Please note, these are the actual video-recorded proceedings from the live CME event and may include the use of trade names and other raw, unedited content.

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Current and Future Management of Metastatic CRPC

Howard I Scher, MD
D. Wayne Calloway Chair in Urologic Oncology
Co Chair, Center for Molecular Based Therapy
Head, Biomarker Development Initiative
Office of the Physician in Chief
Attending Physician, Genitourinary Oncology Service
Department of Medicine

February 14, 2019

Memorial Sloan Kettering Cancer Center™

Disclosures

Consultant: Amgen (U), ESSA Pharma Inc (U), Janssen (U), Menarini Silicon Biosystems (U), Sanofi Aventis (U), WCG Oncology (C)

Grant/Research support to MSK: Janssen, EPIC Sciences, Illumina, Inc, Innocrin Pharma, Menarini Silicon Biosystems, ThermoFisher

Board of Directors: Asterias Biotherapeutics

Reimbursed Travel: Amgen, Janssen, Sanofi Aventis, Menarini Silicon Biosystems

I will discuss the investigational use in my presentation of:

PARP inhibitors, PSMA directed radionuclide therapy

A 60-year-old man receiving ADT for M0 disease after radical prostatectomy is found to have asymptomatic bone metastases. What systemic treatment would you most likely recommend?

What systemic treatment would you most likely recommend if the patient were 80 years old?

	Age 60	Age 80
 EMMANUEL S ANTONARAKIS, MD	Sipuleucel-T	Sipuleucel-T
 A OLIVER SARTOR, MD	Sipuleucel-T	Abiraterone
 HOWARD I SCHER, MD	Abiraterone or enzalutamide	Abiraterone or enzalutamide
 MATTHEW R SMITH, MD, PHD	Abiraterone	Abiraterone
 CORA N STERNBERG, MD	Abiraterone or enzalutamide	Abiraterone or enzalutamide

A 60-year-old man receiving ADT for M0 disease after radical prostatectomy is found to have widespread, moderately symptomatic bone metastases. What systemic treatment would you most likely recommend?

What would you most likely recommend if the patient were 80 years old?

	Age 60	Age 80
 EMMANUEL S ANTONARAKIS, MD	Abiraterone	Abiraterone
 A OLIVER SARTOR, MD	Abiraterone	Abiraterone
 HOWARD I SCHER, MD	Enzalutamide or abiraterone	Enzalutamide or abiraterone
 MATTHEW R SMITH, MD, PHD	Abiraterone	Abiraterone
 CORA N STERNBERG, MD	Docetaxel	Docetaxel, abiraterone, or enzalutamide

A 60-year-old man receiving ADT for M0 disease after radical prostatectomy is found to have asymptomatic liver metastases. What systemic treatment would you most likely recommend?

What would you most likely recommend if the patient were 80 years old?

	Age 60	Age 80
 EMMANUEL S ANTONARAKIS, MD	Either abiraterone or enzalutamide, based on patient preference	Either abiraterone or enzalutamide, based on patient preference
 A OLIVER SARTOR, MD	Abiraterone	Abiraterone
 HOWARD I SCHER, MD	—	Abiraterone
 MATTHEW R SMITH, MD, PHD	Docetaxel	Abiraterone
 CORA N STERNBERG, MD	Docetaxel	Docetaxel if possible, enzalutamide if cannot tolerate chemotherapy

A 60-year-old man receiving ADT for PSA-only recurrence after radical prostatectomy is found to have asymptomatic bone metastases. He receives abiraterone with an initial response. Seven months later his PSA begins to rise, but he remains asymptomatic. What would you most likely recommend?

 EMMANUEL S ANTONARAKIS, MD	Test for AR-V7 and then decide
 A OLIVER SARTOR, MD	High dose testosterone
 HOWARD I SCHER, MD	Test for AR-V7 and then decide
 MATTHEW R SMITH, MD, PHD	Continue abiraterone
 CORA N STERNBERG, MD	Evaluate further for other visceral disease, consider docetaxel if continued PD on bone scan or otherwise

Do you believe that there are currently enough data to support the use of AR-V7 testing in making decisions regarding the use of hormone therapy in PC?

 EMMANUEL S ANTONARAKIS, MD	Yes
 A OLIVER SARTOR, MD	Yes
 HOWARD I SCHER, MD	Yes
 MATTHEW R SMITH, MD, PHD	No
 CORA N STERNBERG, MD	No, not with current methodology

Do you generally perform microsatellite instability (MSI) testing for your patients with prostate cancer?

Do you generally perform multiplex genomic testing (ie, next-generation sequencing) for your patients with metastatic prostate cancer who have a good performance status but have exhausted all available treatment options?

	MSI testing	Multiplex genomic testing
 EMMANUEL S ANTONARAKIS, MD	Yes, at first diagnosis of metastatic disease	Yes
 A OLIVER SARTOR, MD	Yes, at diagnosis of castration-resistant metastatic disease	Yes
 HOWARD I SCHER, MD	Yes, at first diagnosis and at diagnosis of castration-resistant disease	Yes
 MATTHEW R SMITH, MD, PHD	Yes, with castration-resistant metastatic disease in later lines	Yes
 CORA N STERNBERG, MD	Yes, with castration-resistant metastatic disease in later lines	Yes

Current and Future Management of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

- **Impact of earlier use of chemotherapy and secondary hormonal therapy for M0 or metastatic hormone-sensitive prostate cancer on the selection and sequencing of systemic treatment for mCRPC**

- Published research findings documenting the correlation between the presence of androgen receptor splice variant 7 (AR-V7) and outcomes with secondary hormonal therapy and chemotherapy; current clinical role of AR-V7 in patients with mCRPC

- Incidence of microsatellite instability/mismatch repair deficiency (MSI/MMR) in patients with mCRPC; indications for MSI/MMR testing and current role of immune checkpoint inhibitors in patients with and without MSI-high/MMR-deficient disease

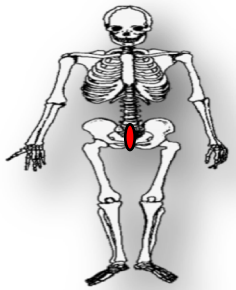
- Other promising agents and strategies under investigation in mCRPC

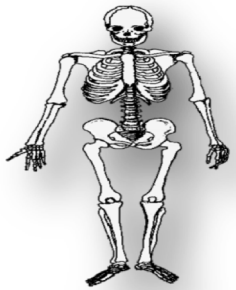
The Castration Resistant Prostate Cancer Therapeutics Landscape in 2019:
A Range of Options, an Evolving Biologically Based Disease Taxonomy, Approved Targeted Agents, With Uncertainty on How Best to Use Them in Practice

Non-Castrate
Diagnoses: 164,690

Castration Resistant
Deaths: 29,430

Clinically Localized Disease → Rising PSA → Clinical Metastases: Non-Castrate / Non-Metastatic CRPC → mCRPC: Pre-Chemo → mCRPC: 1st Line Chemo → mCRPC: Post-Chemo





Denosumab

Apalutamide
Enzalutamide

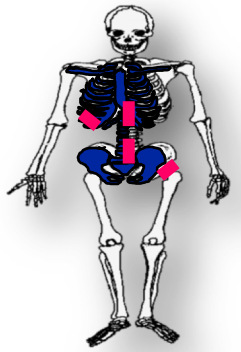
Sipuleucel-T
Abiraterone
Enzalutamide

Docetaxel

Abiraterone
Cabazitaxel
Enzalutamide

CRPC with Bone Metastases
Radium-223

MSI-H or dMMR Deficient
Pembrolizumab



Olaparib
Rucaparib
Breakthrough Designation.

7 Approved Drugs,
1 Genetically Based,
2 With a Breakthrough Designation and Uncertainty on How Best to Use Them in Practice

Modified from Scher and Heller. Urology. 2000.

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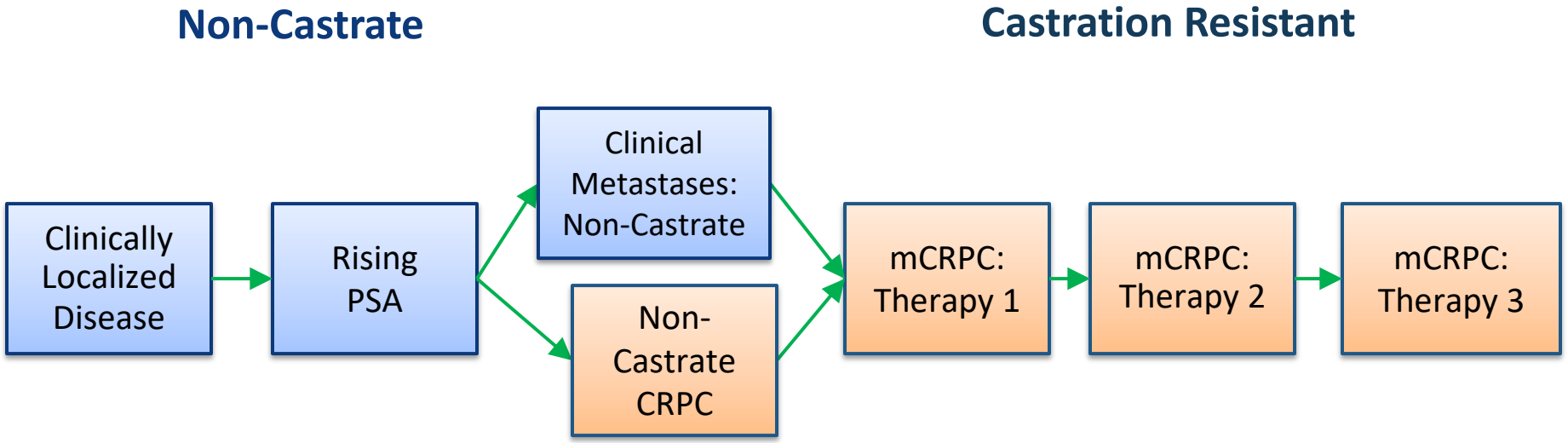
Use and Study of Approved Drugs in Non-Castrate States is Changing the Standards of Care Making the Relapsing and Progressing Tumors More Resistant and Biologically Diverse



Docetaxel (2004)
Sipuleucel-T (2010)
Cabazitaxel (2010)
Abiraterone Acetate (2011, 2012)
Enzalutamide (2012, 2014)
Radium-223 (2013)
Pembrolizumab (2017)
Olaparib (2015)
Breakthrough Designation

Prior therapy influences the biology of the relapsing tumor.

Biologic profiling is important when a management decision is needed.

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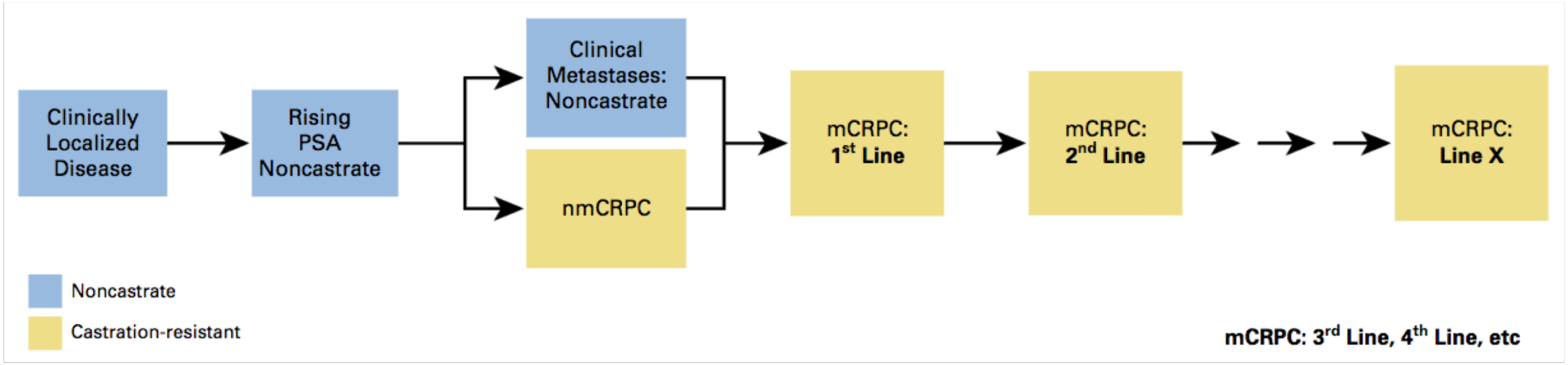
The Patient Populations Treated in Registration Trials of the Approved Drugs No Longer Exist



Action: Detail prior therapies **in the order administered**: including start and stop dates, and response if applicable

Biopsy and Rebiopsy metastatic disease: Molecular characterization

Blood based diagnostics: CTC, cf DNA, immune

Scher HI, et al. J Clin Oncol, 2016

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- **Published research findings documenting the correlation between the presence of androgen receptor splice variant 7 (AR-V7) and outcomes with secondary hormonal therapy and chemotherapy; current clinical role of AR-V7 in patients with mCRPC**

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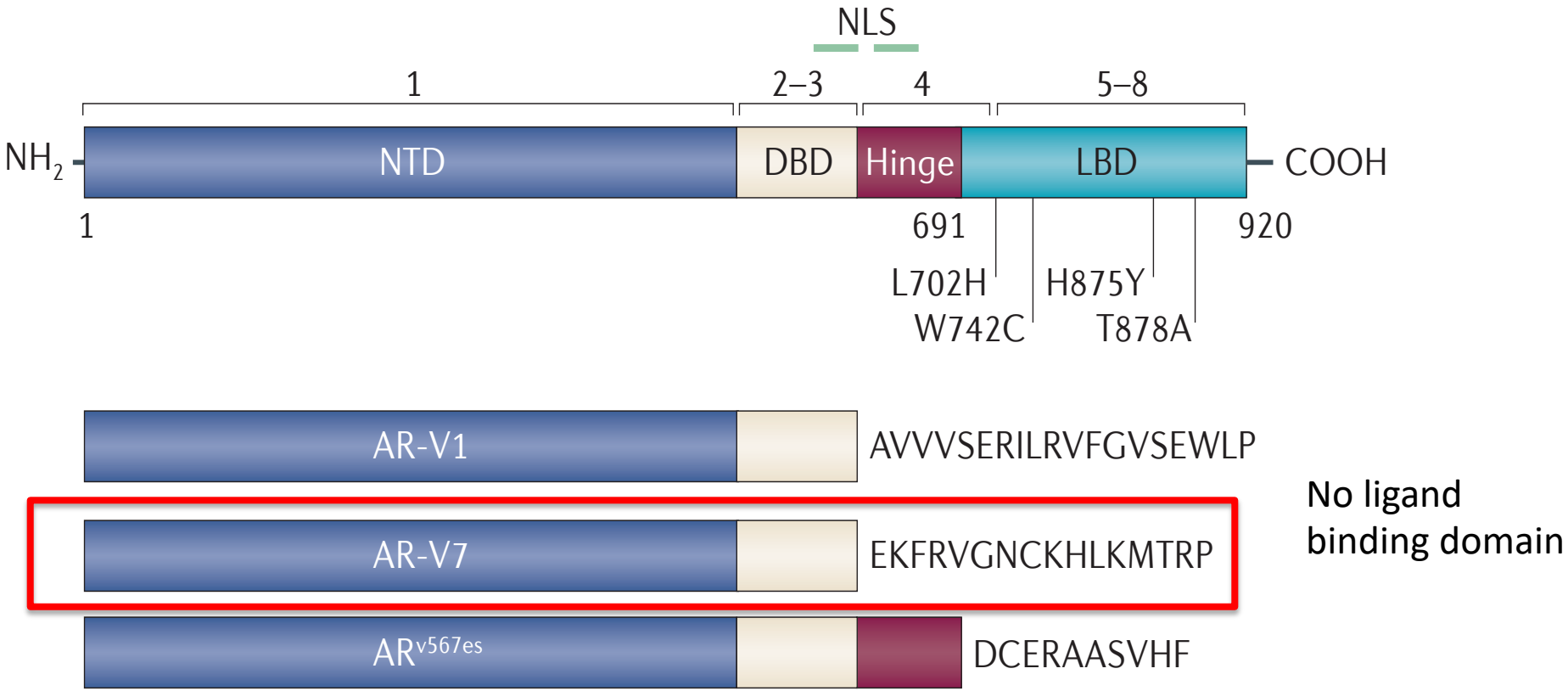
Domain Structure of the AR Illustrating Cancer Associated Missense Mutations and Splice Variants: Oncogenic Changes That Can Drive Tumor Growth



No ligand binding domain

AR splice variants lack the ligand binding domain, signal independent of ligand, and can be detected by blood based assays (liquid biopsies) by PCR or antibodies.

Watson et al., Nat Rev Cancer 15:701, 2015

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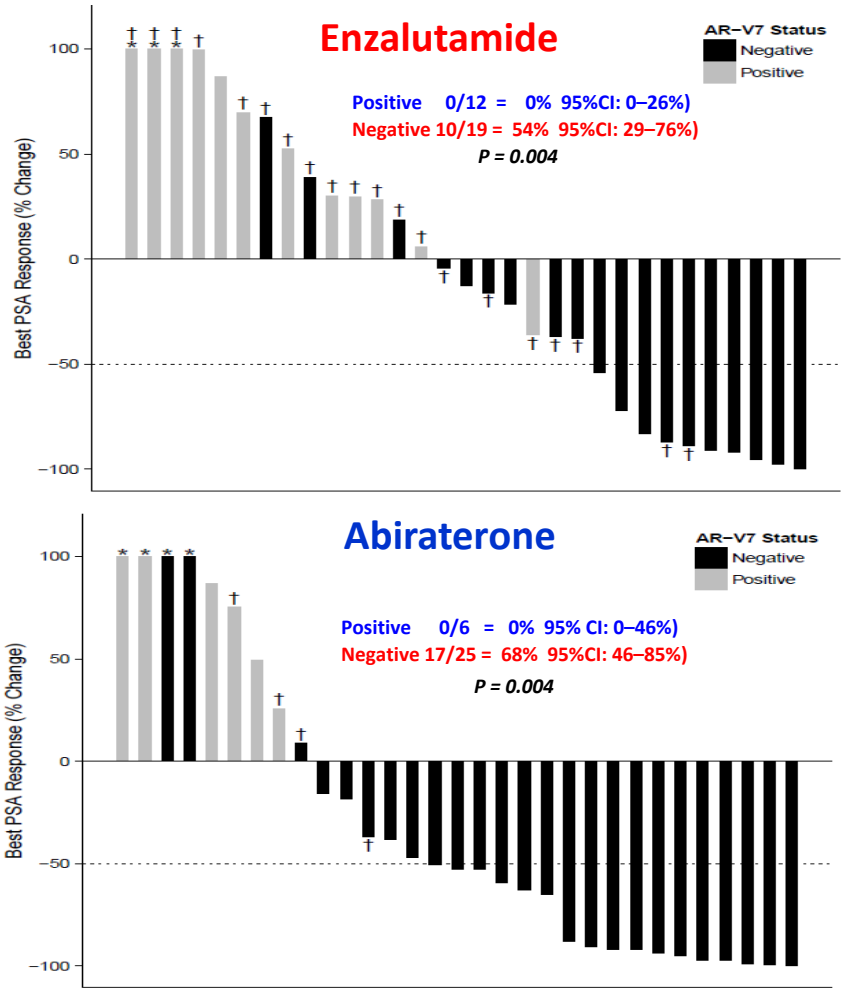
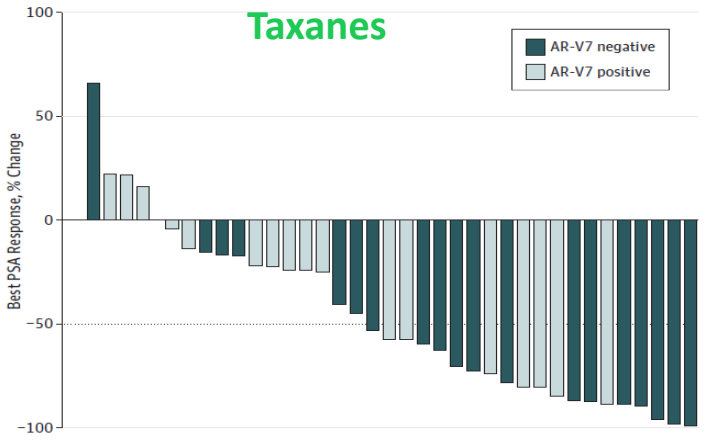
JHU Investigators Showed That AR V7 Predicts Sensitivity to Enzalutamide, Abiraterone and Taxanes and is Prognostic

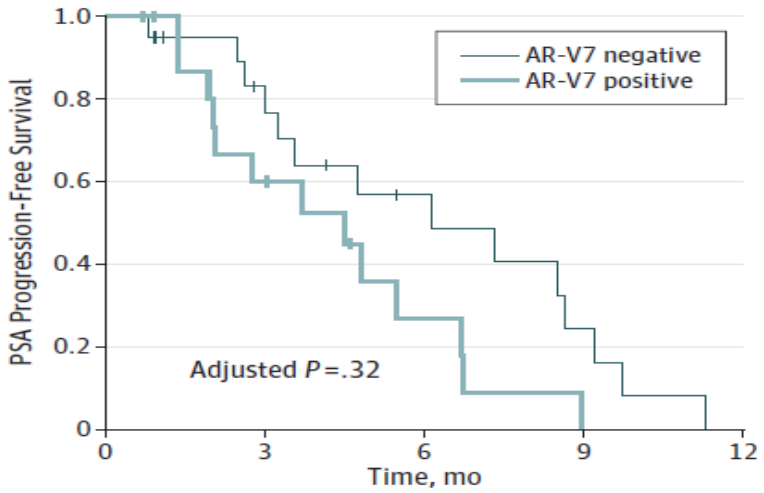
A PCR Assay Performed on Captured Circulating Tumor Cells



Antonarakis et al., NEJM 371:1028, 2014



AR-V7 and Prognosis



Antonarakis ES et al., JAMA Oncol 1:582, 2015

There is a Large Body of Literature Reporting on AR-V7 Detection With a Range of Assays: Too Few Follow the Path for Biomarker Development

1. **Context of use**: The management decisions – *diagnostic* and/or *therapeutic* - influenced by the biomarker result.

2. **Method (Analytical) validation**: The process of ***assessing the assay and its measurement performance characteristics***, and determining the range of conditions under which the assay will give reproducible and accurate data – **in effect, a marriage.**

3. **Clinical validation**: The ***sequence of trials that generate the evidence*** linking a biomarker with biological processes and clinical endpoints.

4. **Clinical utility**: Therapy guiding: Demonstrating that ***"use of the test to direct management"*** produces a favorable balance of benefits to harms leading to improved outcomes compared to non-use of the test.

https://www.fda.gov/drugs/developmentapprovalprocess/

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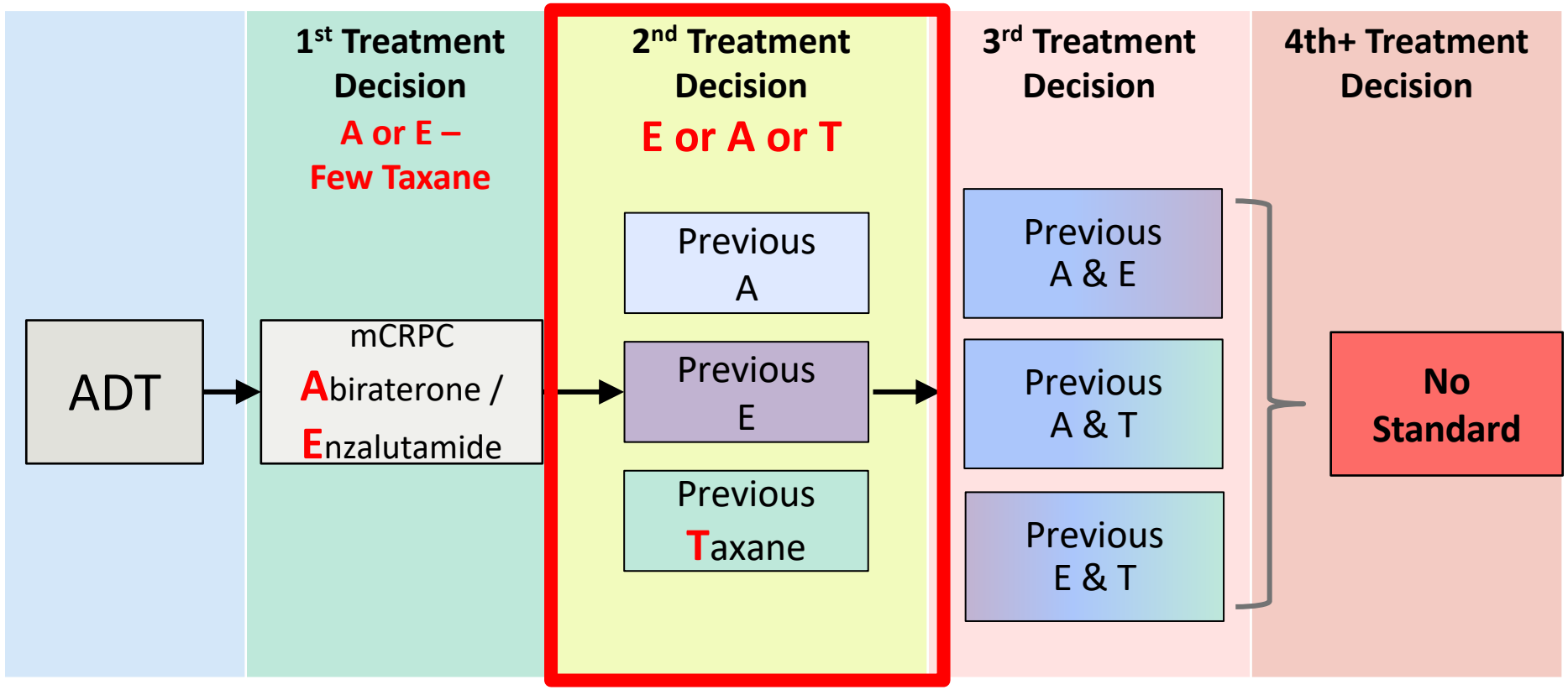
Focusing on Decision Points for USE of Standard of Care FDA Approved Drugs to Inform Clinical Utility: The 2nd Line or Greater Decision is Critical



Associating the test result with clinical outcomes:
PSA response, time to progression, time on drug, survival.

SOC: standard of care approved drugs

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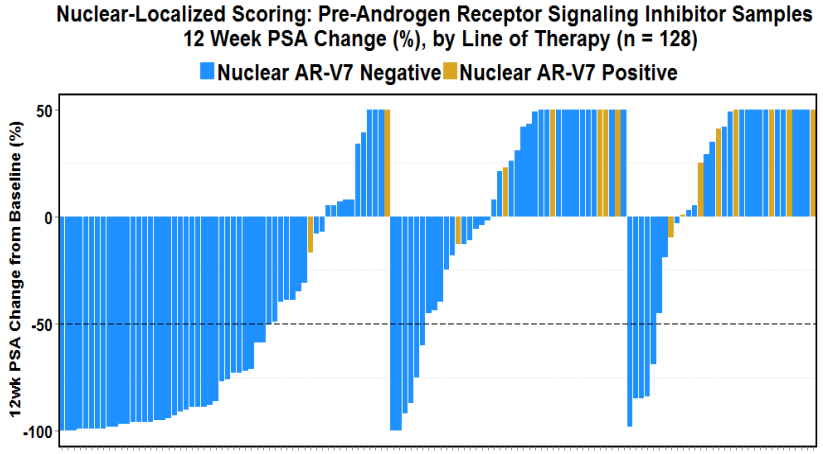
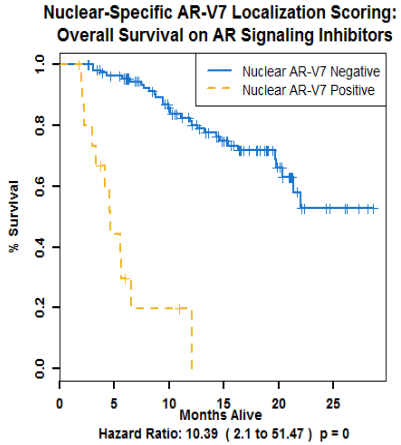
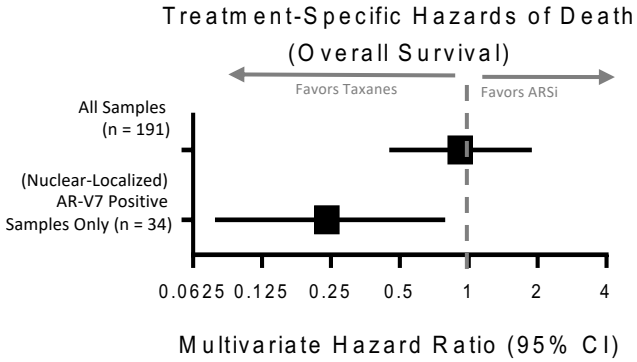
Only Nuclear AR-V7 Protein Expression Was Predictive of Improved Overall Survival with Taxane Based Therapy

Nuclear AR-V7+ PSA response & OS on ARSi baseline patients

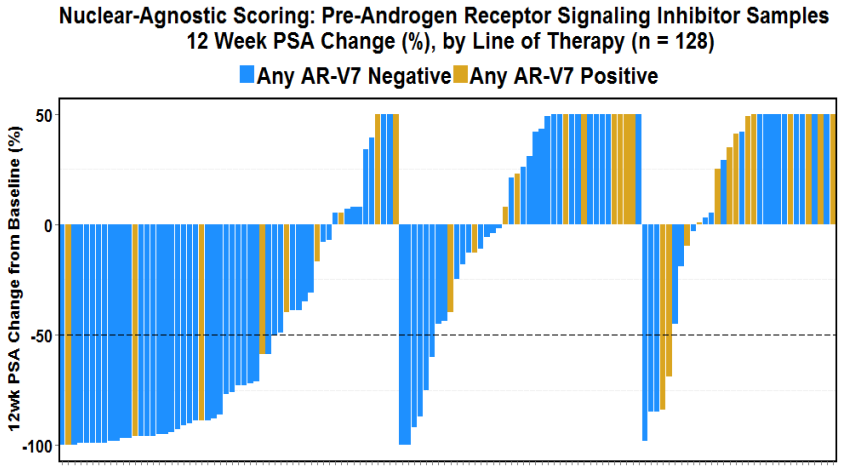


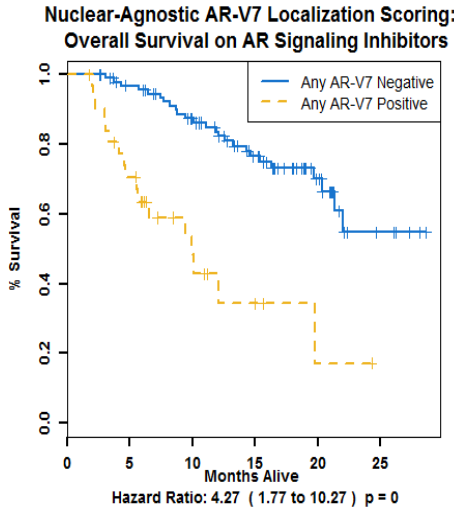


Nuclear AR-V7 protein scoring predicts taxane benefit

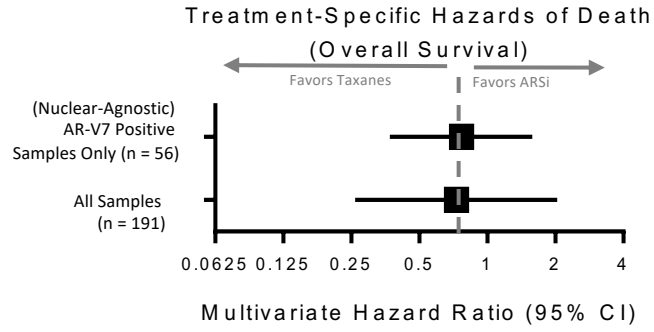


Any AR-V7+ PSA response & OS on ARSi baseline patients





AR-V7 localization agnostic scoring is *not* predictive of taxane benefit



Scher et al., Eur Urol 71:874, 2017.

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Oncotype DX AR-V7 Nucleus Detect™ Test to Predict Treatment Response in Metastatic Disease and Proposed LCD Released

PROPOSED/DRAFT Local Coverage Determination (LCD): MolDX:

Oncotype DX AR-V7 Nucleus Detect for Men with Metastatic Castrate Resistant Prostate Cancer (MCRPC) (DL37701)

Posted:	**03.15.18**
Comment period start:	**03.26.18**
Comment period end:	**05.10.18**
Proposed LCD posted:	**10.08.18**
Comment period end:	**11.23.18**
Coverage	**12.10.18**

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http://www.oncotypeiq.com/en-US/prostate-cancer/healthcare-professionals/oncotype-dx-ar-v7/about-the-test

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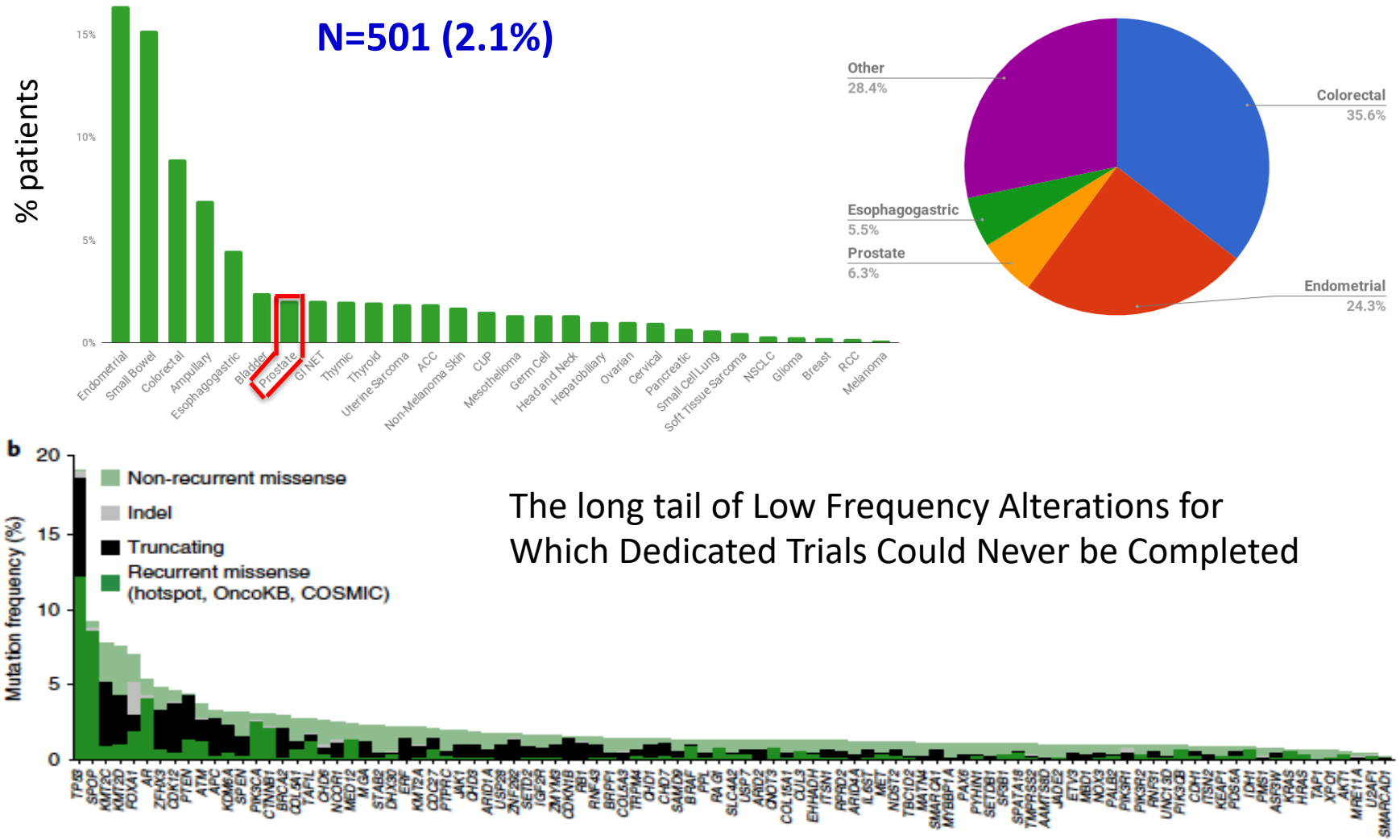
- Other promising agents and strategies under investigation in mCRPC

MSI-High Cancers Respond to Check Point Inhibitors But 40% of MSI-H Cases Occur in Cancers Where Frequency is <2%

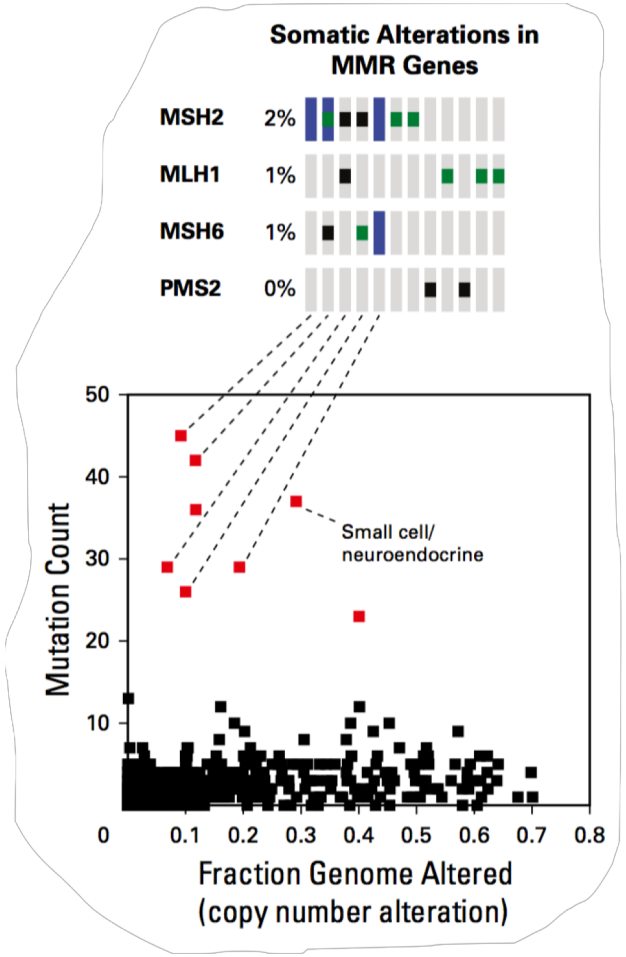


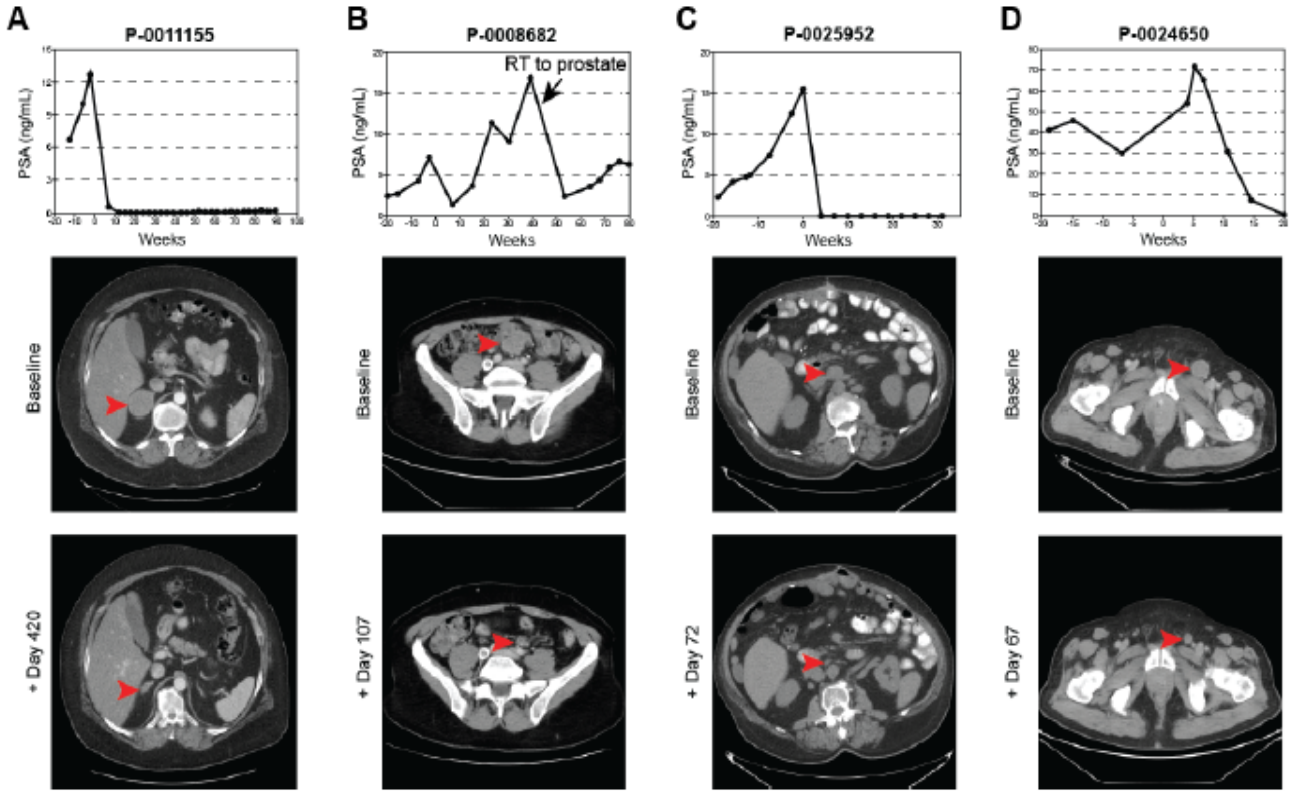
The long tail of Low Frequency Alterations for Which Dedicated Trials Could Never be Completed

Armenia et al. Nat Genet 50:645, 2018

MSI-high/Hypermutated Prostate Cancers Are Only 2-3%* of the Population but Identifying Them Can be Life Changing for the Patient

May 23, 2017: Pembrolizumab Approved for Solid Tumors Based on the Profile





Abida et al., JCO Precis Oncol 2017 [July, 2017]

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MSI in Prostate Cancer

1. The rate of MSI-H in unselected prostate cancer population is ~2.5%, with germline mutations of the Lynch syndrome variety occurring in ~25%. (0.6% overall).

2. MSI can occur as an acquired process during prostate cancer evolution, arguing for profiling of a recent sample whenever possible

3. MSI-H status can be detected through targeted NGS.
   Scored as: High >10, Intermediate 3-9, Low <3.
   For intermediate levels there is a default to IHC.

4. Still early, but clinical benefit may occur in ~50% of MSI-H prostate cancer patients who receive anti-PD1/PDL1 therapy

*Abida et al., JAMA Oncol 2018 (In press).

NEPTUNES: Phase II Trial of Nivolumab with Ipilimumab in Patients with mCRPC and Immunogenic Signature

Clinical Trial Identifier: NCT03061539 (Open)
Estimated Enrollment: 175

Eligibility:
- mCRPC that is immunogenic biomarker positive*
- ≥1 prior lines of systemic therapy for mCRPC
- PS 0 - 1

→ Nivolumab + ipilimumab q3wks up to 4 doses → 6 wk gap after last combination dose → Nivolumab 480 mg q4wks up to 1 year or until PD/toxicity

*Mismatch repair deficiency by IHC or defective DNA repair detected by a targeted sequencing panel or high inflammatory infiltrate defined on multiplexed IHC criteria

Primary Endpoint: Composite response rate

A response is considered being achieved if any of the following criteria are met: Radiological response, PSA response ≥ 50% at least 4 wks later, or conversion of CTC count from ≥5 cells/7.5 ml at baseline to <5 cells/7.5 ml by a second CTC test at least 4 wks later

www.clinicaltrials.gov (Accessed February 2019)

Initial Results from a Phase II Study of Nivolumab (NIVO) Plus Ipilimumab (IPI) for the Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC; CheckMate 650)

Sharma P et al.

Genitourinary Cancers Symposium 2019; Abstract 142

CheckMate 650: Initial Efficacy and Safety Results

Cohort 1: Pts with PD after 2nd-gen hormone therapy, no prior chemo; Cohort 2: Pts with PD after taxane-based chemotherapy

		Cohort 1	Cohort 2
ORR % (95% CI), n/N[a]		**26** (10–48), 6/23	**10** (2–27), 3/30
PD-L1[b]	≥1%	2/4 (50)	2/8 (25)
	<1%	4/23 (17)	0/20 (0)
DDR[b]	+	2/5 (40)	2/5 (40)
	–	4/14 (29)	1/9 (11)
HRD[b]	+	2/3 (67)	1/2 (50)
	–	4/16 (25)	2/12 (17)
TMB[b,c]	High	6/10 (60)	3/6 (50)
	Low	0/9 (0)	0/8 (0)
PSA response[d]		6/28 (21)	5/40 (13)

n/N (%) unless noted [a]In pts with baseline measurable disease

[b]In pts with quantifiable tissue

[c]High/low TMB = above/below median (74.5 mutations/pt)

[d]Confirmed/unconfirmed PSA decline ≥50% from baseline in pts with baseline and ≥1 postbaseline PSA result

- Grade 3-4 treatment-related adverse events occurred in 39% and 51% of pts in cohorts 1 and 2
- One Grade 5 event occurred in each cohort.

Sharma P et al. Genitourinary Cancers Symposium. 2019;Abstract 142.

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Keynote-365 Cohort A: Pembrolizumab (pembro) plus Olaparib in Docetaxel-Pretreated Patients (pts) with Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

Yu EY et al.

Genitourinary Cancers Symposium 2019; Abstract 145.

KEYNOTE-365: Early Results (Median Follow-up: 11 Months)

PSA response, pts w/elevated PSA at baseline, n/N (%)	5/39 (13)
ORR RECIST v1.1, pts w/measurable disease, n/N (%)	2/28 (7); 2 PRs
DCR, n/N (%)	
Measurable disease	9/28 (32)
Nonmeasurable disease	3/13 (23)
Total	12/41 (29)
Composite response rate, n/N (%)	6/41 (15)
Median (95% CI) time to confirmed PSA progression, wk	16 (14, 21)
Median (95% CI) rPFS per PCWG-modified RECIST, mo	5 (4, 8)
Median (95% CI) OS, mo	14 (8, NR)

Yu EY et al. Genitourinary Cancers Symposium 2019; Abstract 145.

Ongoing/Planned Phase III Studies of Anti-PD-1/PD-L1 Checkpoint Inhibitors in mCRPC

Study	Target N	Randomization	Primary Endpoint(s)	Estimated Primary Completion
KEYNOTE-641 Not yet recruiting	1200	• Pembrolizumab + Enzalutamide • Placebo + Enzalutamide	• OS • rPFS	Nov 2023
KEYNOTE-921 Not yet recruiting	1000	• Pembrolizumab + Docetaxel • Placebo + Docetaxel	• OS • rPFS	Sept 2021
KEYLYNK-010 Not yet recruiting	780	• Pembrolizumab + Olaparib • Abiraterone + Prednisone or Enzalutamide	• OS • rPFS	Oct 2021
IMbassador250 Active, not recruiting	730	• Atezolizumab + Enzalutamide • Enzalutamide	• OS	Nov 2020

Ongoing androgen deprivation with serum testosterone <50 ng/mL (<2.0 nM) in all studies

Clinicaltrials.gov, Accessed February 2019

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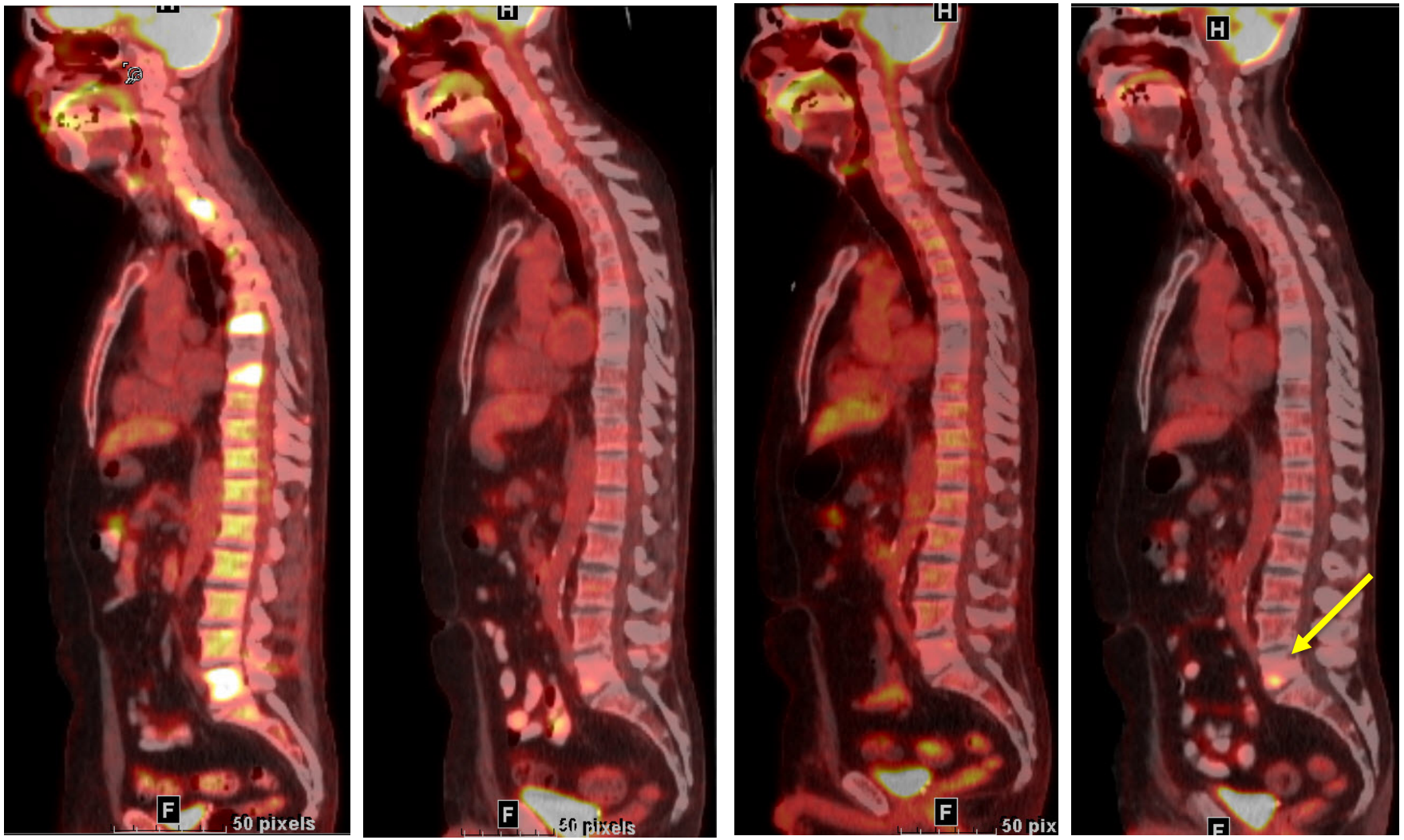
Continued Clinical Benefit: Response in All Lesions Followed by Single Site Progression - Systemic Therapy Continued and Patient Referred for SBRT



	3/10/16	3/28/17	9/25/17	6/7/18
PSA	HIGH	< 1	Rising	Continued Rise

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