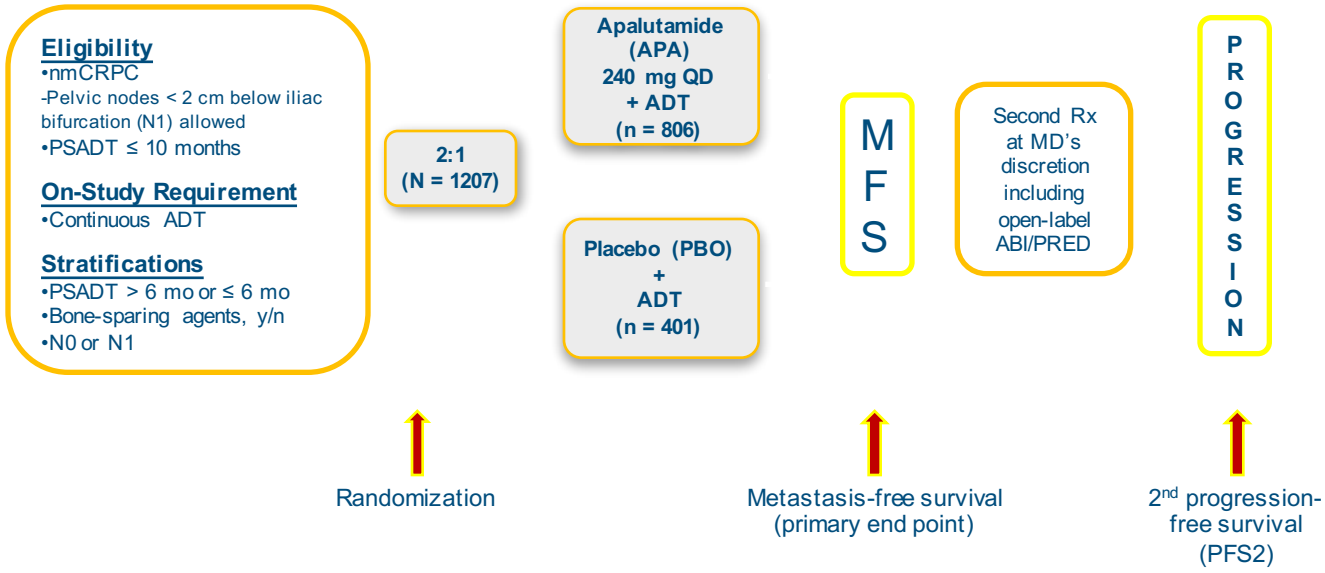
Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer

Maha Hussain, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Per Rathenborg, M.D., Neal Shore, M.D., Ubirajara Ferreira, M.D., Ph.D., Petro Ivashchenko, M.D., Eren Demirhan, Ph.D., Katharina Modelska, M.D., Ph.D., De Phung, B.S., Andrew Krivoshik, M.D., Ph.D., and Cora N. Sternberg, M.D.

ABSTRACT

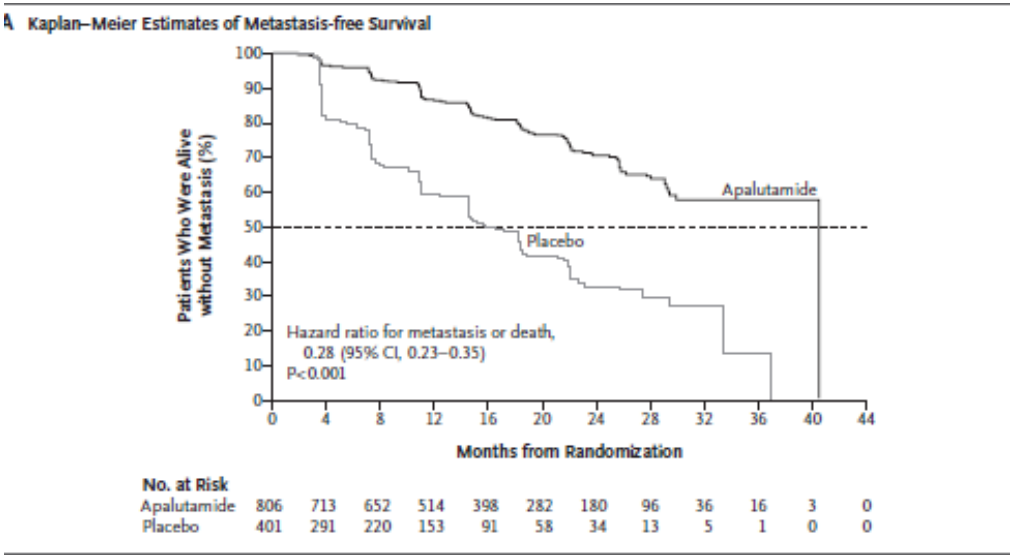
SPARTAN: Overall Study Design

- Phase 3 placebo-controlled, randomized international study



ABI/PRED = abiraterone acetate plus prednisone; nmCRPC = nonmetastatic castration-resistant prostate cancer; MFS = metastasis-free survival.

Presented by: Eric Small, MD, FASCO; NCT01946204.



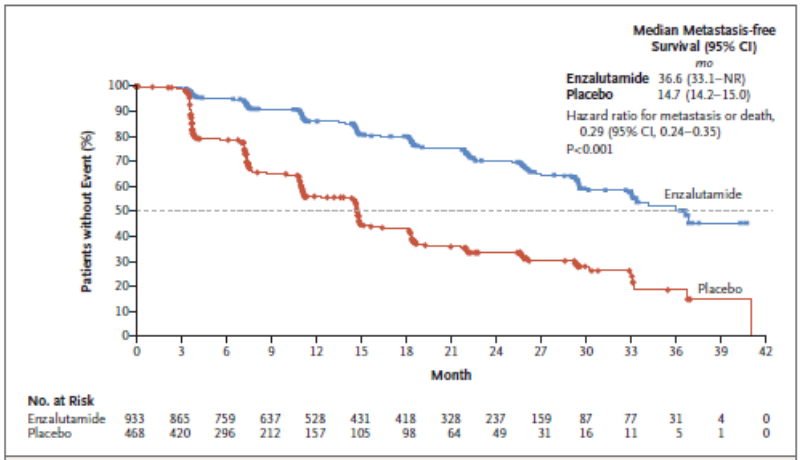


Figure 1. Kaplan–Meier Estimate of Metastasis-free Survival.
Shown are data for the primary end point of metastasis-free survival. The dashed line indicates the median. The hazard ratio was based on a Cox regression model that was stratified according to the prostate-specific antigen (PSA) doubling time (<6 months vs. ≥6 months) and previous or current use of a bone-targeting agent (yes vs. no), with trial group as the only covariate and a value less than 1.00 favoring enzalutamide treatment. Symbols indicate censored data. NR denotes not reached.

Hussain M, et al. N Engl J Med 2018,378:2465; Smith M, et al. N Engl J Med 2018, 378:1408

Table 3. Adverse Events.

Adverse Event*	Apalutamide (N=803)		Placebo (N=398)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients (%)			
Any adverse event	775 (96.5)	362 (45.1)	371 (93.2)	136 (34.2)
Serious adverse event	199 (24.8)	—	92 (23.1)	—
Adverse event leading to discontinuation of the trial regimen	85 (10.6)	—	28 (7.0)	—
Adverse event associated with death	10 (1.2)	—	1 (0.3)	—
Adverse events that occurred in ≥15% of patients in either group†				
Fatigue‡	244 (30.4)	7 (0.9)	84 (21.1)	1 (0.3)
Hypertension	199 (24.8)	115 (14.3)	79 (19.8)	47 (11.8)
Rash‡	191 (23.8)	42 (5.2)	22 (5.5)	1 (0.3)
Diarrhea	163 (20.3)	8 (1.0)	60 (15.1)	2 (0.5)
Nausea	145 (18.1)	0	63 (15.8)	0
Weight loss	129 (16.1)	9 (1.1)	25 (6.3)	1 (0.3)
Arthralgia	128 (15.9)	0	30 (7.5)	0
Falls‡	125 (15.6)	14 (1.7)	36 (9.0)	3 (0.8)
Other adverse events of interest				
Fracture‡	94 (11.7)	22 (2.7)	26 (6.5)	3 (0.8)
Dizziness	75 (9.3)	5 (0.6)	25 (6.3)	0
Hypothyroidism‡	65 (8.1)	0	8 (2.0)	0
Mental-impairment disorder§	41 (5.1)	0	12 (3.0)	0
Seizure‡	2 (0.2)	0	0	0

Smith M, et al. N Engl J Med 2018, 378:1408

Table 3. Adverse Events.

Event	Enzalutamide Group (N=930)		Placebo Group (N=465)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	808 (87)	292 (31)	360 (77)	109 (23)
Any serious adverse event*	226 (24)	—	85 (18)	—
Adverse event leading to discontinuation of trial regimen	87 (9)	—	28 (6)	—
Adverse event leading to death	32 (3)	—	3 (1)	—
Most common adverse events, occurring in ≥5% of patients†				
Fatigue	303 (33)	27 (3)	64 (14)	3 (1)
Hot flush	121 (13)	1 (<1)	36 (8)	0
Nausea	106 (11)	3 (<1)	40 (9)	0
Diarrhea	91 (10)	3 (<1)	45 (10)	2 (<1)
Hypertension	111 (12)	43 (5)	24 (5)	10 (2)
Fall	106 (11)	12 (1)	19 (4)	3 (1)
Constipation	85 (9)	2 (<1)	32 (7)	2 (<1)
Dizziness	91 (10)	4 (<1)	20 (4)	0
Arthralgia	78 (8)	1 (<1)	32 (7)	1 (<1)
Asthenia	82 (9)	11 (1)	28 (6)	1 (<1)
Decreased appetite	89 (10)	2 (<1)	18 (4)	1 (<1)
Back pain	73 (8)	2 (<1)	33 (7)	1 (<1)
Headache	85 (9)	2 (<1)	21 (5)	0
Hematuria	62 (7)	16 (2)	36 (8)	13 (3)
Urinary tract infection	38 (4)	7 (1)	30 (6)	3 (1)
Weight loss	55 (6)	2 (<1)	7 (2)	0
Urinary retention	20 (2)	4 (<1)	28 (6)	5 (1)
Adverse events of special interest				
Hypertension‡	114 (12)	43 (5)	25 (5)	11 (2)
Major adverse cardiovascular event§	48 (5)	34 (4)	13 (3)	8 (2)
Mental impairment disorders¶	48 (5)	1 (<1)	9 (2)	0
Hepatic impairment	11 (1)	5 (1)	9 (2)	2 (<1)
Neutropenia	9 (1)	5 (1)	1 (<1)	1 (<1)
Convulsion	3 (<1)	2 (<1)	0	0
Posterior reversible encephalopathy syndrome	0	0	0	0

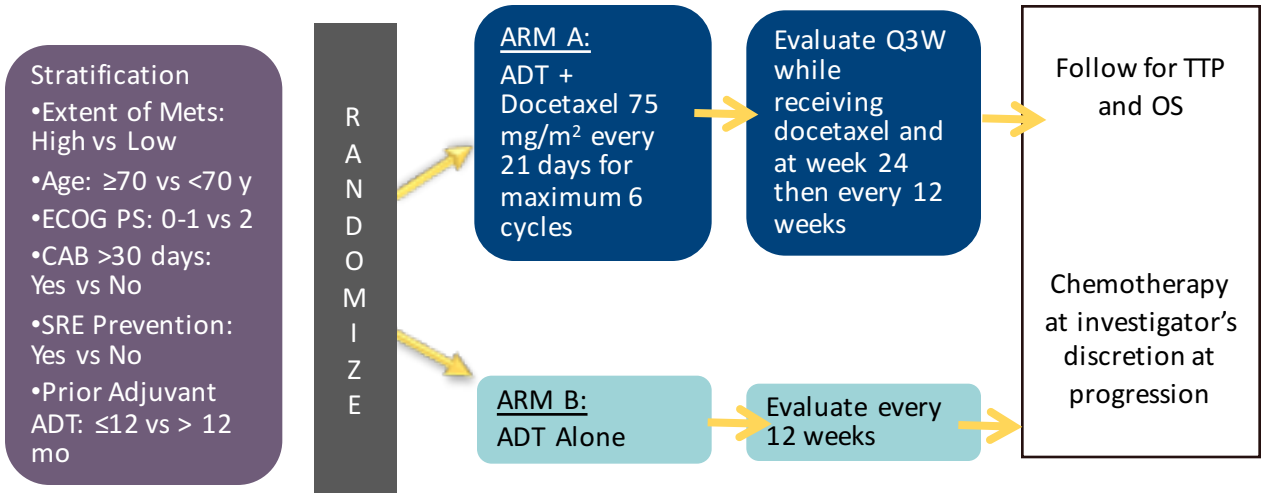
Hussain M, et al. N Engl J Med 2018,378:2465.

Metastatic Prostate Evolving Natural History

- 1982: 30% of patients presented with de novo metastatic prostate cancer
- 2018: Approximately 3% in the US (higher in other areas of the world)
- ADT as standard of care with typical initial response duration in the 24-36 month range
- Evidence that PSA nadir predicts survival

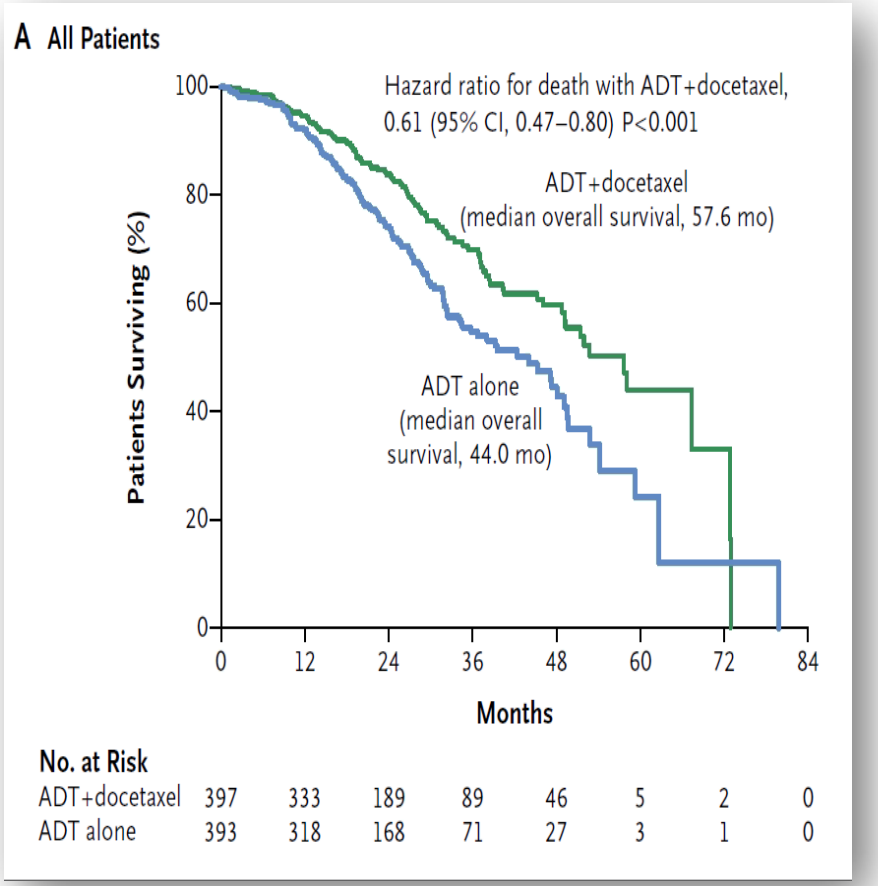
E3805: CHAARTED

- 790 patients (median age, 63 years)
- Primary endpoint: OS
- ADT allowed up to 120 days prior to randomization
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication, but no daily prednisone



ADT = androgen-deprivation therapy; CAB = complete androgen blockade; ECOG PS = Eastern Cooperative Oncology Group Performance Status; OS = overall survival; Q3W = every 3 weeks; SRE = skeletal-related event; TTP, time to progression.

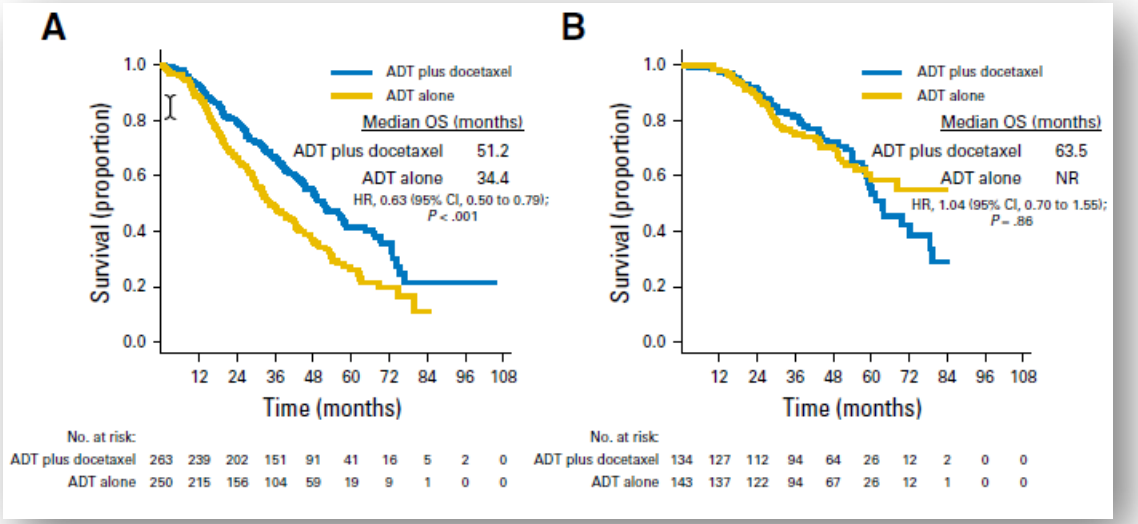
Sweeney C et al. 2014 American Society of Clinical Oncology Annual Meeting (ASCO 2014). Abstract LBA2.



Sweeny CJ, et al. N Engl J Med 2015; 373:737-746

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial

Christos E. Kyriakopoulos, Yu-Hui Chen, Michael A. Carducci, Glenn Liu, David F. Jarrard, Noah M. Hahn, Daniel H. Shevrin, Robert Dreicer, Maha Hussain, Mario Eisenberger, Manish Kohli, Elizabeth R. Plimack, Nicholas J. Vogelzang, Joel Picus, Matthew M. Cooney, Jorge A. Garcia, Robert S. DiPaola, and Christopher J. Sweeney

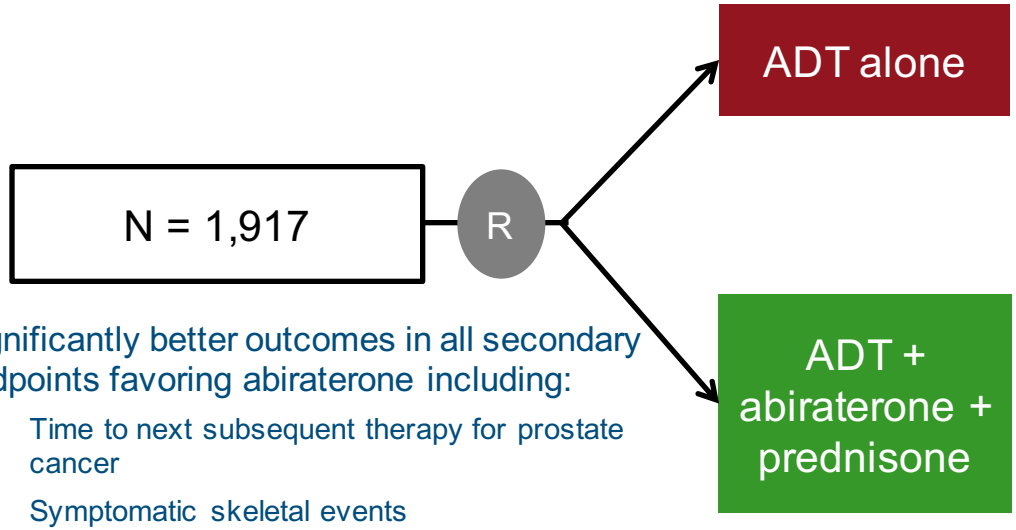


Three Relevant Clinical Trials and a Meta-Analysis

Trial	N (Median Age)	Significant Difference in OS?	% With De Novo Mets	% With High-Volume Disease	Planned Subset Analysis for Low-Risk Men
GETUG-AFU-15[1]	385 **(64 y)**	No	71	52	No (no benefit in any post hoc subset)
CHAARTED[2]	790 **(63 y)**	Yes	75	65	Yes
STAMPEDE[3]	1,817 (M+) **(65 y)**	Yes	96	Not stated	No
META-ANALYSIS[4]	2,992	Yes	87		No

1. Gravis G et al. *Lancet Oncol*. 2013;14:149-158. 2. Sweeney CJ et al. *N Engl J Med*. 2015;373:737-746.
3. James ND et al. *Lancet*. 2016;387:1163-1177. 4. Vale CL et al. *Lancet Oncol*. 2016;17:243-256.

LATITUDE: Abiraterone for Prostate Cancer Not Previously Treated With Hormone Therapy



- Significantly better outcomes in all secondary endpoints favoring abiraterone including:
  - Time to next subsequent therapy for prostate cancer
  - Symptomatic skeletal events

Median follow-up: 30.4 months

Median OS	34.7 months
Median radiographic PFS	14.8 months
Median OS	not reached
Median radiographic PFS	33.0 months

Fizazi K, et al. *N Engl J Med*. 2017;377(4):352-360.

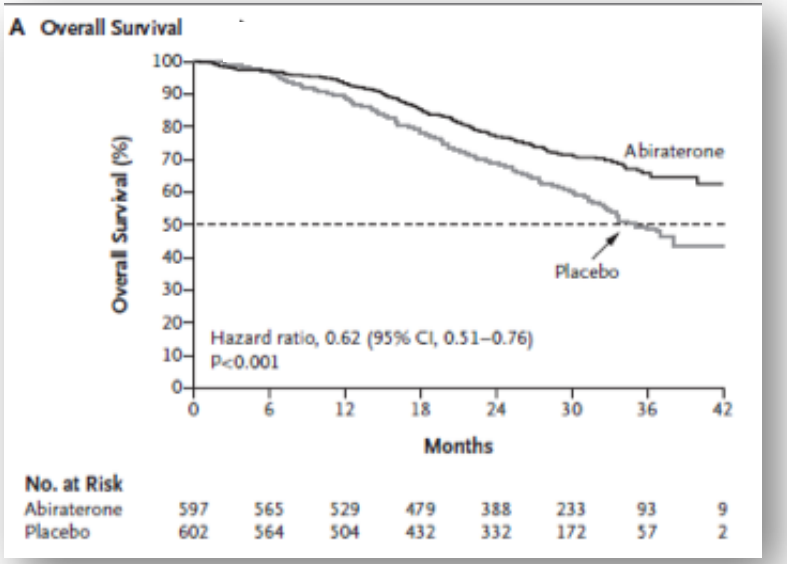
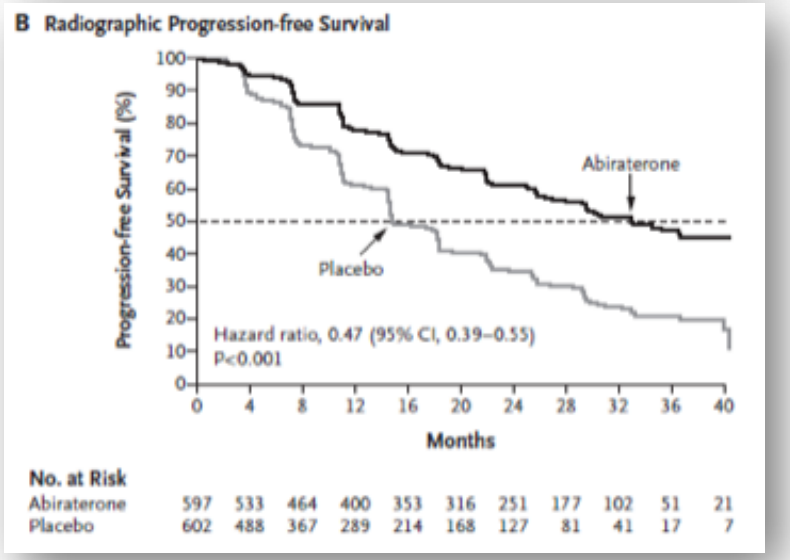


Figure 1. Kaplan–Meier Estimates of the Two Primary End Points.

Shown are data for overall survival (Panel A) and for radiographic progression-free survival (Panel B). The dashed lines indicate the median. The median rate of overall survival was not reached in the abiraterone group and was 34.7 months in the placebo group; the corresponding medians for progression-free survival were 33.0 months and 14.8 months. CI denotes confidence interval.



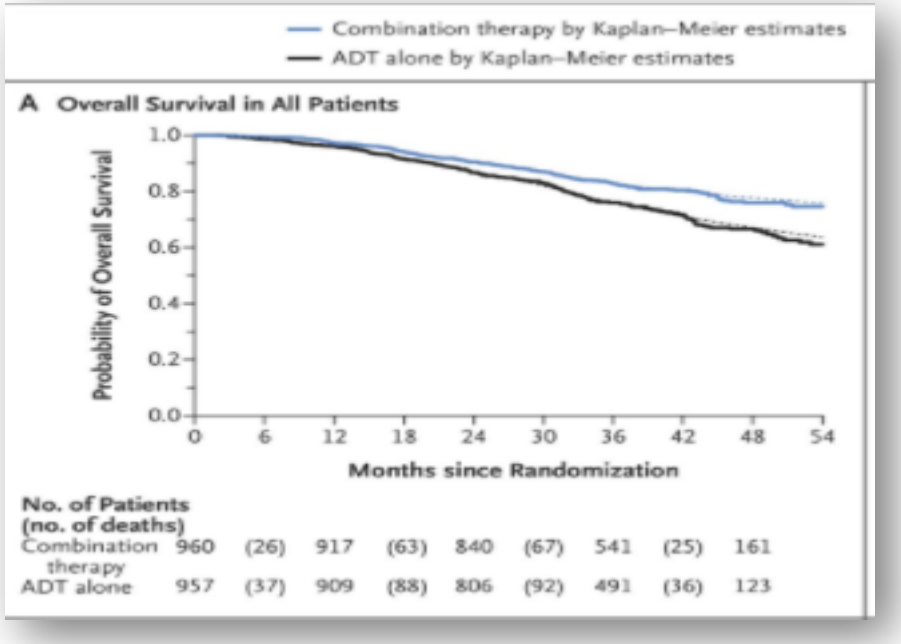
LATITUDE: Abiraterone + Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

- Common AEs
  - Hypertension
  - Hypokalemia
  - Back pain
  - Increased ALT
  - Cardiac disorders

	Abiraterone Group (N = 597)	Placebo Group (N = 602)
Any adverse event (AE)	558 (93%)	557 (93%)
Grade 3 or 4 AE	374 (63%)	287 (48%)
Any serious AE	165 (28%)	146 (24%)
Any AE leading to treatment discontinuation	73 (12%)	61 (10%)
AE leading to death	28 (5%)	24 (4%)

Fizazi K, et al. *N Engl J Med*. 2017;377(4):352-360.

STAMPEDE: Overall Survival With Abiraterone



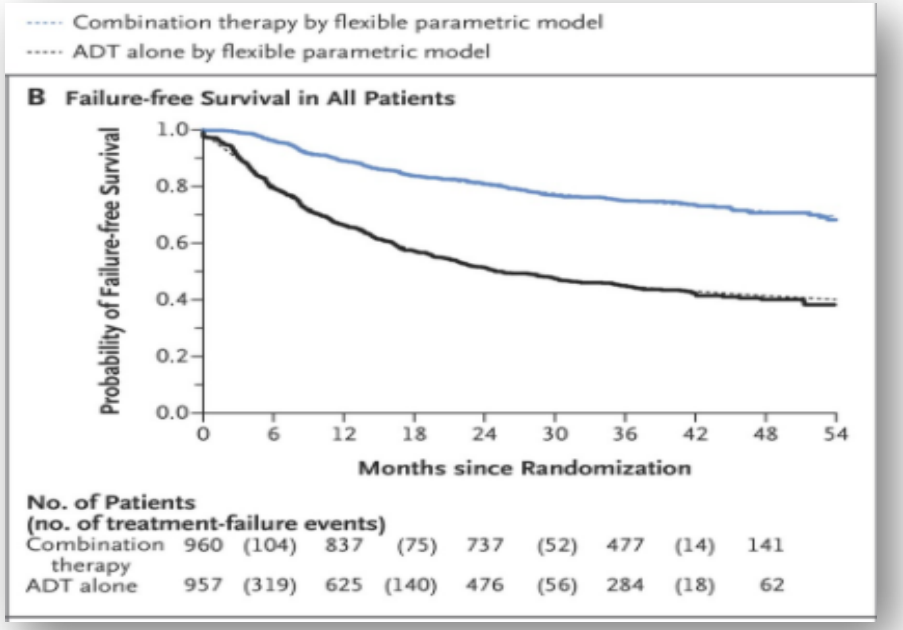
Deaths:
ADT+ abiraterone + P: 184
ADT: 262

HR	**0.63**
95% CI	0.52 to 0.76
P	< .001

3-year FFS:
ADT + abiraterone + P: 83%
ADT: 76%

James ND et al. *N Engl J Med.* 2017;377:338-351.

STAMPEDE: FFS With Abiraterone



Events:
ADT + abiraterone + P: 248
ADT: 535

HR	**0.29**
95% CI	0.25 to 0.34
P	< .001

3-year FFS:
ADT + abiraterone + P: 75%
ADT: 45%

James ND et al. *N Engl J Med.* 2017;377:338-351.

Characteristics of Enrolled Patients: CHAARTED/LATITUDE/STAMPEDE

	CHAARTED	LATITUDE	STAMPEDE
High volume	Presence of visceral metastases	Presence of visceral metastases	
Bone lesions	≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis	≥3	
Gleason score		≥8	8-10
PSA level			≥40 ng/mL
T stage			T3/4
High-risk prognostic features		≥2	

Current mCSPC Datasets in One Slide

- High level summary of treatment effect on OS as measured by hazard ratio (HR)
- HV-High: volume ≥ 4 bone mets with one beyond axial skel and/or visceral mets
- PR-Poor risk: de novo metastatic + ≥ 2 of (GI ≥ 8+ ≥3 bone mets + visceral mets; NB: 20% of LATITUDE poor risk are de novo low volume)[6]
- HR(OS): Hazard ratio for overall survival
- N/R: not reported (yet)

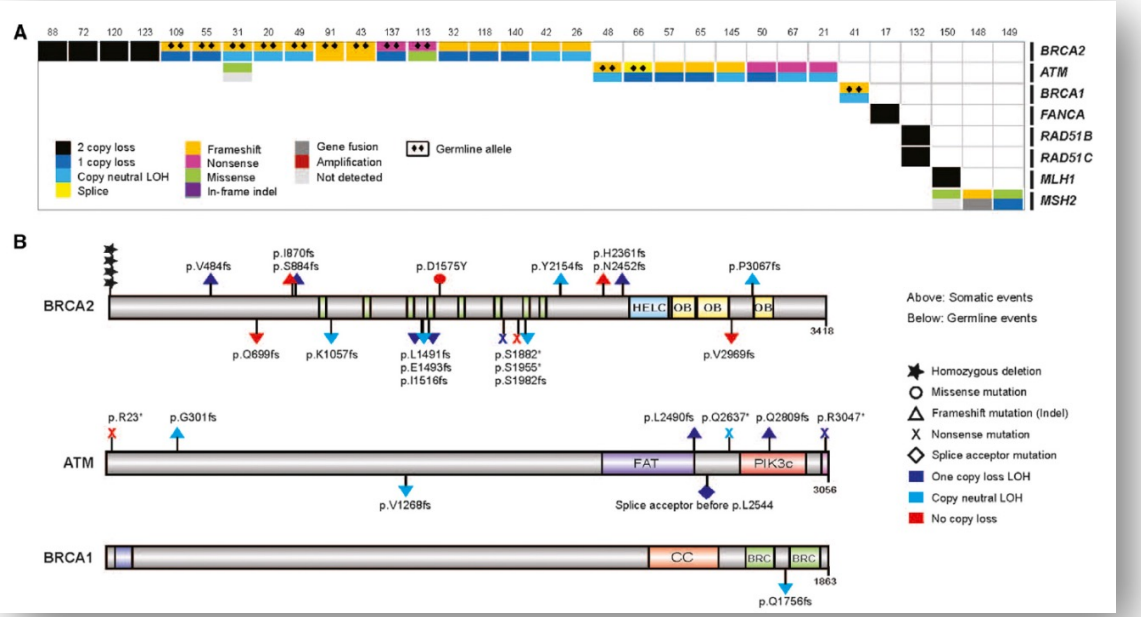
Trial	All M1	High Volume /Poor Risk	Low Volume	Median Follow-up (mos)
ADT + / Docetaxel				
GETUG15[1]	HR(OS): 0.88	HR(OS)-HV: 0.78	HR (OS): 1.02	83.9
CHAARTED[2]	HR(OS): 0.72	HR(OS)-HV: 0.63	HR (OS): 1.04	57.6
STAMPEDE-Doc[3]	HR(OS): 0.76	N/R	N/R	43
ADT +/- Abiraterone				
LATITUDE[4]	N/A	HR (OS)-PR: 0.62	[6]*20% (OS: N/R yet) (post hoc to align with other studies)*	30.4
STAMPEDE-Abi[5]	HR(OS): 0.61	N/R	N/R	40

Courtesy of Chris Sweeney, MBBS, Dana-Farber Cancer Institute; 1. Gravis et al Lancet Oncology 2015; 2. Kyriakopolous et al JCO 2018 in press; 3. James et al Lancet 2015; 4. Fizazi et al NEJM 2017; 5. James et al NEJM 2017; 5. Fizazi et al GU ASCO 2018,

Initial Management of Patients with Metastatic Prostate Cancer

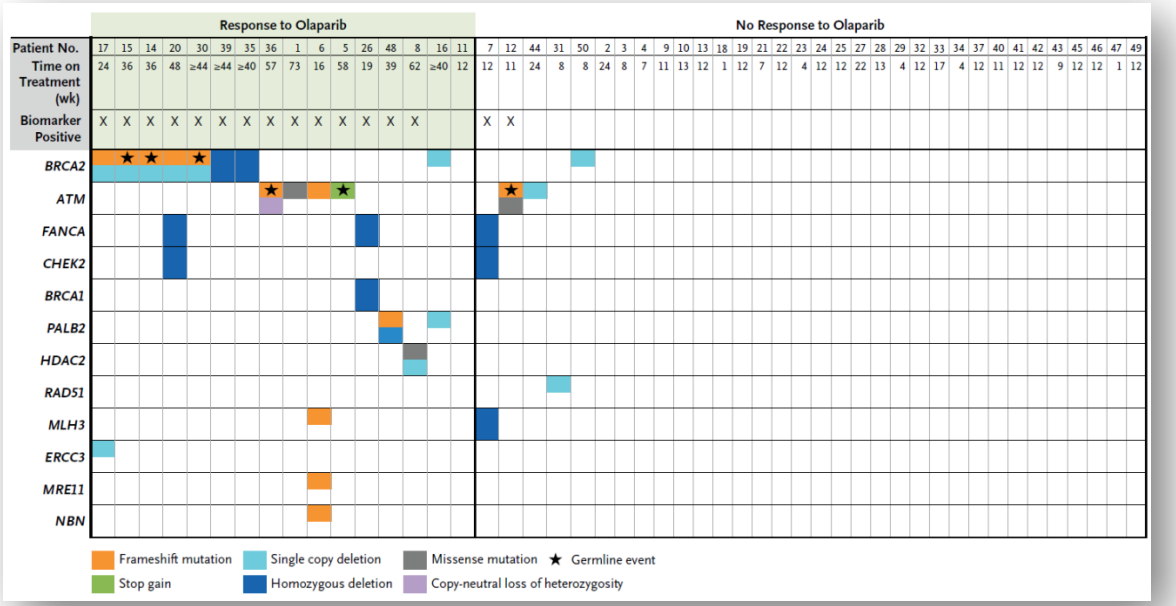
- For patients with high-volume (ECOG)/poor risk based on LATITUDE either docetaxel or abiraterone has striking level 1 evidence to support use
- Given data free zone re: selection issues that will impact on patient decision making include
  - Economics
  - Duration of therapy
  - Toxicity
  - World view
- Low volume patients do not benefit from docetaxel
- Less clear re: low-volume patients and abiraterone
- If some is good, more is better (i.e., docetaxel then abiraterone is making it up as you go along)
  - Enroll to ongoing studies

DNA-Repair Defects Can Be Inherited, Somatic, or Both



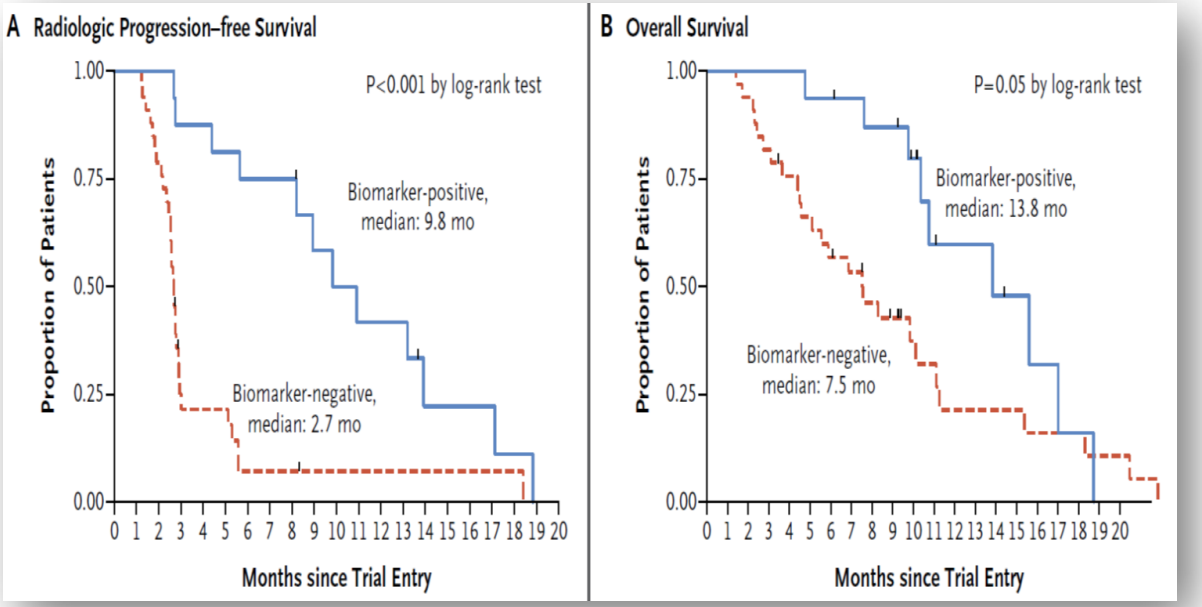
Robinson et al, 2015.

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer



Mateo et al, 2015.

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer



Mateo J, et al. N Engl J Med 2015;373:1697-1708

Why Are Germline Mutations Important?

- Poor prognosis and early age of onset
- Implications for future therapies
  - Today, PARP inhibitors, platinum agents, and PD1 inhibitors
  - Tomorrow, perhaps others
- Implications for family members that may require careful monitoring or even prophylactic surgery
  - ~70% of women with a BRCA2 pathologic mutation develop breast cancer, ~40% for ovarian cancer

Pritchard et al, 2016; Mersch et al, 2015.

Molecular Characteristics of Localized and Advanced Prostate Cancer

- TCGA whole exome sequencing of 333 localized PC (26% were Gleason ≥ 8)
  - 19% had germline or somatic aberrations of DNA damage repair pathway
- Pritchard et al: 692 metastatic prostate cancer unselected for FH/age
  - 11.8% with DNA repair pathway aberrations (BRCA2 5.3%, CHEK2 1.9%)
- Robinson et al.: 150 metastatic bx from mCRPC pts
  - 23% of mCRPC have DNA repair pathway aberrations
  - 8% germline

Abeshouse A, et al. Cell 2015;163:1011-25; Robinson D, et al. Cell 2015;16:1215-28; Pritchard CC, et al. N Engl J Med 2016;375:443-53.

Inherited DNA-Repair Gene Mutations in Men With Metastatic PC

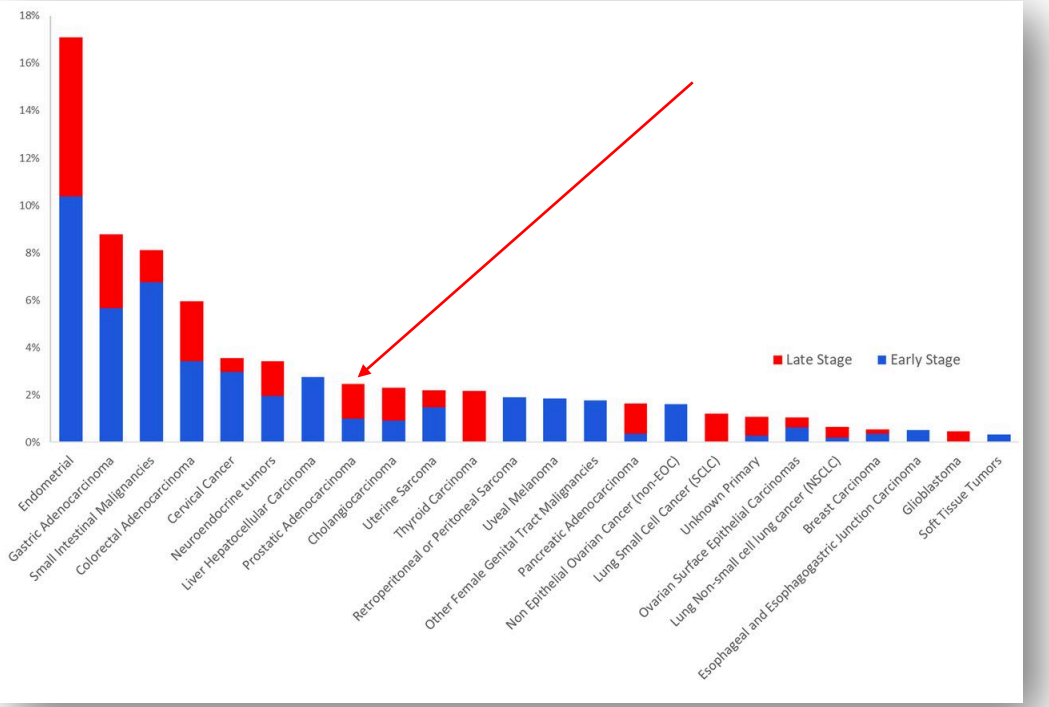
- 11.8% of men with metastatic prostate cancer
  - BRCA2: 5.4%
  - CHEK2: 1.9%
  - ATM: 1.6%
  - BRCA1: 0.9%
  - RAD51D and PALB2: 0.4% each
- 4.6% of men with localized prostate cancer

Pritchard CC, et al. N Engl J Med 2016;375:443-53.

DNA Damage Repair as a Therapeutic Target

- BRCA 1 and 2 and PALB2 are proteins that repair double-strand DNA breaks
- When the gene for either protein is mutated, the change can lead to errors in DNA repair that can eventually cause neoplastic growth
- When subjected to enough damage at one time, the altered gene can cause the death of the cells
- PARP1 is a protein that is important for repairing single-strand breaks
- Drugs that inhibit PARP1 cause multiple double strand breaks and as these double-strand breaks cannot be efficiently repaired, cell death results

Mismatch Repair Deficiency Across 12,019 Tumors



Dung T. Le et al. Science 2017;science.aan6733

MSI-High Prostate Cancer

- Approval with pembrolizumab
- Incidence
  - Localized PC ~2%
  - Autopsy series of mCRPC ~12%
    - Pritchard et al., Nature Com 2014
  - Ongoing testing suggests 5-6% of mCRPC
- Suggests all patients with mCRPC should be tested

Pembrolizumab Response Rate by Tumor Type.*

Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

* Response was as defined by RECIST. "Other cancers" includes one patient each with the following tumor types: bladder, esophageal, sarcoma, thyroid, retroperitoneal, small-cell lung cancer, and renal cell cancer (includes two patients who could not be evaluated and were considered not to have had a response). A + sign indicates that the response was ongoing at the time of data cutoff.

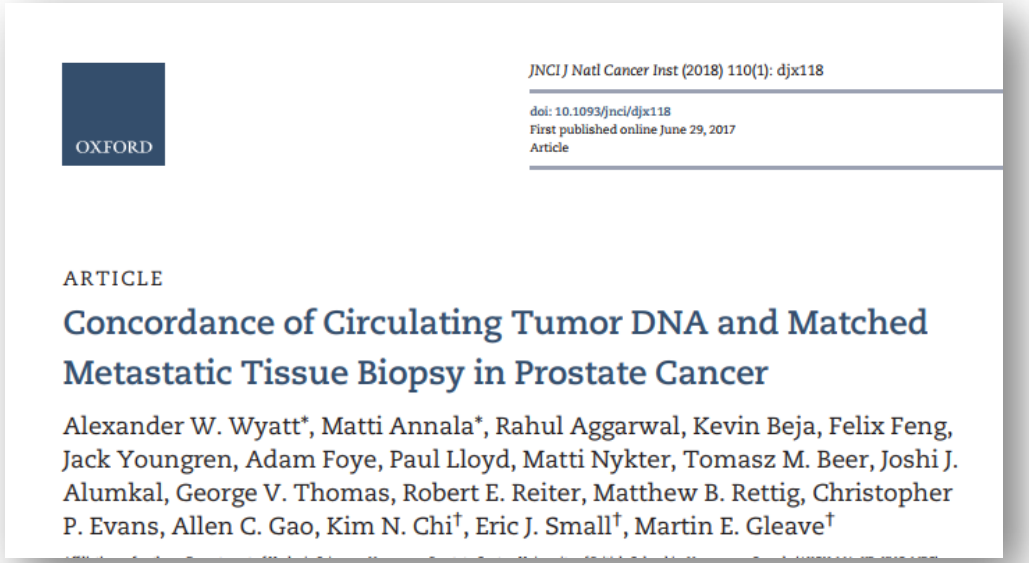
Lemery et al. *N Engl J Med* 2017; Pritchard et al. Nature Com 2014

Targeted Therapy

- 23% of mCRPC harbor DNA repair pathway aberrations
- 8% harbor germline findings
- PARP inhibitors
  - Olaparib (NCT01972217)
  - Niraparib (NCT02500901)
  - Rucaparib (NCT02952534)
- 4% of metastatic prostate cancer have variants in PIK3CB
- Fusion and amino acid substitution mutations are potential oncogenic driver mutations
- AZD8186 (NCT01884285)

Vaccines: Prostvac (conflicting phase 2 trial results), DCVAC

Robinson D, et al. *Cell*. 2015;161(5):1215-1228.



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Article

ARTICLE

Concordance of Circulating Tumor DNA and Matched Metastatic Tissue Biopsy in Prostate Cancer

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Methods: We performed targeted sequencing across 72 clinically relevant genes in 45 plasma cell-free DNA samples collected at time of metastatic tissue biopsy. We compared ctDNA alterations with exome sequencing data generated from matched tissue and quantified the concordance of mutations and copy number alterations

Results: Copy number profiles between matched liquid and solid biopsy were highly correlated, and individual copy number calls in clinically actionable genes were 88.9% concordant

Conclusions: Our study shows that, in the majority of patients, a ctDNA assay is sufficient to identify all driver DNA alterations present in matched metastatic tissue and supports development of DNA biomarkers to guide mCRPC patient management based on ctDNA alone

Among the Things That Need Sorting Out

- Germline and/or somatic testing in all prostate cancer patients, in those with metastatic disease, mCRPC?
  - Baseline, at progression to mCRPC?
  - Tumor tissue, liquid biopsy?
- If/when PARP approved in mCRPC, is there a rationale to treat selected patients with carboplatin-based therapy, and when?
- If patients with mismatch repair deficiency are identified early, when do you sequence pembrolizumab?

"Everyone has a photographic memory. Some just don't have film."

—Steven Wright

Management of Medication Toxicities

Medication Review

Apalutamide

- Dosing: 240 mg once daily with or without food
- Dose-adjust for
  - Hepatic: ≥ Child-Pugh C not studied
  - Renal: eGFR < 29 mL/min/1.73 m^2 not studied
- ADEs
  - Common: fatigue, HTN, rash, nausea, arthralgia, weight loss
  - Warning: falls/fractures, thyroid dysfunction, seizures, QT prolongation
- Monitoring
  - BL: Testosterone, PSA, LFTs, BMP, BP, TSH
  - Monthly: PSA, LFTs, BMP, BP

Erleada (apalutamide) [package insert]. Horsham PA: Janssen Products LP; 23018.

Abiraterone

- Dosing: 1000 mg daily with prednisone
  - 5 mg ONCE daily (castration sensitive)
  - 5 mg TWICE daily (castration resistant)
- Administration
  - Abiraterone on an empty stomach 1 hour before or 2 hours after food
    - YONSA formulation (125mg tablets) 500 mg daily with or without food given with methylprednisolone 4 mg BID
  - Prednisone with food
- Dose-adjust for
  - Hepatic: ≥ Child-Pugh B
  - Renal: None

Zytiga (abiraterone) [package insert]. Horsham PA: Janssen Products LP; 2018; Yonsa (abiraterone) [package insert]. Cranbury NJ: Sun Pharma; 2018.

Abiraterone ADEs and Monitoring

- ADEs
  - Common: joint swelling or discomfort, hypokalemia, edema, hot flashes, diarrhea, UTI, HTN, urinary frequency, nocturia, URI
  - Warnings
    - Mineralocorticoid excess, adrenal insufficiency, hepatotoxicity
- Monitoring
  - BL: Testosterone, PSA, LFTs, BMP (potassium and phosphate), BP
  - Q 2 wk x 12 wk: LFTS
  - At 2 wk: BMP (potassium and phosphate)
  - Monthly: PSA, LFTs, BMP (potassium and phosphate), BP

Zytiga (abiraterone) [package insert]. Horsham PA: Janssen Products LP; 2018; Yonsa (abiraterone) [package insert]. Cranbury NJ: Sun Pharma; 2018.

Enzalutamide

- Dosing: 160 mg once daily with or without food
- Dose-adjust for
  - Hepatic: ≥ Child-Pugh C not studied
  - Renal: CrCl < 30 not studied
- ADEs
  - Common: Asthenia and fatigue, back pain, decreased appetite, hot flashes, musculoskeletal pain, peripheral edema, arthralgia, diarrhea, weight loss, headache, HTN
  - Warnings: Seizure activity
- Monitoring
  - BL: CBC, BMP, T. Bili, LFTs, PSA, Testosterone, BP
  - Monthly: BMP, T. Bili, LFTs, BP
  - Bone scan at 13 weeks (if known bone mets)

Xtandi (enzalutamide) [package insert]. Northbrook IL: Astellas Pharma US Inc; 2018.

Docetaxel

- Dosing – 75 mg/m^2 IV on day 1 every 21 days
- Dose-adjust for
  - Hepatic: do not use for T Bili > ULN or AST and/or ALT >1.5 x ULN with alk phos >2.5 x ULN
  - Renal: no dose adjustments needed
- ADEs
  - Common: fluid retention, hypersensitivity reactions, peripheral neuropathy, fatigue
- Monitoring: CBC, renal, liver – prior to each cycle

Taxotere (docetaxel) [package insert]. Bridgewater NJ: Sanofi-Aventis US LLC; 2015.

Olaparib

- Dosing: 400 mg PO BID with or without food
  - Avoid grapefruit, grapefruit juice, and Seville oranges (increases olaparib levels)
- Dose adjust for:
  - Hepatic: ≥ Child-Pugh B not studied
  - Renal: CrCl ≤ 50
- *Do not take if exposed to temperatures greater than 104°F

Lynparza (olaparib) [package insert]. Wilmington DE: AstraZeneca Pharmaceuticals LP; 2018.

Olaparib: Monitoring

- ADEs
  - Common: anemia, N/V, fatigue, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, URI, cough, musculoskeletal pain, rash, back pain
  - Warnings: MDS AML have occurred, pneumonitis, embryo-fetal toxicity
- Monitoring
  - BL: CBC, BMP, LFTs,
  - At 2 weeks: CBC, BMP, LFTs
  - Every month: CBC, BMP, LFTs
  - Physical exam as indicated, CT at BL and Q 8 weeks

Lynparza (olaparib) [package insert]. Wilmington DE: AstraZeneca Pharmaceuticals LP; 2018.

Pembrolizumab

- Dosing – 200mg once every 3 weeks for MSI-H tumors
- Dose-adjust for
  - Hepatic: has not been studied in moderate (T Bili > 1.5 – 3x ULN and any AST) or severe (T Bili >3 x ULN with any AST)
  - Renal: No dose adjustment needed
- ADEs
  - Common: fatigue, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, musculoskeletal pain
  - Serious: Immune-mediated ADEs
- Monitoring: CBC, CMP, TSH (baseline and q6 weeks)

Keytruda (pembrolizumab) [package insert]. Whitehouse Station NJ: Merck & Co Inc; 2018.

Supportive Care and ADE Management

ADEs

- Hot flashes
- Fatigue
- Bone health

Hot Flashes

- Occurs in up to 80% of patients who receive ADT for prostate cancer
  - Can affect sleep, mood, QOL
- Non-pharmacologic treatments
  - Avoid alcohol, caffeine, cigarettes, heat, hot beverages, spicy foods, tight clothing
  - Exercise, acupuncture, relaxation techniques
  - Cooler room temperature

Harvard Health Publications. Hot flashes in men: an update. Accessed 23 Sep 2015. http://www.health.harvard.edu/newsweek/Hot-flashes-in-men-An-update.htm.

Hot Flashes: Pharmacologic Treatment

Study	Treatment	Efficacy
Irani et al. Randomized, double-blind trial (n = 919)	Venlafaxine ER 75 mg/day vs. Medroxyprogesterone 20 mg/day vs. Cyproterone 100 mg/day	• Venlafaxine, medroxyprogesterone, and cyproterone significantly decreased hot flash score from baseline • Cyproterone and medroxyprogesterone > venlafaxine • Cyproterone not available in US
Loprinzi et al. Randomized, double-blind, placebo-controlled (n = 214)	Gabapentin 300 mg QHS vs. Gabapentin titrated to 300 mg TID vs. placebo	• Gabapentin significantly reduced hot flash scores compared to placebo • Gabapentin 900 mg/day more effective than 300 mg/day • Gabapentin well tolerated, similar side effects seen compared to placebo

Irani J, Solomon L, Oba R et al. Lancet Oncol. 2010;11:147-154; Loprinzi CL, Dueck AC, Khoyratty BS et al. Ann Oncol. 2009;20:542-549.

Hot Flash Summary

- Treatment options
  - Venlafaxine 37.5–75 mg PO daily
    - ADEs: nausea, appetite loss, constipation
  - Gabapentin 300 mg PO daily x 3 days, then BID x 3 days, then TID
    - ADEs: dizziness, drowsiness
  - Medroxyprogesterone 20 mg PO daily
    - ADEs: vascular disorders, increased weight

Fatigue

- Rarely an isolated symptom
  - Pain, emotional distress, anemia, sleep disturbances, poor nutrition, decreased functional status, medications, comorbidities
- Approach
  - Identify, treat, and manage contributing factors if possible
  - Non-pharmacologic treatment (energy conservation, physical activity, yoga, massage, music therapy, relaxation, physical/occupational therapy, cognitive behavioral therapy)
  - Pharmacologic treatments

Fatigue: Pharmacologic Treatments

- 2 out of 7 placebo-controlled trials show efficacy with methylphenidate
  - 5 mg BID (max 40 mg/day)
  - ADEs: insomnia, appetite suppression, headache, hypertension
- No benefit with dextroamphetamine
- 2 pilot studies support efficacy with modafinil
  - 100-200 mg daily (max 400 mg/day)
  - ADEs: headache, nausea, dizziness

Escalante CP. Cancer-related fatigue: Treatment. UpToDate. 2018. Accessed 10 October 2018. Retrieved at: https://www.uptodate.com/contents/cancer-related-fatigue-treatment?search=cancer%20related%20fatigue&source=search_result&selectedTitle=1~28&usage_type=default&display_rank=1#H10.

Bone Health

- ADT decreases bone mineral density and increases the risk of bone fractures in men with prostate cancer
- Prevention
  - Lifestyle – smoking cessation, vitamin D/calcium supplementation, regular weight bearing or resistance exercise
  - Pharmacologic – bisphosphonate or denosumab if have bone mets
- Calcium/Vitamin D supplementation
  - 1000 – 1200 mg daily (calcium)
  - 800 – 1000 units daily (vitamin D)

Skolarus TA. Overview of approach to prostate cancer survivors. UpToDate. 2018. Accessed 10 October 2018. https://www.uptodate.com/contents/overview-of-approach-to-prostate-cancer-survivors?search=bone%20health%20in%20prostate%20cancer&sectionRank=1&usage_type=default&anchor=H841006000&source=machineLearning&selectedTitle=2~150&display_rank=2#H841006000.

Medication Comparison

Medication Comparison

	Administration	Cost
Apalutamide 240 mg daily	4 tablets daily with or without food	$13,104 (per 30 days)
Abiraterone 1000 mg	4 tablets (250 mg) or 2 tablets (500 mg) once daily on an empty stomach	$12,278.40 (per 30 days)
Abiraterone 500 mg	4 tablets once daily with or without food	$11,050.80 (per 30 days)
Enzalutamide 160 mg daily	4 capsules daily with or without food	$13,086 (per 30 days)
Docetaxel	IV once every 21 days	$365.15 (per dose)
Olaparib 400 mg BID	4 tablets twice daily with or without food	$33,326.40 (per 30 days)
Pembrolizumab	IV once every 21 days	$2,789.78 (per dose)

**Based on UpToDate pricing (accessed 10/5/18)

ADE Management Summary

- Current agents for prostate cancer are generally well tolerated with manageable toxicities
- Important to consider patient when choosing between available oral agents
- Monitor patients closely for ADEs and address as appropriate
  - Remember to utilize dietitians, social workers, pharmacists, nurses, primary care to help with management as needed

Questions?

SMARTIE

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