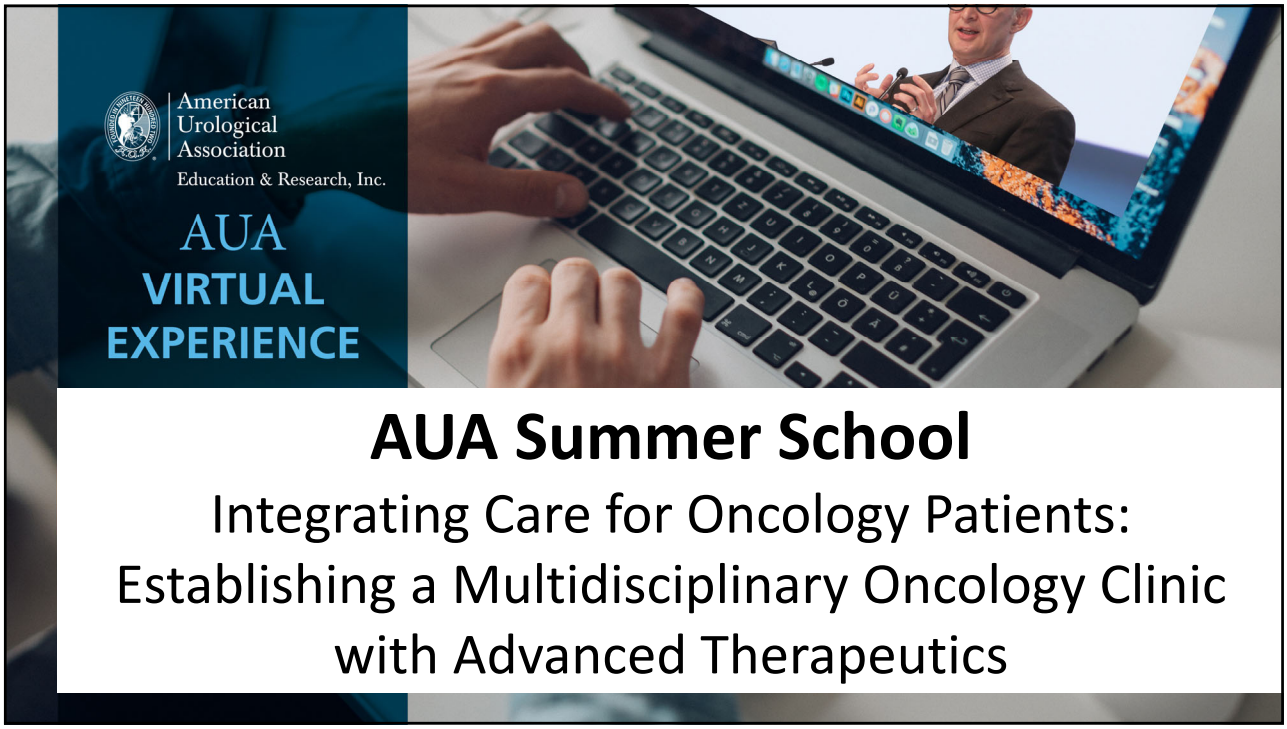

AUA Summer School

Integrating Care for Oncology Patients: Establishing a Multidisciplinary Oncology Clinic with Advanced Therapeutics

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Accreditation: The American Urological Association (AUA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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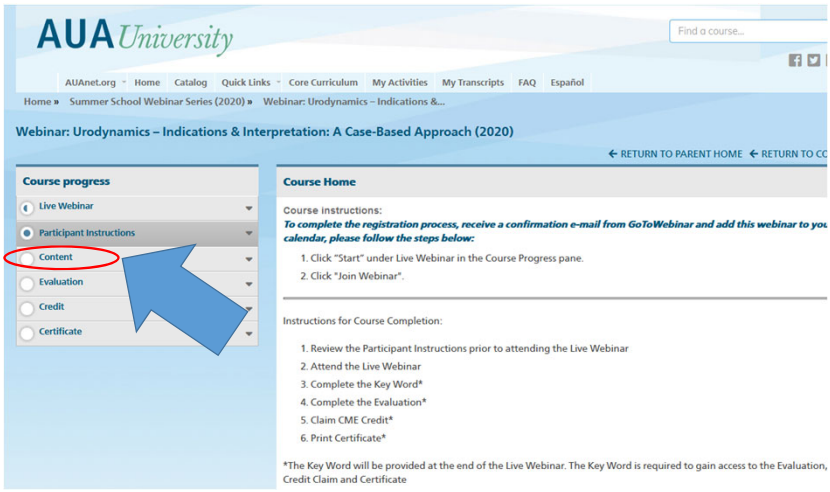
Course Handouts



1. Take Course
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CME Credits: Upon completion of course evaluations, you will have the opportunity to claim CME credits and obtain a certificate.

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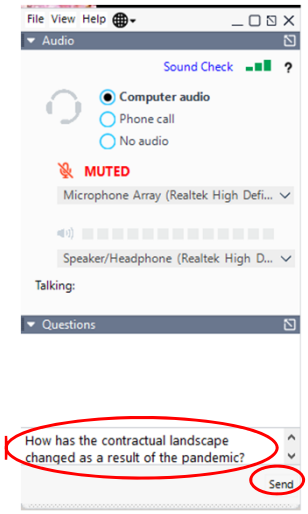
We Need YOU To Actively Participate!



Submit Questions for
Faculty or AUA Staff

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Thank you!

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Acknowledgements

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Knowledge Assessment

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Question 1

A multidisciplinary treatment team may include:

A. Advanced Practice Provider
B. Radiation Oncologist
C. Pain Management
D. Dietitian
E. All of the Above

Question 2

Recently approved pembrolizumab for BCG-unresponsive, high risk, non-muscle invasive bladder cancer requires presence of the following:

A. PD-L1 positive status

B. Stage T1

C. Carcinoma in situ with or without papillary tumors

D. Failed treatment with gemcitabine

E. None of the Above

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Question 3

Which is NOT critical when considering the role of upfront cytoreductive nephrectomy?

A. IMDC Risk Groups.
B. MDA Surgical Criteria.
C. Burden of the tumor that can be debulked.
D. Ability to do a minimally invasive approach.
E. Urgency of systemic therapy.

Question 4

Germline genetic testing is recommended for prostate cancer patients with:

A. High risk disease
B. Very high-risk disease
C. Regional spread
D. Metastatic disease
E. All of the above

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Question 5

A 57-year-old man previously underwent prostatectomy and adjuvant radiation therapy and was then started on androgen deprivation therapy at the time of PSA recurrence. He now has a rising PSA (doubling time 3M) with negative imaging and a castrate level testosterone.
Which of the following is most appropriate?

A. Patient should undergo repeat imaging in six months
B. Bicalutamide should be initiated for MO CRPC.
C. Enzalutamide or apalutamide should be initiated for MO CRPC.
D. Ketoconazole could be considered for treatment of M0 CRPC.

Integrating Care for Oncology Patients: Establishing a Multidisciplinary Oncology Clinic with Advanced Therapeutics

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Learning Objectives

After participating in this course, attendees will be able to:

1. Describe the components of a multidisciplinary urologic cancer clinic and identify the best structure for the practice.
2. Deliver advanced therapeutics based on current and emerging best evidence including immunotherapy in urologic oncology patients.
3. Identify opportunities for shared care and team-based approaches of patients with urologic cancers including advanced prostate, bladder, and kidney cancer.
4. Describe advances in genomic testing and personalized medicine for urologic cancers.
5. Differentiate between new therapeutics that expand the treatment options for patients with urologic cancers and alter the definitions of cancer treatment.

Course Faculty

Alicia Morgans, MD, MPH
Associate Professor of Medicine, Division of Hematology/Oncology
Northwestern University Feinberg School of Medicine

Kelvin A. Moses, MD, PhD, FACS
Associate Professor of Urology
Vanderbilt University Medical Center

Brian Shuch, MD
Associate Professor of Urology
Director, UCLA Kidney Cancer Program

Kelly Stratton, MD
Associate Professor of Urologic Oncology
University of Oklahoma, Stephenson Cancer Center

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Introduction to the Multidisciplinary Oncology Clinic

Stephenson CANCER CENTER
The UNIVERSITY of OKLAHOMA

Kelly L. Stratton, MD
Associate Professor, Department of Urology
University of Oklahoma

Objectives:

- Describe the components of a multidisciplinary urologic cancer clinic
- Examine the best clinic structure based on practice specific factors
- Assess the benefit of advanced practice providers in a multidisciplinary cancer clinic

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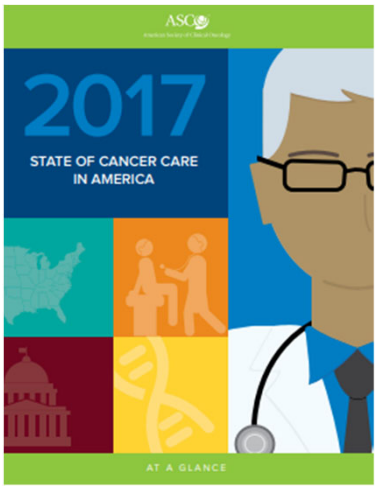
Evolving Roles of Oncology Providers:

- Deliver coordinated, **multidisciplinary**, patient-centered cancer care across multiple cancer care settings and in a system that may not have been built on team-based models and does not readily or consistently share patient information.



MDC Recognized for Improved Care

- Health Care systems and Governments have recognized multidisciplinary care as a way to improve cancer patient outcomes
- Several countries including United Kingdom, Canada, and Australia have established national guidelines for the use of MDC teams in cancer care

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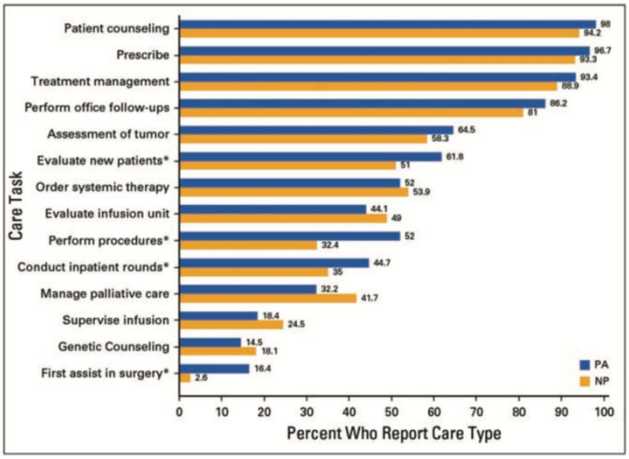
Multidisciplinary Clinic

- Several options for creating a multidisciplinary clinic
  - All-in-one approach:
    - Single clinic space with multiple specialists who can evaluate patients simultaneously
  - Virtual Clinics:
    - Same day/different locations
    - Different days/different locations
  - Tumor Boards

Using Advanced Practice Providers

- Growing patient care demands have outpaced practicing physicians
- AAPs: important clinical role
  - Order entry
  - Medicine management
  - Wound care
  - Pain management
  - Collaboration with PCP
- 85% of AAPs in surgical oncology setting have both independent and shared visits



Bruinooge SS, et al. JAAPA 2018 Dec;31:1–12.

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Conclusions:

- Urologists remain central figures in the care of urologic cancer patients
- Utilization of MDC clinics allows multiple specialties to participate in treatment planning
- New therapeutic opportunities increasing rely on MDC patient care
- Incorporation of APPs in MDC care may reduce provider workload while improving patient access to care

Multidisciplinary Approach to Prostate Cancer

Alicia Morgans, MD, MPH
Associate Professor of Medicine
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Northwestern University Feinberg School of Medicine

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Disclosures

- Honoraria: Astellas, Janssen, Sanofi
- Consulting or Advisory Role: AstraZeneca, Astellas, Janssen, Sanofi, Genentech, Bayer, Myovant, AAA
- Research Support: Bayer, Seattle Genetics, Dendreon, Genentech

Outline

- mHSPC
  - Systemic therapy
  - Treatment of the primary?
- M0CRPC
  - Patient Selection
- Complications of ADT
  - Approach to bone health
- Personalization – genetic testing
- Summary

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Opportunities for Multi-D Care in mHSPC

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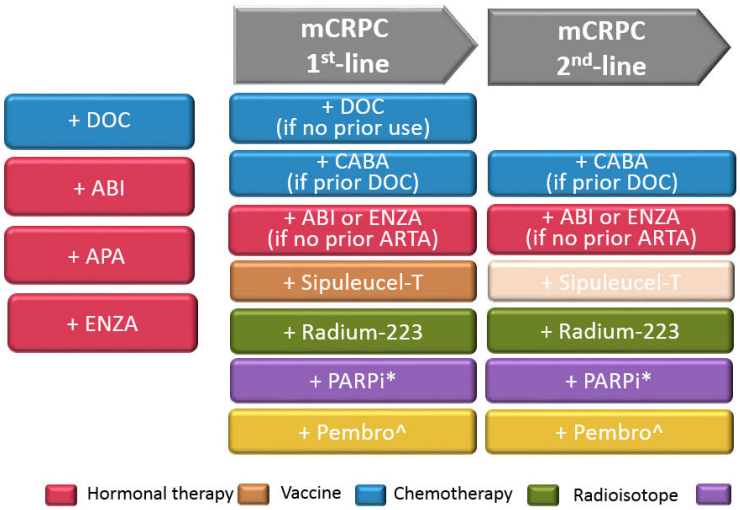
Choices in mCSPC affect options in mCRPC!



* Olaparib for men with HRR mutations, after AR targeted therapy, before or after taxane; Rucaparib for men with BRCA1 or BRCA2 mutations after AR targeted therapy and taxane. Mutations can be germline or somatic.

^ FDA approved for men with tumors identified as having high microsatellite instability (MSI high).

Hormonal therapy | Vaccine | Chemotherapy | Radioisotope | PARP Inhibitor | Immunotherapy

ABI, abiraterone acetate + prednisone; APA, apalutamide; CABA, cabazitaxel; DOC, docetaxel; ENZA, enzalutamide; PARPi = PARP inhibitor (olaparib or rucaparib per FDA indication); Pembro, pembrolizumab; mCRPC, metastatic castration-resistant prostate cancer; Immunotherapy is pembrolizumab (MSI tumors only), ARTA, AR targeted therapy

Adapted from A. Birtle, Women for Mankind Symposium, ESMO October 2018.

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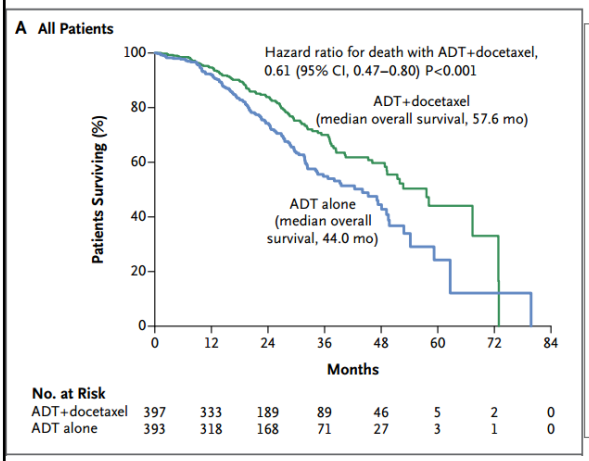
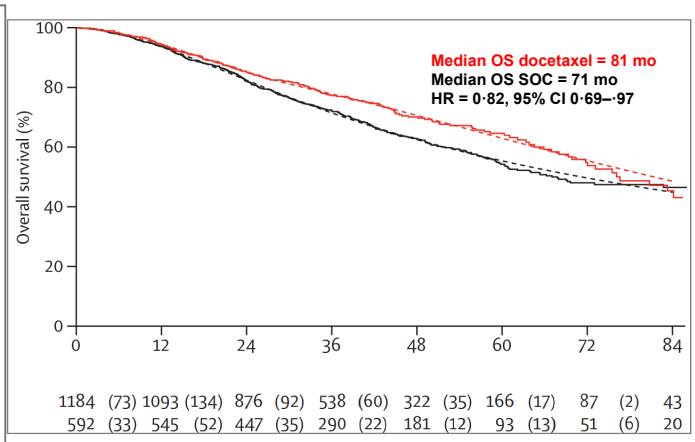
Chemohormonal Therapy

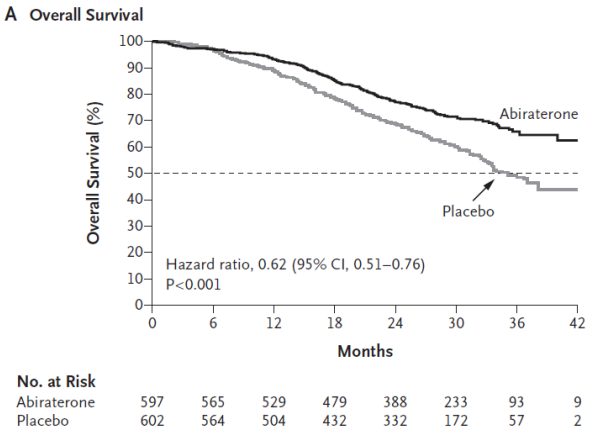


Sweeney C, et al. N Engl J Med. 2015.

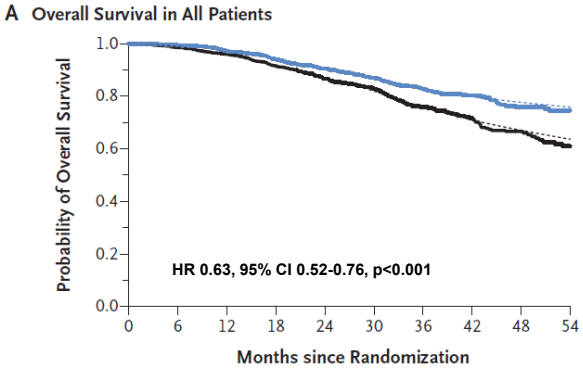


James ND, et al. Lancet. 2016.

Abiraterone Acetate



Fizazi K, et al. N Engl J Med 2017;377:352-60.



James ND, et al. N Engl J Med 2017.

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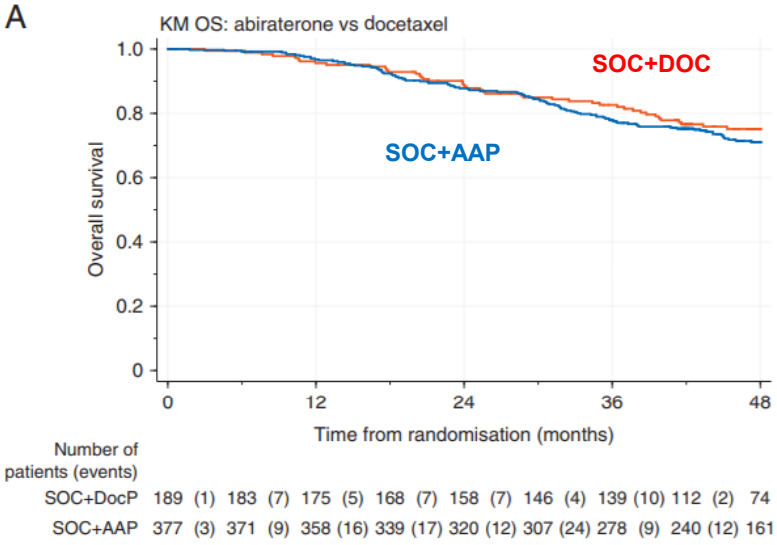
STAMPEDE Comparison: Chemohormonal vs Abiraterone

STAMPEDE Comparison – Overall Survival

A

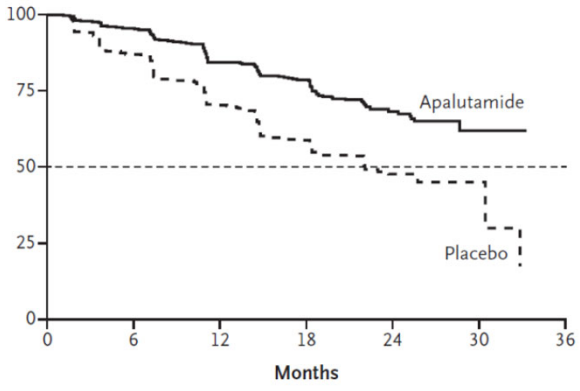


Number of patients (events)																						
SOC+DocP	189	(1)	183	(7)	175	(5)	168	(7)	158	(7)	146	(4)	139	(10)	112	(2)	74
SOC+AAP	377	(3)	371	(9)	358	(16)	339	(17)	320	(12)	307	(24)	278	(9)	240	(12)	161

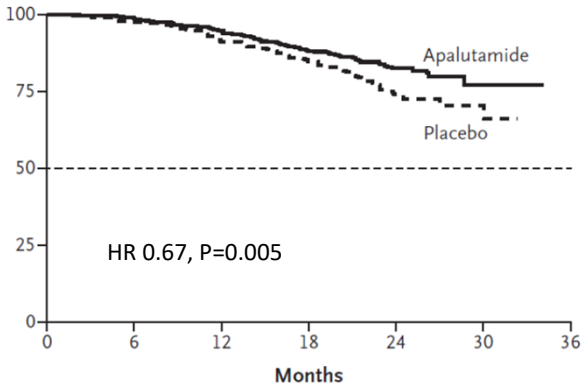
TITAN: Apalutamide for mHSPC

Phase 3 Placebo-Controlled, Randomized International Study

Radiographic Progression-Free Survival

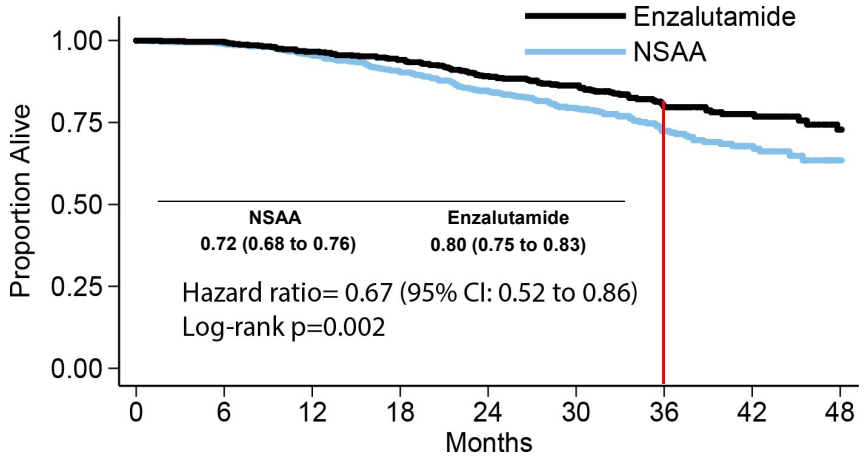


Overall Survival



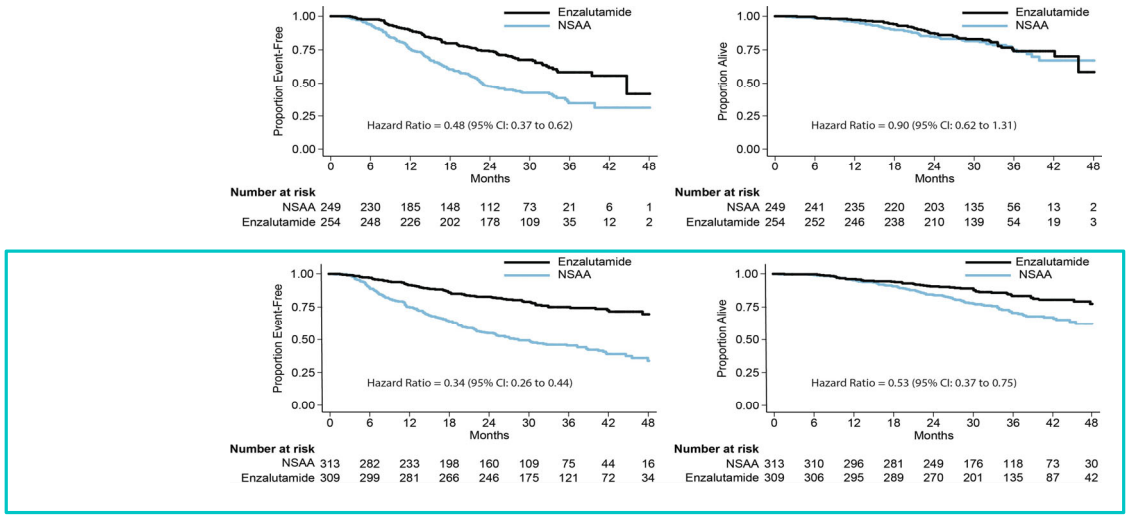
Chi et al (2019) *N Engl J Med 381*: 13-24

ENZAMET
Primary Endpoint: Overall Survival



Davis et al (2019) *N Engl J Med 381*: 121-131

ENZAMET: Concurrent Docetaxel



Davis et al (2019) *N Engl J Med 381*: 121-131

Treatment Options for mCSPC 2020

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Prostate Cancer

SYSTEMIC THERAPY FOR CASTRATION-NAIVE PROSTATE CANCER[oo]

M0 →
- Observation (preferred)[q] or ADT[t,ss]

M1[pp,qq,rr] →
- ADT[t] with one of the following:
  - Preferred regimens:
    - Apalutamide (category 1)[t]
    - Abiraterone (category 1)[t]
    - Docetaxel 75 mg/m^2 for 6 cycles[tt] (category 1)[uu]
    - Enzalutamide (category 1)[t]
  - Other recommended regimens:
    - Fine-particle abiraterone (category 2B)[t]
  - EBRT[o] to the primary tumor for low-volume M1[tt]
  - or ADT[t,ss]

→
- Physical exam + PSA every 3–6 mo
- Imaging for symptoms or increasing PSA[f]

→ Progression[gg,vv]

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MRC Clinical Trials Unit — Smarter Studies, Global Impact, Better Health

STAMPEDE

UCL

Radiotherapy to the primary tumour for men with newly-diagnosed metastatic prostate cancer: Survival results from STAMPEDE

CC Parker, ND James, CD Brawley, NW Clarke, G Attard, S Chowdhury, W Cross, DP Dearnaley, S Gillessen, C Gilson, RJ Jones, MD Mason, R Millman, C Eswar, J Gale, JF Lester, DJ Sheehan, AT Tran, MKB Parmar, MR Sydes.

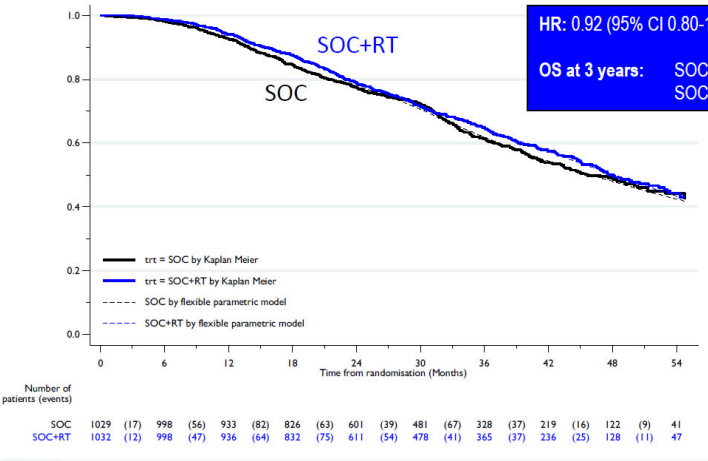
MUNICH 2018 ESMO congress

The ROYAL MARSDEN NHS Foundation Trust

CANCER RESEARCH UK

Overall survival: all patients

Events 391 SOC | 370 SOC+RT



HR: 0.92 (95% CI 0.80-1.06); p=0.266

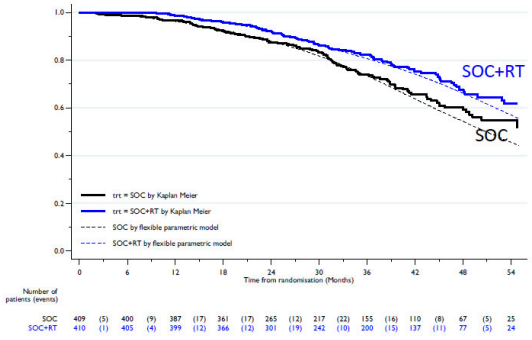
OS at 3 years: SOC = 62%
SOC+RT = 65%

MUNICH 2018 ESMO congress

MRC CTU at UCL

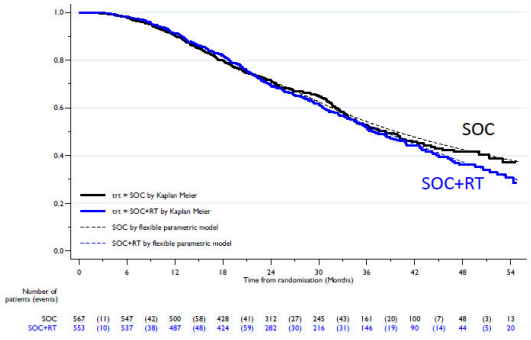
Overall survival: metastatic burden subgroup analysis

Low burden



HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%): SOC = 73%
SOC+RT = 81%

High burden



HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%

MUNICH 2018 ESMO congress

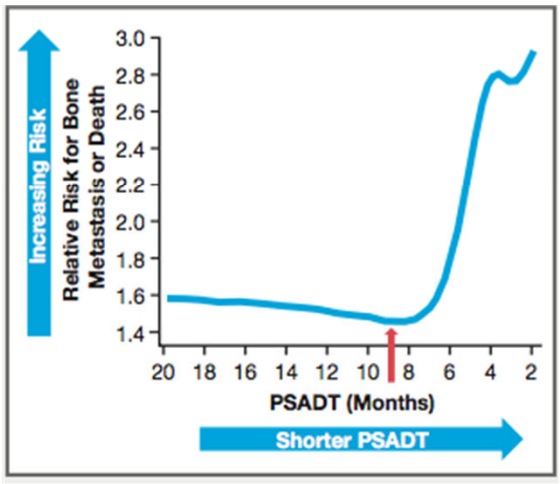
MRC CTU at UCL

Multidisciplinary Approach

- mHSPC now includes multiple choices for combination systemic therapy
  - De novo and high volume mHSPC should consider docetaxel ("6 cycles and done")
  - All mHSPC should consider abiraterone, apalutamide, and enzalutamide
- Treatment of the primary cancer in low-volume mHSPC should be considered
- Multidisciplinary teams can guide personalized choices

Opportunities for Multi-D Care in m0CRPC

Risk of Metastases Increases as PSA Doubling Time Falls



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Study Designs: SPARTAN, PROSPER, ARAMIS

SPARTAN: Apalutamide vs Placebo

Key Eligibility Criteria
- nmCRPC (central review)
- Baseline PSA ≥2 ng/mL
- Rising PSA despite castrate testosterone level (≤50 ng/dL)
- PSADT ≤10 months

2:1
N = 1,207

- Apalutamide 240 mg once daily + ADT (n = 806)
- Placebo + ADT (n = 401)

Primary endpoint: MFS

Secondary endpoints: Safety, time to PSA progression, time to symptomatic progression, OS, PSA response, QOL

PROSPER: Enzalutamide vs Placebo

Key Eligibility Criteria
- M0 CRPC (central review)
- Rising PSA despite castrate testosterone level (≤50 ng/dL)
- Baseline PSA ≥2 ng/mL
- PSADT ≤10 months

2:1
N = 1,401

- Enzalutamide 160 mg/day + ADT n = 933
- Placebo + ADT (n = 468)

Primary endpoint: MFS

Secondary endpoints: Safety, time to PSA progression, time to use of new antineoplastic therapy, OS, PSA response, and QOL

ARAMIS: Darolutamide vs Placebo

Key Eligibility Criteria
- nmCRPC
- Baseline PSA ≥2 ng/mL
- PSADT ≤10 mo

2:1
N = 1,509

- Darolutamide 1200 mg/day + ADT n = 955
- Placebo + ADT (n = 554)

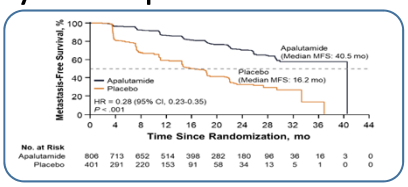
Primary endpoint: MFS

Secondary endpoints: OS, time to first symptomatic skeletal event, time to initiation of first cytotoxic chemotherapeutic, time to pain progression, safety, and tolerability

Smith MR, et al. *N Engl J Med.* 2018;378:1408-1418; Hussain M, et al. N Engl J Med. 2018;378:2465-2474. Fizazi K, et al. NEJM.2019;1235-1246.

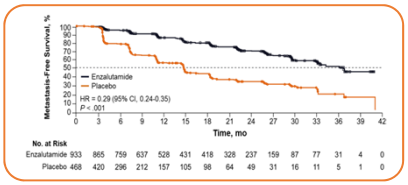
Primary Endpoint: Metastasis Free Survival

SPARTAN
Apalutamide



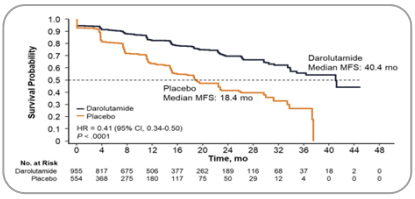
- **72% reduction of distant progression or death**
- **Median MFS: APA 40.5 vs PBO 16.2 months**
- **24-month MFS benefit**

PROSPER
Enzalutamide



- **71% reduction of distant progression or death**
- **Median MFS: ENZA 36.6 vs PBO 14.7 months**
- **22-month MFS benefit**

ARAMIS
Darolutamide



- **59% reduction of distant progression or death**
- **Median MFS: DARO 40.4 vs PBO 18.4 months**
- **22-month MFS benefit**

Smith M, et al. *N Engl J Med*. 2018;378:1408-1418.
Hussain M, et al. N Engl J Med. 2018;378:2465-2474.
Fizazi K, et al. N Engl J Med. 2019;380:1235-1246.

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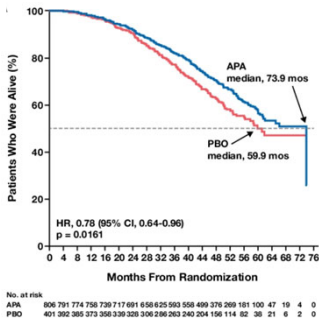
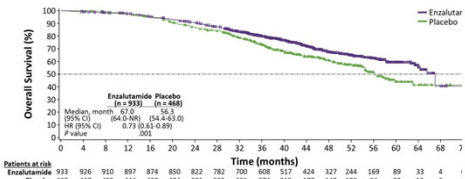
Secondary Endpoint: Updated Overall Survival

SPARTAN
Apalutamide



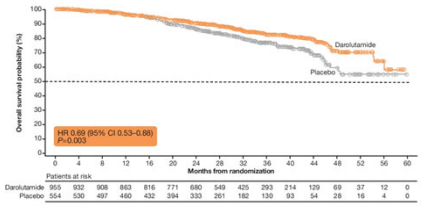
- **22% reduction in risk of death**
- **HR = 0.78 (95% CI, 0.64-0.96)**
- ***P* = .0161**

PROSPER
Enzalutamide



- **27% reduction in risk of death**
- **HR = 0.73 (95% CI 0.61-0.89)**
- ***P* = .001**

ARAMIS
Darolutamide



- **31% reduction in risk of death**
- **HR = 0.69 (95% CI, 0.53-0.88);**
- ***P* = .003**

Small EJ, et al. ASCO 2020. Abstract 5516. Sternberg CN, et al. ASCO 2020. Abstract 5515. Fizazi K, et al. ASCO 2020. Abstract 5514.

Multidisciplinary approach

- Patient selection is important in treating BCR
  - PSADT ≤10 months is associated with higher risk of metastasis or death in BCR
  - Coordination between teams can get systemic therapy to patients with M0CRPC more efficiently
- Treatment of men with M0CRPC with enzalutamide, apalutamide, or darolutamide prolong MFS and OS vs placebo
- Multidisciplinary teamwork is important as patients will need more intensive systemic therapy early – should happen before they become metastatic if possible!

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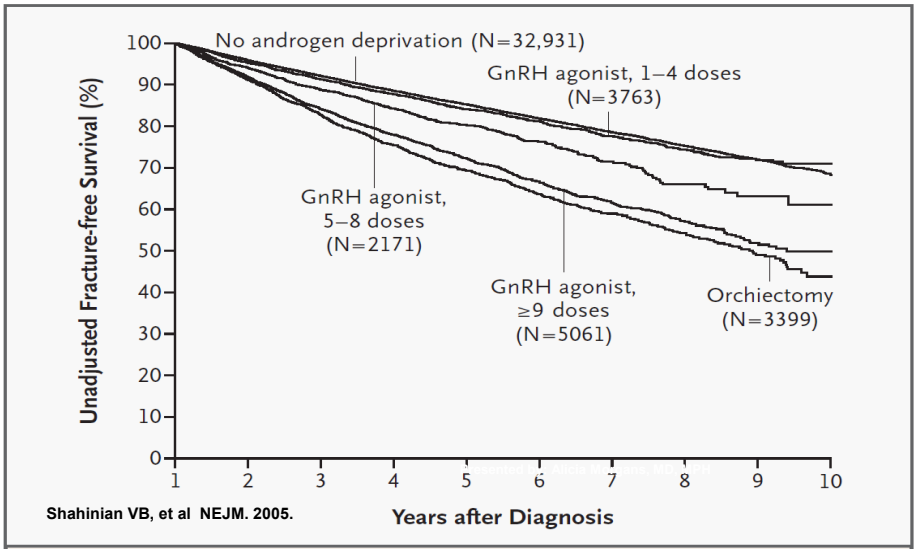
Opportunities for Multi-D Care in Bone Health

ADT and Fracture



Shahinian VB, et al NEJM. 2005.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Prostate Cancer

Bone Health Guidelines

- NCCN Guidelines:
  - Follow guidelines set forth by the National Osteoporosis Foundation
    - Use daily supplemental calcium (1000-1200 mg/day) and vitamin D3 (400-1000 IU/day)
    - Consider additional pharmacologic therapy:
      - 10 y probability of hip fracture ≥3%
      - 10 y probability of major osteoporosis-related fracture ≥ 20%
    - Baseline bone density test in men at increased risk of fracture
      - Elderly
      - Heavy alcohol use
      - Current smoker
      - Sustained exposure to steroids

NCCN Guidelines®: Prostate Cancer (Version 2.2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: NCCN.org.
https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9

National Osteoporosis Foundation

Multidisciplinary approach

- Coordination between teams essential
  - Who owns bone health?
- Fragility fracture prevention for men on long term ADT (>2 years)
- SSEs prevention for men with mCRPC
- Is the approach different to capturing these different populations?

Opportunities for Multi-D Care in Genetic Testing

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INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Risk Group	Clinical/Pathologic Features			Imaging[f,g]	Germline Testing[c]	Molecular/ Biomarker Analysis of Tumor[c]	Initial Therapy
Very low[d]	Has all of the following: • T1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e] • PSA density <0.15 ng/mL/g			Not indicated	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Not indicated	See PROS-3
Low[d]	Has all of the following but does not qualify for very low risk: • T1–T2a • Grade Group 1 • PSA <10 ng/mL			Not indicated	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[i]	See PROS-4
Intermediate[d]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRF): ▸ T2b–T2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive[e]	• Bone imaging[h]: not recommended for staging • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[i]	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive[e]	• Bone imaging[h]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[i]	See PROS-6
High	Has no very-high-risk features and has at least one high-risk feature: • T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended	Consider if life expectancy ≥10 y[i]	See PROS-7
Very high	Has at least one of the following: • T3b–T4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended	Not routinely recommended	See PROS-7

See Footnotes for Initial Risk Stratification And Staging Workup For Clinically Localized Disease (PROS-2A)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Prostate Cancer

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GENETIC AND MOLECULAR BIOMARKER ANALYSIS FOR ADVANCED PROSTATE CANCER

Risk group	Clinical/pathologic features	Germline testing	Molecular and biomarker analysis of tumor[l]	Initial therapy
Regional	Any T, N1, M0	Recommended[c,k]	Consider tumor testing for homologous recombination gene mutations and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR)[dd,ee]	See PROS-10
Metastatic[ff]	Any T, Any N, M1	Recommended[c,k]	Consider tumor testing for homologous recombination gene mutations and for MSI or dMMR [dd,ee]	See PROS-14

Engl J Med 2016;375:443-453). Germline genetic testing is recommended for all men with high risk, very high risk, regional, or metastatic prostate cancer. Genetic counseling resources and support is critical and pre-test counseling is preferred when feasible. Post-test genetic counseling is recommended if a mutation is identified.

Multidisciplinary approach

- Coordination between teams essential
  - Who owns genetic testing?
  - How does workflow ensure testing of appropriate patients?
  - Is the testing approach different for localized vs metastatic patients?
    - Where does the genetic counselor fit in?

Summary

- Multidisciplinary care opportunities span the continuum of prostate cancer.
- Engaging multi-disciplinary teams can
  - Enhance disease specific outcomes (overall and metastasis free survival)
  - Reduce morbidity and mortality, and improve quality of life
  - Identify risk factors for family members to also improve their care

Multidisciplinary Care for Metastatic Castrate Resistant Prostate Cancer

Kelvin A. Moses, MD, PhD, FACS
Associate Professor of Urology
Vanderbilt University Medical Center

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Disclosures

- Speakers' Bureau- Pfizer/Astellas, Dendreon
- Consultant- Pfizer/Astellas

Objectives

- Understand the clinical guidelines for immunotherapy (sipuleucel-T) in mCRPC
- Discuss 2nd generation oral anti-androgens for mCRPC
- Incorporate radium-223 therapy in appropriate patient populations
- Develop a framework for multidisciplinary care of mCRPC patients based on AUA guidelines

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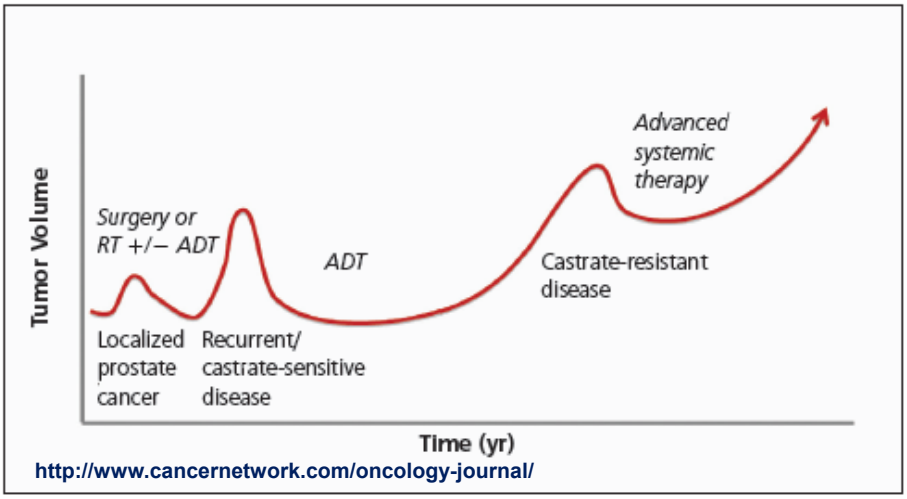
Natural Progression of Prostate Cancer



http://www.cancernetwork.com/oncology-journal/

Castrate Resistant Prostate Cancer

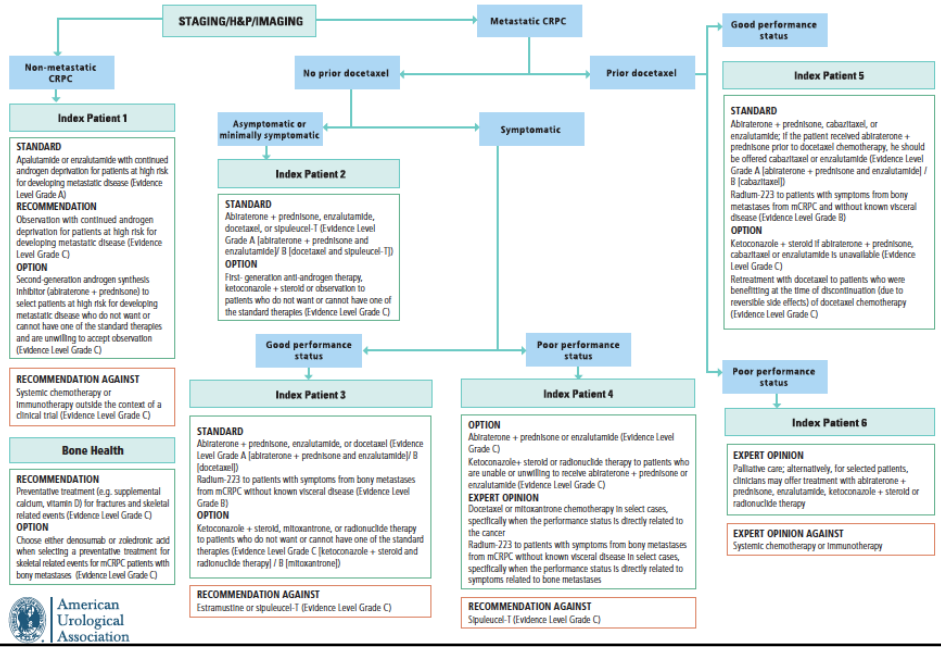
Castrate-resistant prostate cancer (CRPC) is defined by disease progression despite androgen-deprivation therapy (ADT) and a serum Testosterone <50ng/dl, and any of the following:

1) Three consecutive rises in serum prostate-specific antigen (PSA)

2) Progression of pre-existing disease, or

3) Appearance of new metastases

2018 AUA Guidelines for Management of CRPC



Immunotherapy for mCRPC

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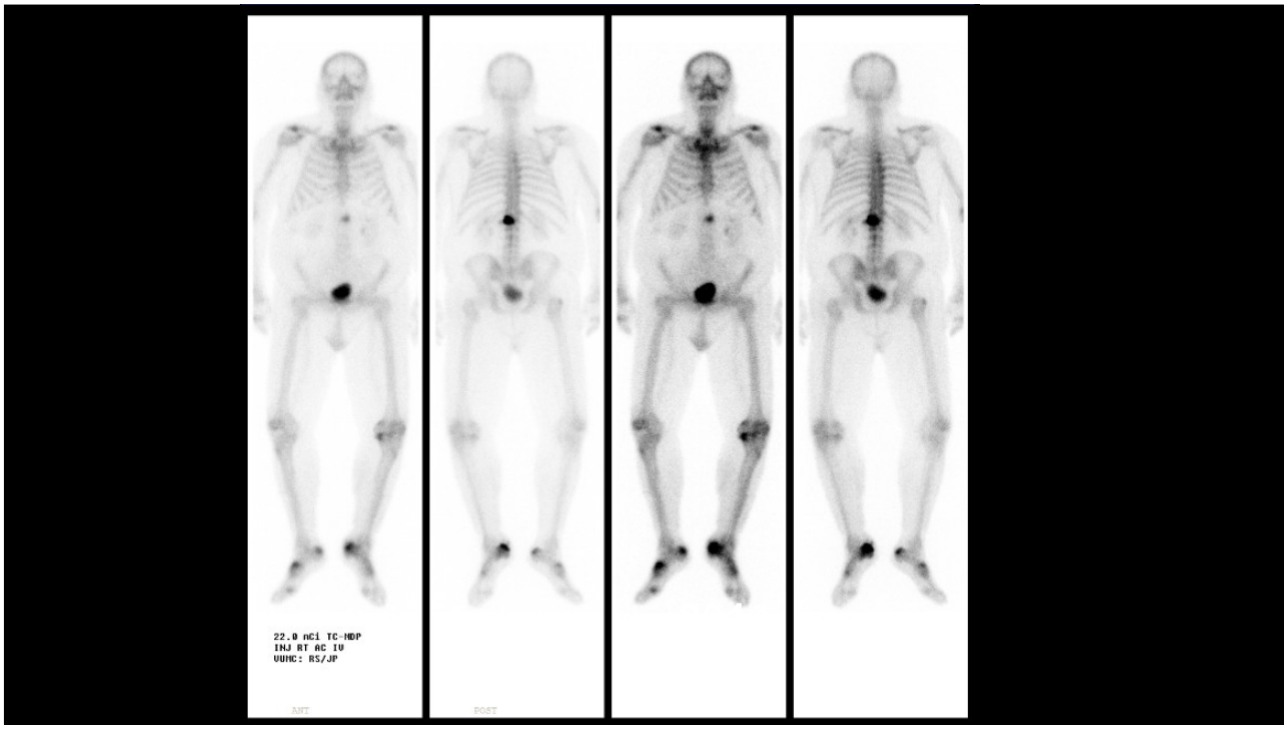
Clinical Scenario

- Mr. S is a 61yo Black man who presents with mCRPC
  - RRP 2012, Gleason 4+4=8, pT2cN0R1
  - PSA nadir to undetectable until 2013 when PSA rose to 3.5 ng/ml
  - Staging imaging negative (CT and Bone Scan)
  - On Lupron 45mg IM q6mo and PSA undetectable until April 2014 when PSA rose to 5 ng/ml
  - Asymptomatic
  - Repeat imaging performed



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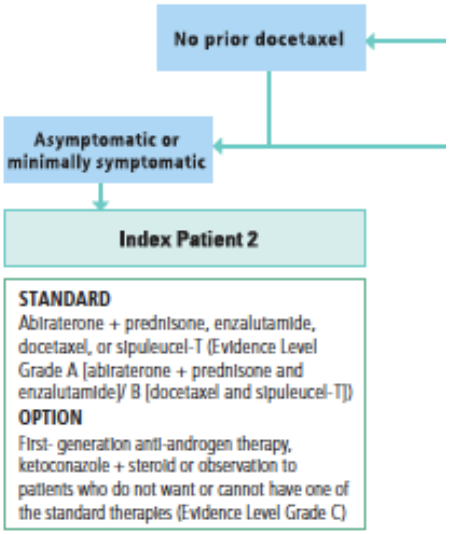
Asymptomatic mCRPC

- Treatment options include:
  - Abiraterone acetate plus prednisone
  - Enzalutamide
  - Sipuleucel-T
  - Docetaxel



Sipuleucel-T

- FDA approved for men with **asymptomatic** metastatic CRPC **with life expectancy > 6 months**
- Side effects include fever/chills, nausea, back pain, infusion reactions, hypertension, rare stroke/thrombotic complications
- Poor candidates for sipuleucel-T include patients with symptomatic disease, rapidly progressive disease (short PSA doubling time), limited life-expectancy, and possibly visceral metastases

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Sipuleucel-T

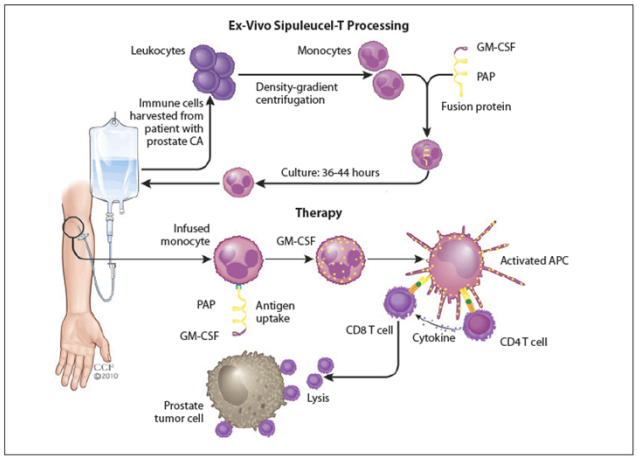


Figure: The diagram illustrates the two steps involved in sipuleucel-T therapy: (1) harvesting the patient's dendritic cells and then pulsing these ex vivo with a recombinant fusion protein made of prostatic acid phosphatase (PAP) and granulocyte–macrophage colony-stimulating factor (GM-CSF); and (2) infusing the cultured cells into the patient, where the PAP–GM-CSF–loaded antigen-presenting cells induce the proliferation of T-cells that recognize and target prostate tumor cells. APC = antigen-presenting cell.

Garcia and Dreicer, Oncology 2011

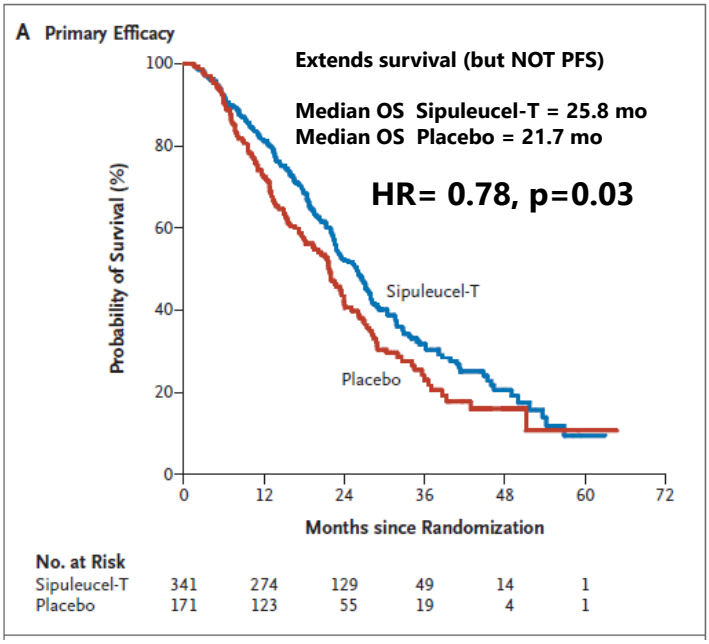
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 29, 2010 VOL. 363 NO. 5

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

There is no PSA or radiographic response associated with treatment

IMPACT Trial, Kantoff et al, NEJM 2010



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Rationale for Early Sipuleucel-T in mCRPC

- IMPACT trial demonstrated a 22% reduction in risk of death
  - 4.1 month improvement in median survival
- Independent prognostic factors included PSA, LDH, Alkaline phosphatase, ECOG PS, and presence of visceral metastases
- Investigators examined survival based on PSA quartiles

Lower Baseline Prostate-specific Antigen Is Associated With a Greater Overall Survival Benefit From Sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) Trial

Paul F. Schellhammer, Gerald Chodak, James B. Whitmore, Robert Sims, Mark W. Frohlich, and Philip W. Kantoff

	Baseline PSA, ng/mL			
Variable	≤22.1 (n = 128)	>22.1-50.1 (n = 128)	>50.1-134.1 (n = 128)	>134.1 (n = 128)
Median OS, mo				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference, mo	13.0	7. 1	5.4	2.8
HR (95% CI)	0.51 (0.31-0.85)	0.74 (0.47-1.17)	0.81 (0.52-1.24)	0.84 (0.55-1.29)

- Not powered to detect a difference within groups
- Quartile groups were not randomized
- Earlier treatment with sipuleucel-T appears to have the greatest survival benefit

Urology 2013

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The PROCEED Registry: Real-World Sipuleucel-T Use

- PROCEED (NCT01306890) enrolled over 1900 real-world mCRPC patients receiving sipuleucel-T (2011-2013)
- Enrolled ~12% African-American patients
  - Allows for prospective examination of outcomes in AA vs Caucasian patients
- Analysis
  - CAU and AA patients (2:1) matched by baseline PSA
  - Overall survival estimated
  - Multivariate analysis for independent factors associated with OS

Slide kindly provided by O. Sartor

Baseline Characteristics in a Matched Subset of PROCEED Patients

	Caucasian (n=420)	African American (n=210)	p-value*
Median age, y (range)	72 (48-93)	71 (42-94)	0.27
ECOG PS, n (%) **0** **1**	 300 (71) 107 (25)	 132 (63) 71 (34)	**0.01**
Worst Gleason sum, n (%) **≤7** **≥8**	 186 (44) 207 (49)	 89 (42) 97 (46)	0.45
Median PSA, ng/mL (IQR)	27.1 (7.2-68.3)	26.5 (8.0-69.4)	0.71
Median hemoglobin, g/dL (IQR)	13.0 (12.1-13.8)	12.1 (11.1-13.0)	**<0.001**
Median alkaline phosphatase, U/L (IQR)	81 (64-115)	87 (68-111)	0.14
Median LDH, U/L (IQR)	186 (155-211)	191 (170-233)	0.13
Prior local therapy, n (%)	326 (80)	149 (73)	**0.02**
Prior chemotherapy, n (%)	83 (20)	21 (10)	**<0.001**

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Overall Survival in CAUs and AAs by PSA Quartiles

Overall Survival by PSA Quartiles	Baseline PSA, ng/mL			
	Q1 < 7.5	Q2 7.5-26.8	Q3 26.81-68.49	Q4 ≥68.5
Median OS, months				
AA	54.3	46.7	28.7	20.5
CAU	37.4	31.9	22.0	18.3
Difference, mo	**16.9**	**14.8**	**6.7**	**2.2**
HR	0.442	0.602	0.800	0.913
(95% CI)	(0.260, 0.753)	(0.386, 0.939)	(0.537, 1.194)	(0.614, 1.360)
p-value	**0.003**	**0.025**	**0.275**	**0.655**

Slide kindly provided by O. Sartor

Clinical Scenario cont'd

- Mr. S received sipuleucel-T and tolerated this well
  - His PSA was stable for approximately 1 year and then rose from 3.8 ng/ml to 6.5 ng/ml
  - Repeat CT and bone scan showed some interval development of bony disease and pelvic lymphadenopathy
  - He was minimally symptomatic with mild lower back pain

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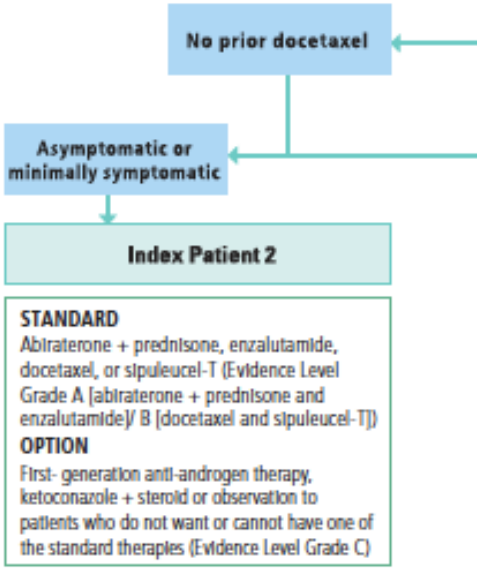
Second Line Oral Anti-Androgen Therapy

Asymptomatic mCRPC

- Treatment options include:
  - **Abiraterone acetate plus prednisone**
  - **Enzalutamide**
  - Sipuleucel-T
  - Docetaxel



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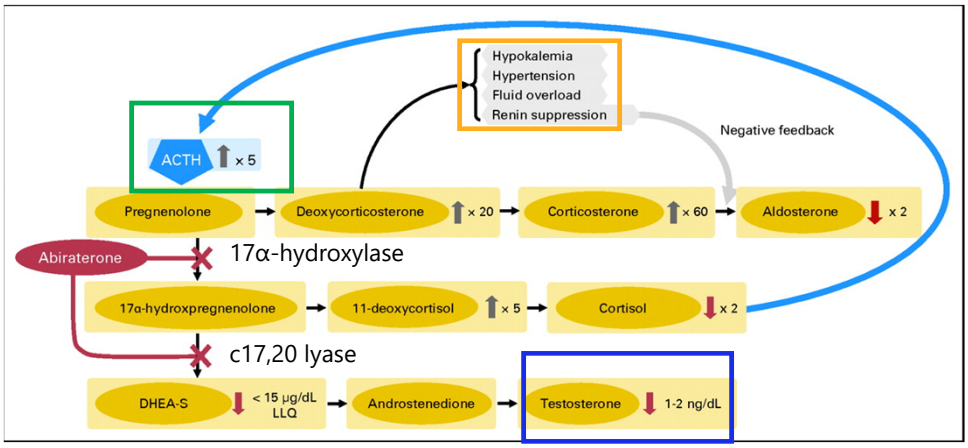
Abiraterone Acetate

- FDA approved for men with metastatic CRPC *before* or *after* chemotherapy
- Common side effects include
  - Hypertension, hypokalemia, fatigue, steroid induced hyperglycemia
- Patients who cannot tolerate systemic steroids, i.e. brittle DM, or with rapidly progressive disease are not good candidates

Abiraterone Acetate

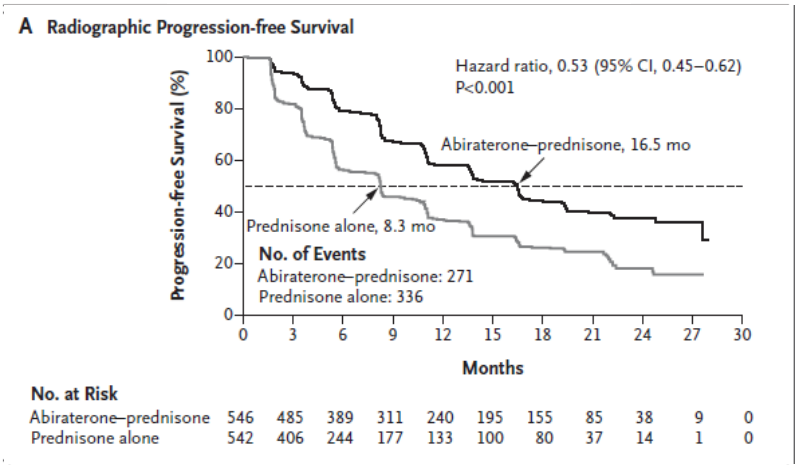


Courtesy of ASCO, J Clin Oncol 2010

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

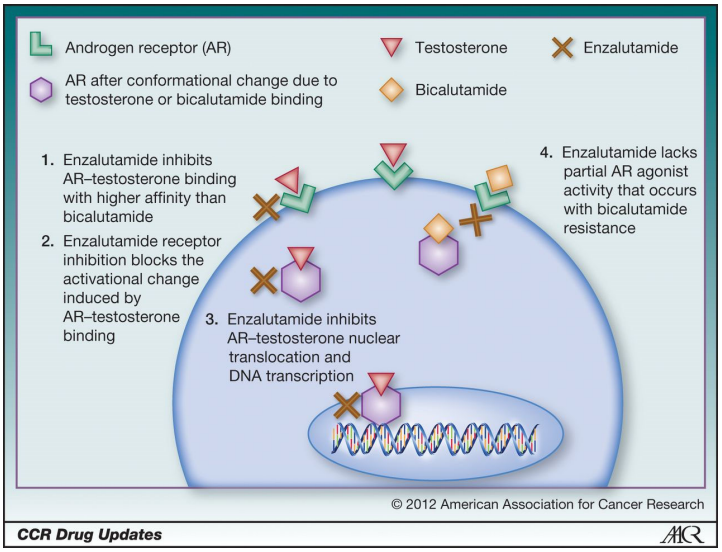


COUGAR Trial, Ryan et al, NEJM 2013

Enzalutamide

- FDA approved for men with metastatic CRPC *before* and *after* chemotherapy
- Common side effects include:
  - HTN, fatigue, constipation/diarrhea, rare seizure
- Relatively contraindicated with history of seizure
- Men with rapidly progressive disease are poor candidates as well

Enzalutamide Mechanism of Action

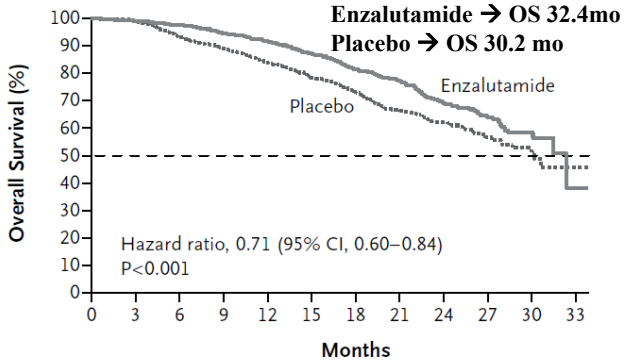


Hoffman-Censits and Kelly, Clin Cancer Res 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enzalutamide in Metastatic Prostate Cancer before Chemotherapy



No. at Risk												
Enzalutamide	872	863	850	824	797	745	566	395	244	128	33	2
Placebo	845	835	781	744	701	644	484	328	213	102	27	2

PREVAIL Trial, Beer et al, NEJM 2014

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Clinical Scenario cont'd

- Mr. S took enzalutamide for 2y, and his PSA declined to undetectable levels
  - After 28 months, his PSA rose to 2.5 ng/ml
  - He then took abiraterone with prednisone for 6 months with continued increase in PSA to 15 ng/ml
  - Repeat bone scan showed >20 bony lesions, CT showed stable lymphadenopathy
  - Now c/o rib, neck and hip pain

Utilization of Radium-223 in mCRPC to the Bone

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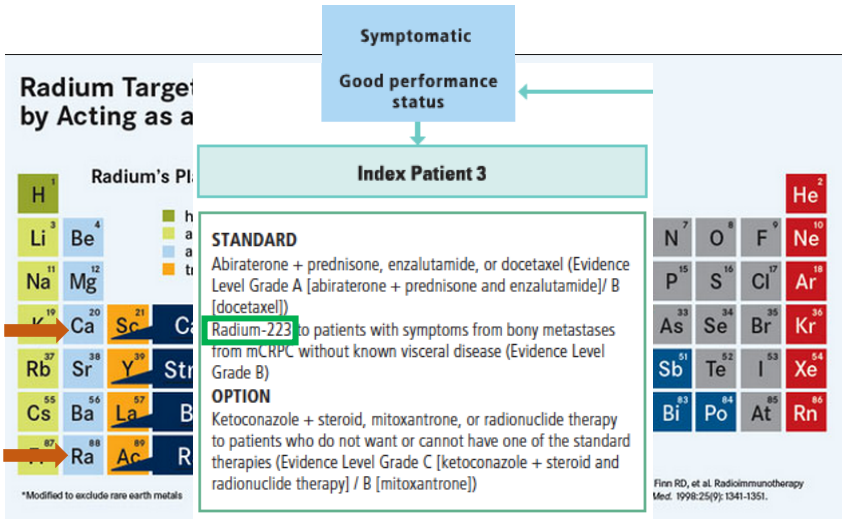
Radium-223

- Bone-seeking isotope that mimics calcium
- Complexes with hydroxyapatite in osteoblastic lesions
- High energy α-particles cause double-stranded breaks in DNA



Radium-223

- FDA approved for men with mCRPC with symptomatic bone metastases *before* or *after* chemotherapy.
- Side effects include nausea, vomiting, diarrhea, peripheral edema, bone marrow suppression, refractory cytopenias (rare)
- Poor candidates
  - History of bone marrow dysfunction/anemia
  - High volume of visceral disease

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ALSYMPCA

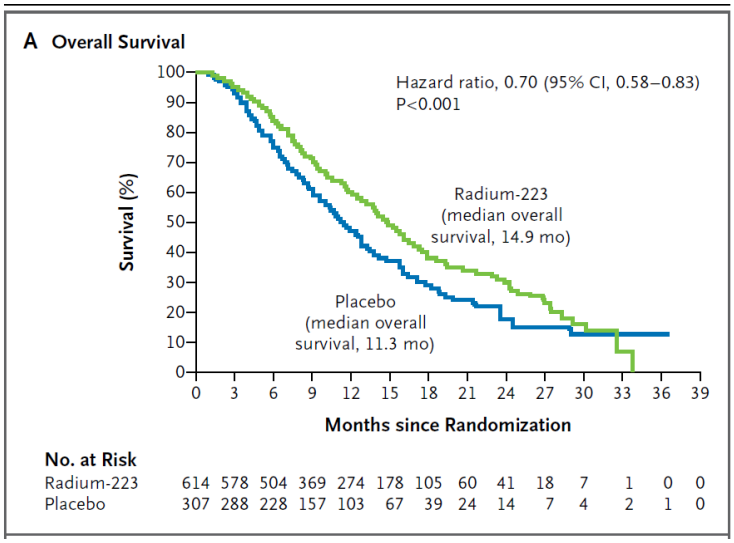
- Phase III international RCT
  - Randomized 2:1 to 6 treatments with radium-223 vs placebo
  - Prolongs OS in men after treatment with docetaxel (or in men ineligible for docetaxel).
  - Prolongs time to symptomatic SRE
- Well-tolerated
  - Similar rates of treatment-related drug discontinuation
  - Similar rates of grade 3-4 complications

Parker et al, NEJM 2013
Sartor et al, Lancet Oncol 2014

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

ALSYMPCA Trial, Parker et al, NEJM 2013



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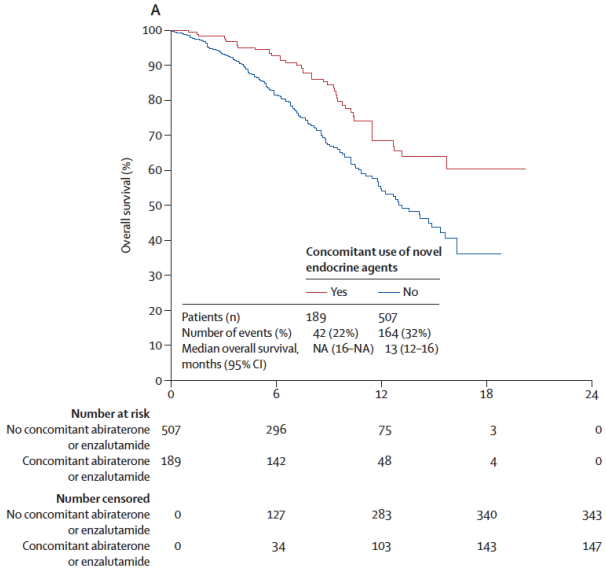
Radium-223 with Concomitant Enzalutamide or Abiraterone

- Phase 3b, early access, open-label, interventional trial
- Concomitant therapies allowed
- Median OS-16mos
  - Concomitant enzalutamide +/- abiraterone=16mos vs 13mos radium alone
- 5% of patients experienced serious adverse event due to treatment

Saad et al, Lancet Oncol 2016



Germline Testing in Advanced Prostate Cancer

- Germline and somatic testing should be performed in men with metastatic prostate cancer (ie. Tempus, Invitae, etc.)
  - BRCA-1
  - BRCA-2
  - ATM
  - PALB2
  - FANCA
  - RAD51D
  - CHEK2
  - CDK12
    - Robinson, 2015; Matida, 2015, Abida, 2017

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PARP Inhibitors for mCRPC

- Poly(adenosine diphosphate-ribose) polymerase inhibitor (PARPi)
- Up to 30% of men with mCRPC harbor deleterious DNA damage repair (DDR) gene mutations
  - Can be somatic, germline or both
- Most commonly: BRCA1, BRCA2, ATM
- PARPi therapy may be effective in mCRPC when one of the DDR mutations is present
  - Robinson, 2015; Cancer Genome Atlas Research, 2015
- Olaparib and rucaparib approved for men with DNA-damage repair mutations following androgen receptor-directed therapy and/or taxane based chemotherapy (ie. BRCA-1, BRCA-2)
  - Mateo, 2015 and 2020; Abida, 2019

Slide courtesy of N. Davis, MD

Multidisciplinary Approach to mCRPC

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Ingredients for a Successful mCRPC Clinic

- Urology- oncology focus
- Medical Oncology- genitourinary/prostate cancer focus
- Mid-Level (NP/PA)- familiar with guidelines, can see stable patients
- Specialty Pharmacy- familiar with payment assistance, oral medications mailed
- Medical Genetics- counseling and germline/somatic testing
- Apheresis Location- for sipuleucel-T (American Red Cross)
- Radiation Oncology/Nuclear Medicine

Summary

- Patients with mCRPC have several options for treatment that are relatively well-tolerated, though optimal sequence has not been determined
- Consider early utilization of sipuleucel-T, particularly in Black men, due to improved survival benefit vs later stage disease
- There are no existing data regarding efficacy of enzalutamide vs abiraterone+prednisone as first oral therapy
- Radium-223 improves survival in men with bone-predominant disease and can safely be used in combination with enzalutamide or abiraterone+prednisone

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Adjuvant treatments and Multidisciplinary Management of mRCC

Brian Shuch, MD
Associate Professor of Urology
Director, Kidney Cancer Program
Alvin & Carrie Meinhardt Endowed Chair
in Kidney Cancer Research

Outline

- Adjuvant Therapy 2020
- Neoadjuvant Therapy
- Cytoreductive Nephrectomy Status
- Case Studies

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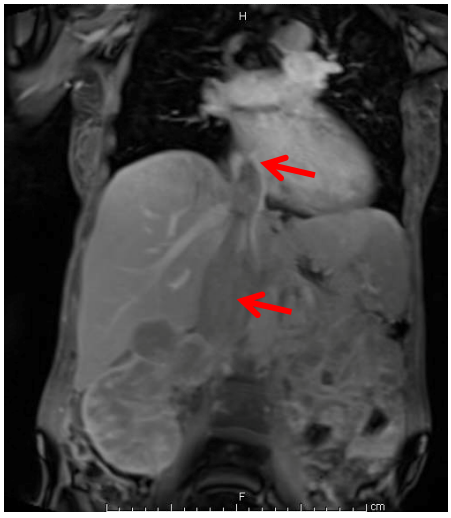
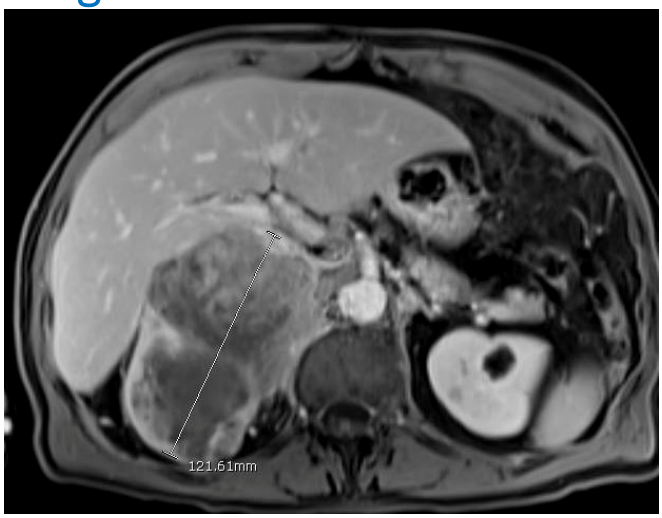
Identification of the High Risk RCC Patient



cT3cN0M0 Patient- recurred at 2 months



cT4N0M0 Patient- recurred at 3 months

Targeted Adjuvant Therapy: Current Status

Trial	Phase	n	Drug	Route	Arms	Histology	Features	1˚ Outcome
SOURCE	III	1656	Sorafenib	PO	1-Placebo 2-Sorafenib 1 yr 3- Sorafenib 3 yrs	All Histology	SSIGN 3-11	DFS
ASSURE	III	1923	Sorafenib Sutent	PO	1-Placebo 2-Sorafenib-9 cycles 3- Sutent-9 cycles	All exept collecting duct or medullary	T1b, G3-4 T2,3,4 N+	DFS
S-TRAC	III	720	Sutent	PO	1-Placebo 2-Sutent-1 yr	Predominant clear cell	UISS High risk	DFS
ARISER	III	864	G250-Ab	IV	1- Placebo 2- G250-Ab x 24 wks	Clear Cell	T1b/2, G3-4 T3,T4 N+	DFS, OS
PROTECT	III	1500	Pazopanib	PO	1-Placebo 2- Pazopanib x 1 yr	Predominant clear cell	T2 (G3-4), T3, T4, N1	DFS
EVEREST	III	1218	Everolimus	PO	1- placebo 2- everolimus x 1 yr	All exept collecting duct or medullary	T1b, G3-4 T2,3,4 N+	DFS, OS
ATLAS	III	592	Axitinib	PO	1- placebo 2- Axitinib x 3 yr	>50%, clear cell RCC	≥T2 or N1	DFS

2018?

2018/9?

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S-TRAC Trial: Disease Free Survival

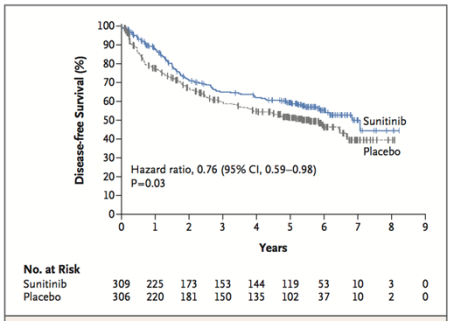

Figure 2. Disease-free Survival.
The median duration of disease-free survival according to independent central review was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group. At the time of data cutoff, an event of disease recurrence, a second cancer, or death had occurred in 113 of 309 patients (36.6%) in the sunitinib group and in 144 of 306 patients (47.1%) in the placebo group.

Trial	Phase	n	Drug	Route	Arms	Histology	Features	1˚ Outcome
S-TRAC	III	720	Sutent	PO	1-Placebo 2-Sutent-1 yr	Predominant clear cell	UISS High risk	DFS

Median DFS (yrs)- 6.8 (5.8-NR) vs 5.6 (3.8-6.6)

1˚ end point was the duration of disease-free survival= first tumor recurrence, the occurrence of metastasis or a secondary cancer, or cancer death

Adjuvant Therapy 2019: Crowded Space

- Four ongoing trials for checkpoint inhibitors
- Room for multiple studies at each institution
- Different patient populations

Protocol	Type	Phase	Subjects	Agent	Comparison	Eligibility	Histology	1˚ Endpoint
EA8143 (PROSPER)	Neo/ Adjuvant	III	766	Nivolimab	Upfront Surgery	T2+ or N+ M0	Clear cell 90% Other subtypes (15%)	RFS
IMMOTION010	Adjuvant	III	664	Atezolizumab	IV Placebo	T2G4, T3aG3/4, T3b/T4, N+ M1 resected NED (met)	Clear Cell Sarcomatoid Features	DFS
KEYNOTE-564	Adjuvant	III	950	Pembrolizumab	IV Placebo	T2G4, T3/4Gany, N1 M1 resected NED (syn)	Clear Cell +/- Sarcomatoid Features	DFS
CheckMate 914	Adjuvant	III	800	Nivolimab + Ipilimumab	IV Placebo	T2G3/4, T3/4Gany, N1	Clear Cell +/- Sarcomatoid Features	DFS

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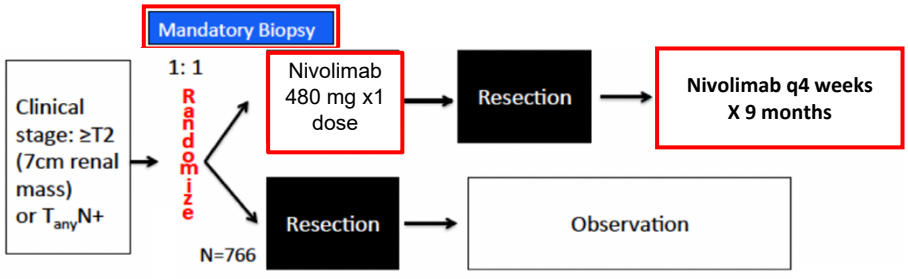
EA8143 PROSPER RCC Workflow



*Stratify by: cT2 or >cT2, cN0 or cN+, histology

SWOG Leading cancer research. Together.

Outline

- Adjuvant Therapy 2019
- Neoadjuvant Therapy
- Current Role of Cytoreductive Nephrectomy
- Case Studies

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New Systemic Therapy and the 1° Tumor

- In the TKI era, responses in the primary tumor were observed
- Neoadjuvant TKI Therapy: "a New Paradigm?"
  - IVC Thrombus--shrinking thrombus ("medical" angio-infarction)
  - Down-sizing- allow NSS, laparoscopic, allow resection
  - Biologic evaluation- Identify rapidly progressors that should not undergo nephrectomy and Lithmus test of agent

Urologists shouldn't practice in a vacuum

Shuch, B et al. *BJU*. 2008

Prospective Neoadjuvant Trials with TKIs

Study	n	Agent	M0 %	% Clear Cell	% Δ in Median/mean Diameter	RECIST Response (%)
Jonasch 2009	50	Bevacizumab	0	96	n/a	0
Cowey 2010	30	Sorafenib	56	70	-9.6	7
Silberstein 2010	12	Sunitinib	58	100	-21.1	28
Hellenthal 2010	20	Sunitinib	80	100	-11.8	5
Powles 2011	66	Sunitinib	0	100	-13	6
Rini 2011	29	Sunitinib	34	75	-22	37
Powles 2013*	102	Pazopanib	0	100	-14	14
Karam 2014	24	Axitinib	100	100	-28.3	46
Alvarez 2014*	23	Pazopanib	100	100	-26	32

- ***Systemic therapy with the primary tumor safe***
- ***Responses in those those with M1 disease ~10% Response***
- ***Does not generally alter surgery for large bulky primaries***

Can Neoadjuvant TKI Change Surgical Approach? Phase 2 Pazopanib Trial

Table 2. *Outcomes in all 28 tumors before and after pazopanib therapy*

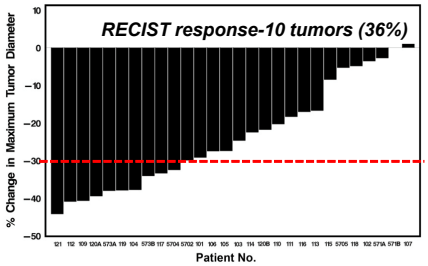
Outcome	Before Pazopanib	After Pazopanib	p Value
Median cm tumor size (range)	7.3 (2.3–10.7)	5.5 (1.8–8.3)	<0.0001
Mean cc tumor vol (IQR)	170 (110–184)	92 (50–118)	<0.0001
Median R.E.N.A.L. score (range)	11 (5–12)	9 (5–12)	<0.0001

6 of 13 (46%) patients for whom PN was not deemed possible underwent PN after treatment

RENAL Score Change

- 1-point - 10
- 2 points- 5
- 3 points- 4
- 4 points- 1

Responses



David Geffen School of Medicine

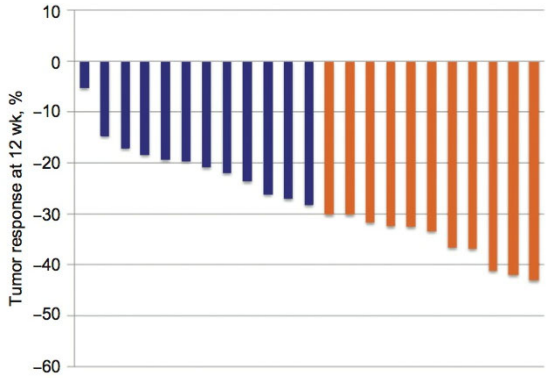
Rini, B. et al. *J. Urology*, 2015, *194*(2), 297–303.

UCLA Health

Experience with Pre-Surgical Axitinib

- 24 patients with cT2+ ccRCC given axitinib x12 weeks
  -All had suspicious of cT3a
- Axitinib stopped 36 hours before

- 28% RECIST response
- Median 10→ 6.9 cm



Karam, J.A. et al (2014). *European Urology.*

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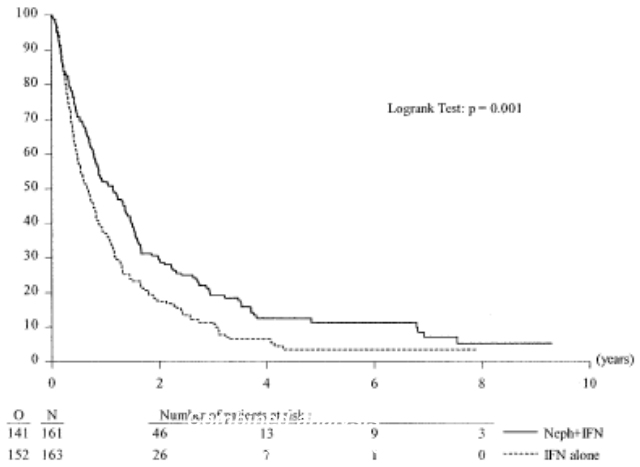
Outline

- Adjuvant Therapy 2019
- Neoadjuvant Therapy
- Cytoreductive Nephrectomy Status
- Case Studies

Randomized Trials by SWOG and EORTC

- In the 1980's, INF-a and surgery only effective Tx
- Cytokine therapy produced limited responses in the 1˚ tumor, therefore SOC of nephrectomy and therapy after
- Both SWOG and EORTC trials identical (INF-a) +/- surgery



Cytoreductive Nephrectomy in The Wrong Patient

- Surgery in poor candidates may worsen outcome
- May limit receipt of systemic therapy (~50% of high risk patients)

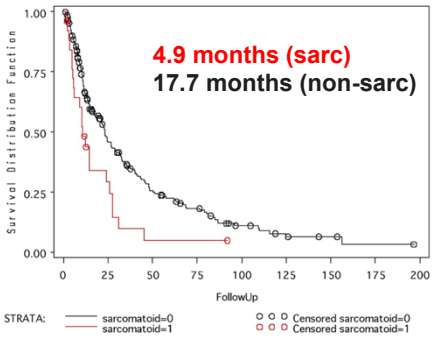


Figure 3. Kaplan-Meier analysis of overall survival (months) of sarcomatoid and nonsarcomatoid groups able to proceed to systemic therapy.

Shuch, B., et al. *Cancer*, 2008
Shuch, B., et al. *J Urol*, 2009, *182*(5), 2164–2171.

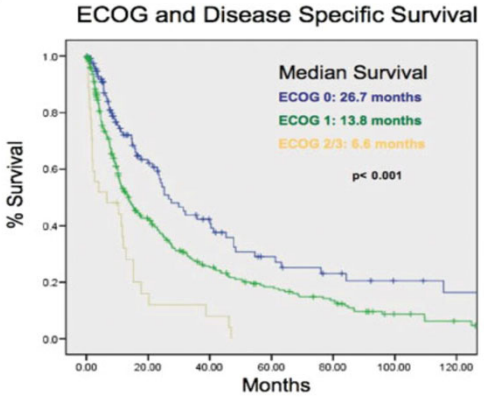


FIGURE 1. This chart illustrates disease-specific survival for patients with renal cell carcinoma who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, and 2.

Phase 2 Trials (Sutent/Pazopanib): Lessons Learned

Series		Powles 2011	Powles 2016
Agent		Sutent	Pazopanib
subjects		66	104
Treatment		12-16 weeks	10-12 weeks
Washout		28 days	2 days
IMDC Group	Intermediate	45 (68%)	83 (82%)
	Poor	21 (32%)	18 (18%)
Nephrectomy		47 (71%)	63 (61%)
Poor Risk Proceeding to Surgery		9 (43%)	8 (44%)
Survival (OS)	Overall	15.2 months	22.7 months
	Poor Risk	9.0 months	5.7 months

Avoid immediate surgery in Poor Risk
Progressors with OS < 4 months (HR 4.5 Death)

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SURTIME: EORTC 30073
Timing of Cytoreductive Nephrectomy

ECOG 0/1
Biopsy proven ccRCC
Resectable, treatment naïve Measurable disease
≤3 high risk factors**
N=458→99

- serum albumin CTCAE v4.0 grade 2 or worse
- serum LDH > 1.5 x UNL
- liver metastases
- symptoms at presentation due to metastases
- retroperitoneal lymph node involvement
- supra-diaphragmatic lymph node involvement
- clinical stage T3 or T4

Cytoreductive Nephrectomy Followed by Sunitinib Goal N=229

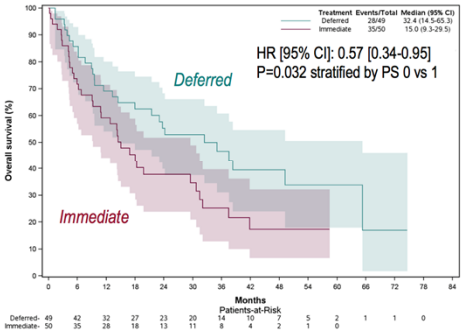
3 cycles (4/2) Sunitinib Followed by Cytoreductive Nephrectomy Goal N=229

1° Endpoint: changed w/ poor accrual PFS then landmark PFR

2˚ End Point

OVERALL SURVIVAL - INTENTION TO TREAT-

2˚ End Point



	Immediate nephrectomy (N=50)	Deferred nephrectomy (N=49)
Survival status		
Dead	35 (70.0)	28 (57.1)
Reason of death		
Progression	30	25
Surgery related toxicity	1	0
Progression and surgery related toxicity	1	0
Cardiovascular disease (not due to toxicity or progression)	1	0
Other (not due to toxicity or progression)	1	0
Unknown	1	3

Median OS HR of 0.57 with deferred surgery

-32.4 months in the deferred CN (remarkably high)

-15.0 months in the immediate CN arm

Bex, A., et al. (2018). Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. *JAMA Oncology*. http://doi.org/10.1001/jamaoncol.2018.5543

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Take Home Points SURTIME

- Small study that under accrued
  - but similar in size to EORTC protocol
- Rate of complications identical
- PFR similar between groups
- OS not 1˚ endpoint but *provocative*

With sutent, deferring CN *not harmful, it may be beneficial* to weeding out the bad actors for 2nd line therapy

CARMENA Trial
Any Benefit of Cytoreductive Nephrectomy?

ECOG 0/1
Biopsy proven M1 ccRCC
Treatment Naïve
No Brain Mets
Less Restrictive
N=576 → 450

Nephrectomy + Sunitinib N=288

Sunitinib Alone N=288

Enrollment:
79 centers over 8 years
81% tx in centers with <3 patients/yr

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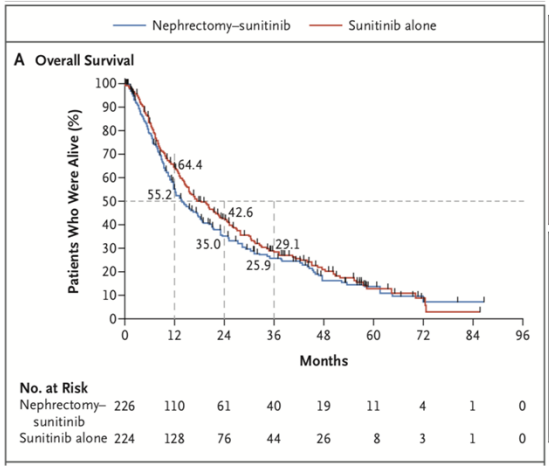

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Nephrectomy–Sunitinib (N=226)	Sunitinib Alone (N=224)
Median age (range) — yr	63 (33–84)	62 (30–87)
Male sex — no. (%)	169 (74.8)	167 (74.6)
MSKCC risk category — no./total no. (%)†		
Intermediate risk	125/225 (55.6)	131/224 (58.5)
Poor risk	100/225 (44.4)	93/224 (41.5)
Median primary tumor size (range) — mm	88 (6–200)	86 (12–190)
Median no. of metastatic sites (range)	2 (1–5)	2 (1–5)
Median tumor burden (range) — mm	140 (23–399)	144 (39–313)
Location of metastases — no./total no. (%)		
Lung	172/217 (79.3)	161/221 (72.9)
Bone	78/217 (35.9)	82/221 (37.1)
Lymph nodes	76/217 (35.0)	86/221 (38.9)
Other	78/217 (35.9)	90/221 (40.7)

Median PT ~60% of total tumor burden

Sunitinib alone **not inferior** to surgery + sunitinib
outcomes very poor

Very sick patients not similar to EORTC/SWOG trials

Role of Cytoreductive Nephrectomy in Checkpoint Inhibitor Era?

- New agents even more potent
  - -9% CR rate in CheckMate 214 with ipi/nivo
- Agents also better tolerated
  - -Less issue with rebound effect and wound healing
  - -no significant peri-operative morbidity with agents in the melanoma or lung cancer literature
- With movement into the first line setting in RCC, what is the role with cytoreductive nephrectomy?

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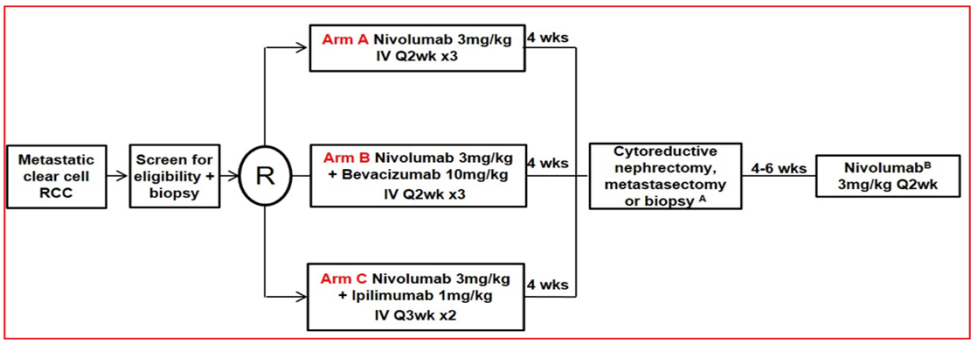
IO Neoadjuvant Therapy

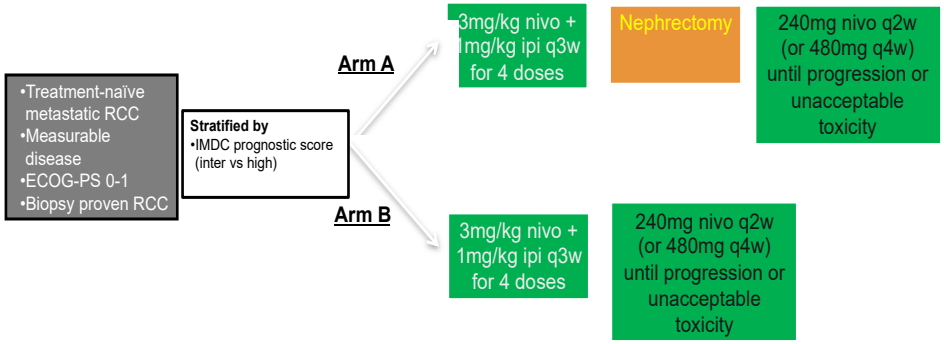
Clinical Trial Schema



- **VEGF and PD1 tx Naïve, Randomized 2:3:2,**
- **Treatments and then restaging at 12 weeks**
- **Biopsy/surgery followed by maintenance Nivo**
- **IHC and gene expression (mRNA nanostring) in tissue**

ASCO 2018

IKCS 2018 Meeting: SWOG Protocol In Development:



Other designs Considered: Surgery vs CPI+ Surgery vs CPI

PI- Kim, Vaishampayan

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Outline

- Adjuvant Therapy 2019
- Neoadjuvant Therapy
- Cytoreductive Nephrectomy Status
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Case 1: Patient with Solitary Functional Kidney

- 63 M with HTN, DM found with 2 cm left renal mass
  -right kidney atrophic
  -creatinine 1.7
- Biopsy--> ccRCC G1/4
- Placed on active surveillance, monitored closely for 1 year and then every 2 years
- Mag 3 split 95/5%

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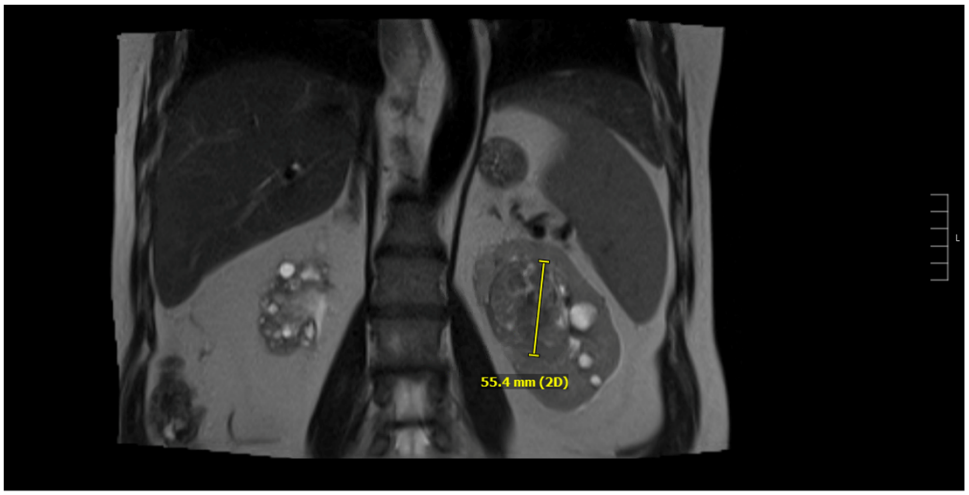
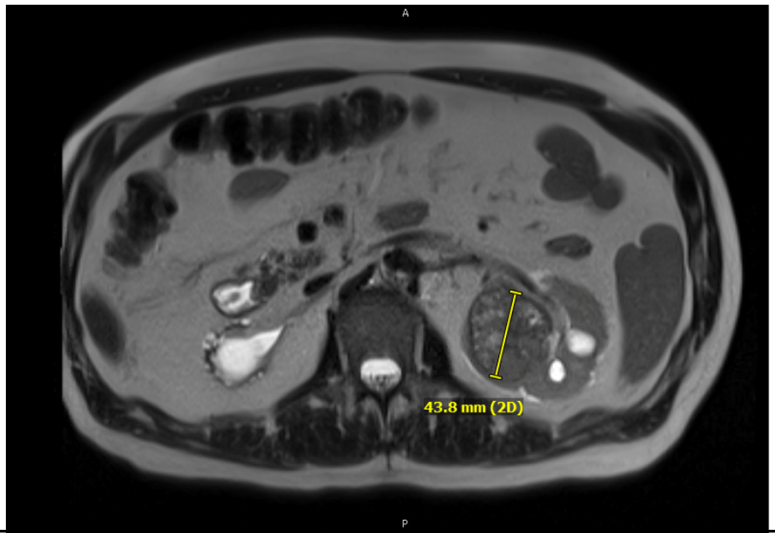
4 years later referred for a 5.5 cm renal mass Nephrometry 10-11/12



4 years later referred for a 5.5 cm renal mass
Nephrometry 10-11/12



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Management

- 12 weeks axitinib given 5 mg bid [OFF-LABEL USE]
  -HTN (meds increased) and fatigue

- Lesion shrunk to 3.7 cm
  -60% reduction in volume/ 33% by RECIST
  -Nephrometry 10/11→9 (lost 1 pt for size, 1 pt for polar)
  -stopped 72 hours preop

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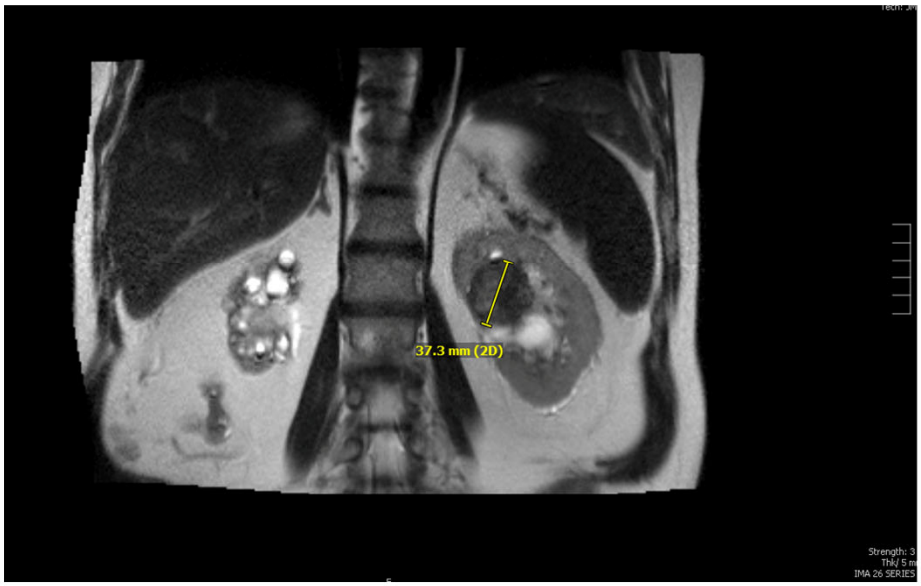

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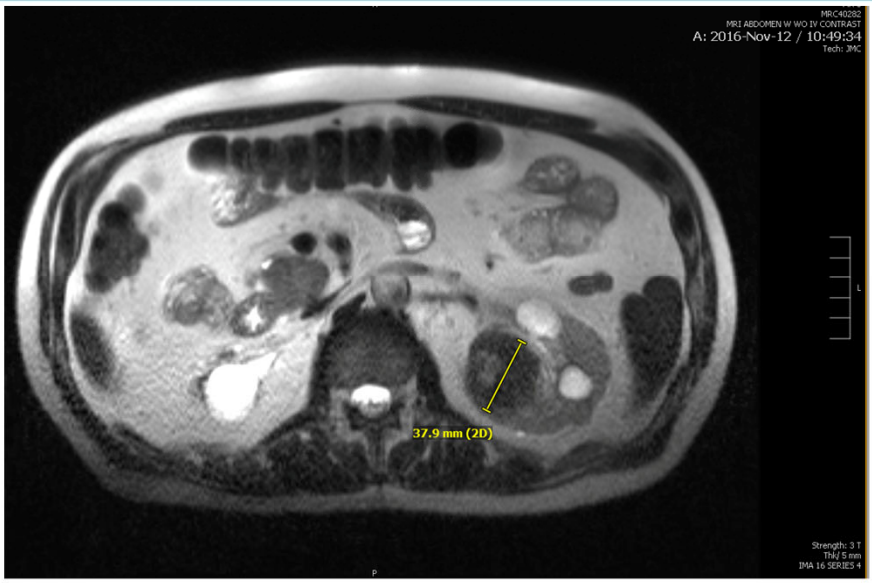

Surgery

- Open partial nephrectomy performed off-clamp
  - -segmental vein thrombus noted and tumor pulled out
  - -800 cc EBL
  - -small leak, sent home w drain (resolved 4 weeks)
- Path T3a ccRCC G2/ neg margins
- Creatinine 1.8
- Disease free 2 years out

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Case 2: Young Man with Aggressive Lesion

- 45 male with history of HTN gross hematuria, found with large renal mass and 2 large lymph nodes
- Family Hx: 2 young autistic children
- No Evidence of metastatic disease
- Cr 0.8

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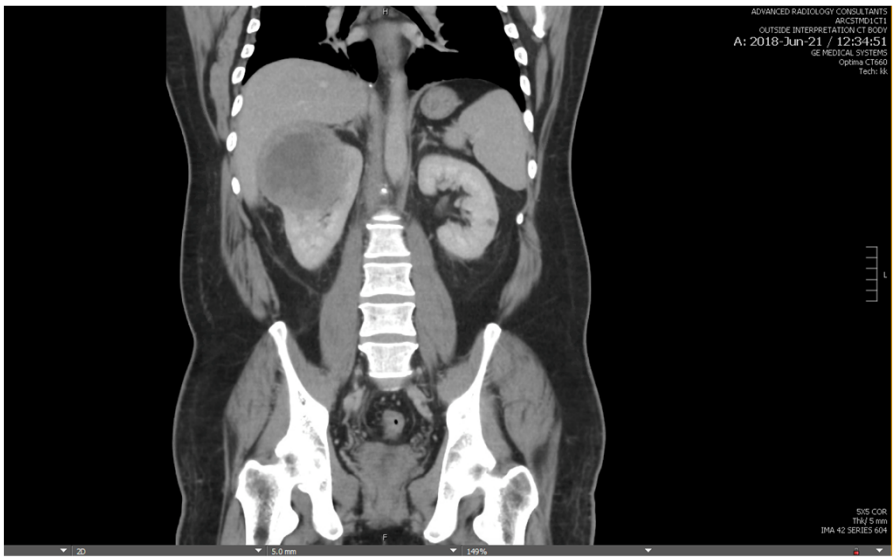
Case 2: Young Man with Aggressive Lesion



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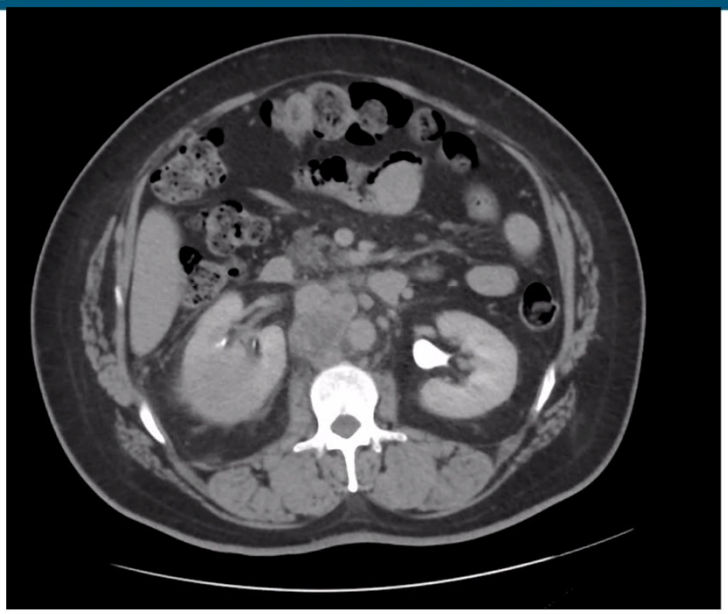

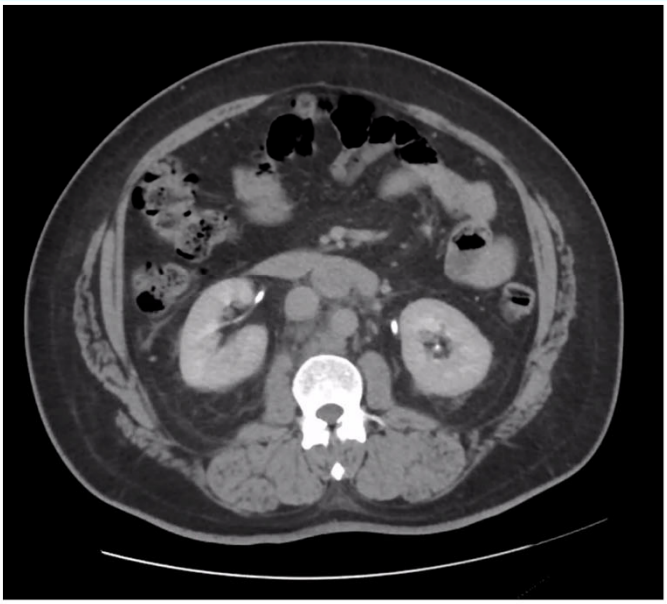

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cT2, N1, M0 RCC

- Placed on ProsperRCC trial
- Randomized to Neoadjuvant treatment
- Perc biopsy showed high grade clear cell
- 2 x Nivo (now amended for x 1 dose of 480)
- Surgery performed
  - -midline R nephrectomy and extensive RPLND
  - -developed postop chylous ascities needing drain

Path and Update

- Path
  -10.6 cm mass
  -unclassified (clear cell and papillary regions)
  -grade 3/4, T3a lesion (perinephric fat), - margins
  -10/15 nodes positive

- Received Nivo post-op (q2 then q4 prior to amendment)
- Now NED 30 months out.

Questions:

bshuch@mednet.ucla.edu

David Geffen School of Medicine

UCLA Health

Multidisciplinary Care for Bladder Cancer

Kelly L. Stratton, MD
Associate Professor, Department of Urology
University of Oklahoma

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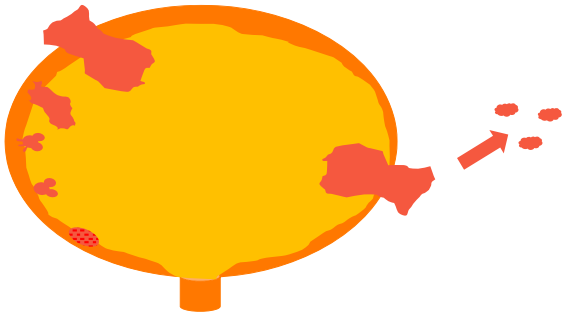
Objectives:

- Describe the multidisciplinary approach to managing bladder cancer
- Examine the role of neoadjuvant chemotherapy prior to radical cystectomy
- Assess the potential for bladder preservation in patients with MIBC
- Discuss advanced therapeutics and emerging treatments of metastatic bladder cancer

Expanding Role for Multidisciplinary Bladder Cancer Care

Urology · Medical Oncology · Radiation Oncology



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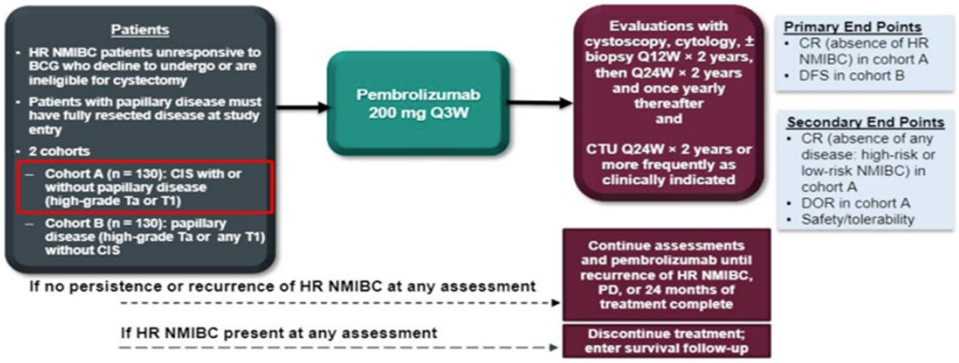
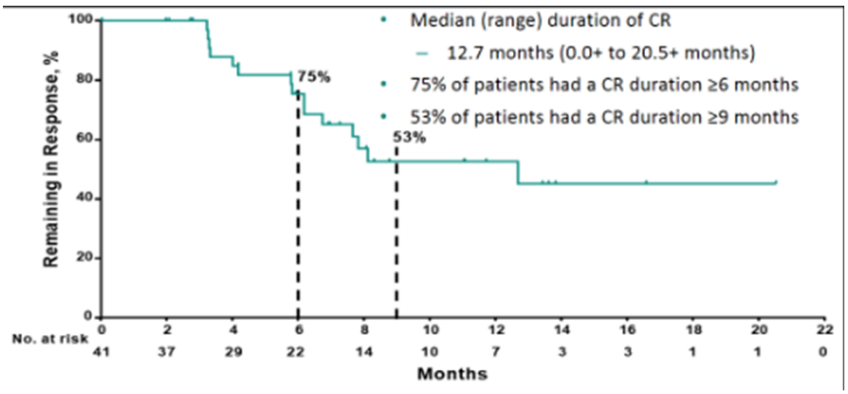
Immunotherapy for NMIBC

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



ASCO GU: J Clin Oncol 37, 2019 (suppl 7S; abstr 350)

Response Duration in Patients with 3M Complete Response



ASCO GU: J Clin Oncol 37, 2019 (suppl 7S; abstr 350)

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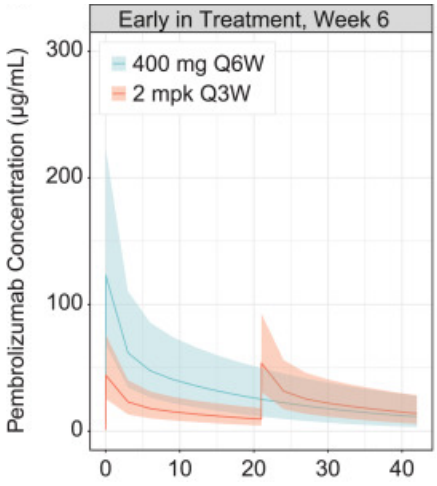
Pembrolizumab: Six-weekly Dosing

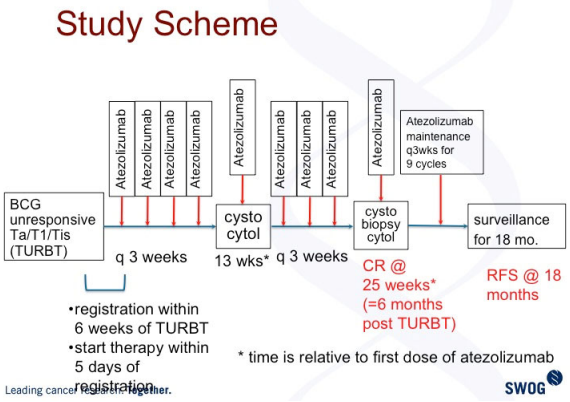
- April 2020: FDA granted accelerated approval to a new dosing regimen of 400 mg every six weeks for pembrolizumab across all currently approved adult indications



EJC Volume 131, May 2020, Pages 68-75

BCG-Unresponsive NMBIC: Atezolizumab

- SWOG 1605:
  - Primary endpoint: pathologic complete response at 6M
  - 75 patients with CIS reported
  - 30 patients (41.1%) had CR at 3M
  - 19 (26.0%) had CR at 6M



Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 5022-5022.

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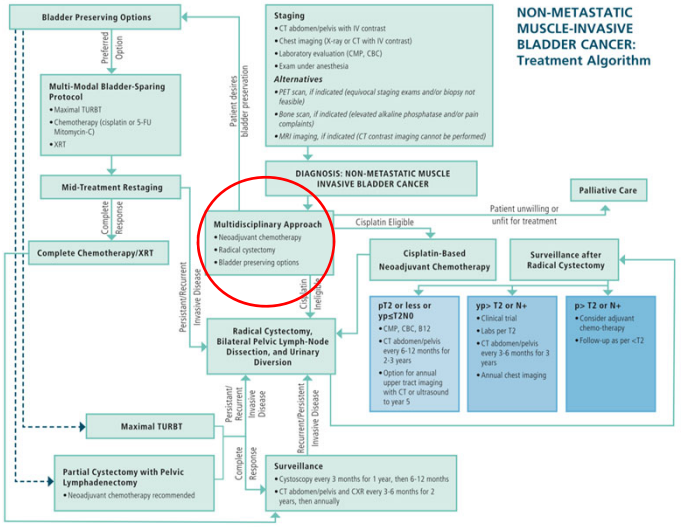
Intravesical Nadofaragene Firadenovec (Adstiladrin)

- Novel intravesical gene-mediated therapy:
  - delivers IFNα2b gene, increasing expression = durable response
- SUO CTC Phase III Trial: BCG-unresponsive NMIBC
  - Primary Endpoint: Complete Response in patients with CIS
  - 103 CIS pts, 55 (53.4%) achieved CR, all by 3 M after treatment
  - 25 (45.5%) remained free of high-grade recurrence at 12M

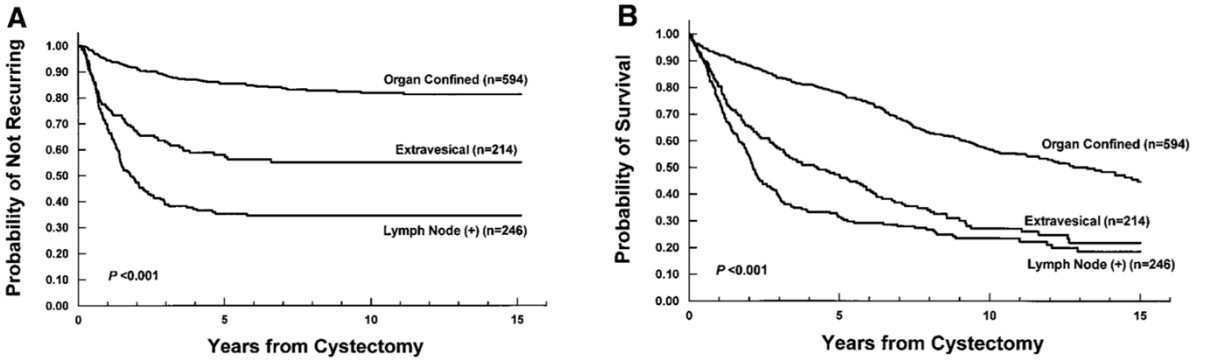
MDC Approach to Improve Bladder Cancer

Treatment of Non-Metastatic MIBC: AUA/ASCO/ASTRO/SUO Guideline



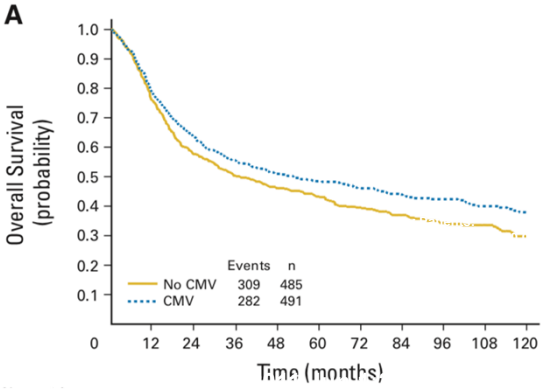
Support MDC Approach

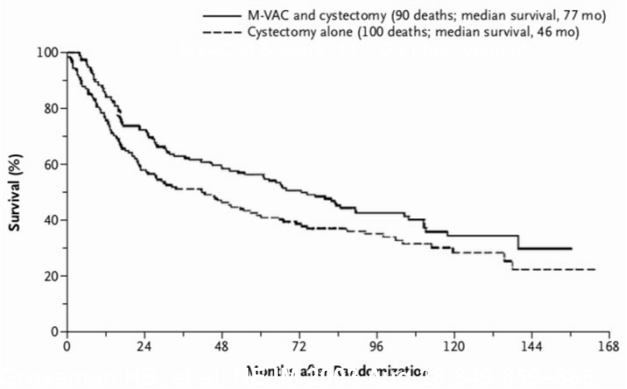
Bladder Cancer Outcomes After Cystectomy



Stein JP, et al. J Clin Oncol 2001 Feb 1;19:666–675.

Benefits of Neoadjuvant Therapy





These two trials identified the potential benefit of NA chemotherapy

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Importance of Surgical Quality

Radical Cystectomy in Patients on SWOG 8710

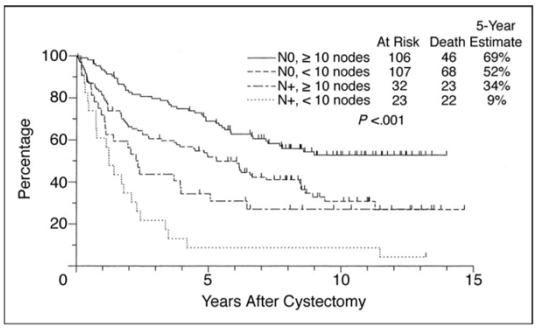


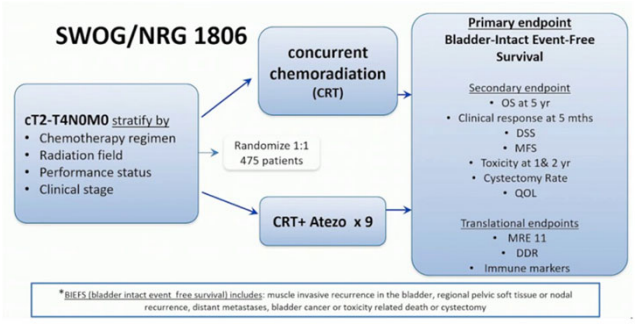
Fig 2. Postcystectomy survival by node status and number of nodes removed.

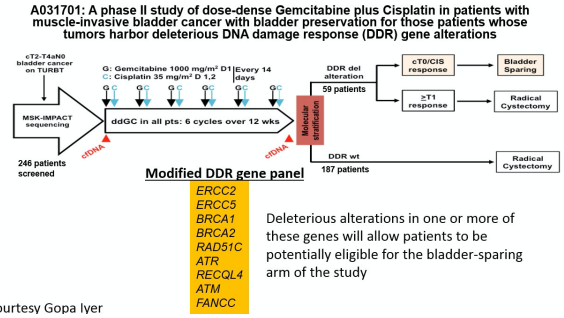
Herr HW, et al. JCO 2004 Jul 15;22:2781–2789.

Treatment	5-year OS	5-year FLR
NA MVAC/RC/PLN ≥10	81%	91%
RC/PLN≥10	66%	90%
NA MVAC/RC/PLN<10	55%	73%
RC/PLN <10	39%	66%
No cystectomy	11%	
+ Surgical Margins	0%	

Dotan et al., JCO 23, no. 16_suppl (June 1 2005) 4531-4531

Bladder Preservation





Deleterious alterations in one or more of these genes will allow patients to be potentially eligible for the bladder-sparing arm of the study

Courtesy Gopa Iyer

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Locally Advanced, Metastatic Bladder Cancer

- First Line:
  - Gemcitabine + Cisplatin
  - Dose-dense MVAC
- Cisplatin Ineligible
- Second-line Treatment

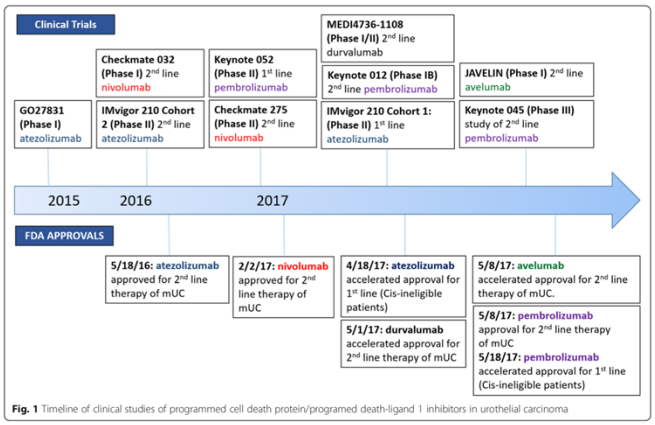

Fig. 1 Timeline of clinical studies of programmed cell death protein/programed death-ligand 1 inhibitors in urothelial carcinoma

Aggen & Drake: J Immunother Cancer 2017 Nov 21;5:94.

Changing Landscape of Metastatic Bladder Cancer

First Line:

Platinum-based Chemotherapy

+

Maintenance Therapy:

Immunotherapy:
Avelumab
Pembrolizumab

Enfortumab Vedotin

Erdafitinib

(FGFR2/3 Alteration)

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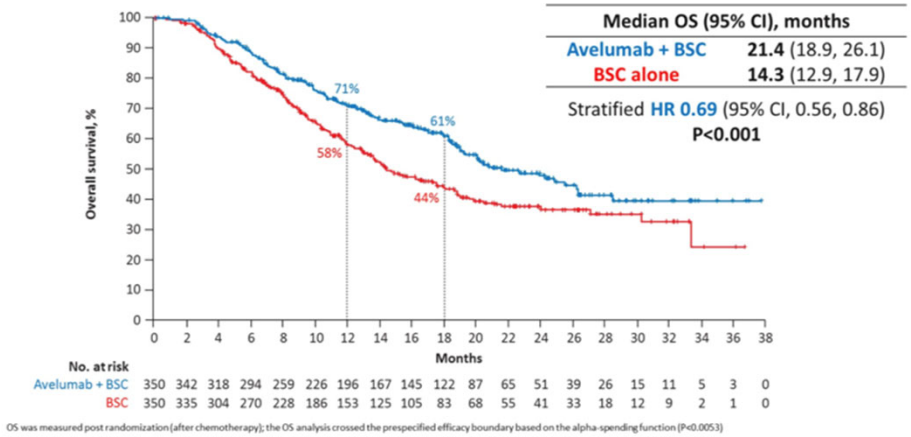
Avelumab Maintenance

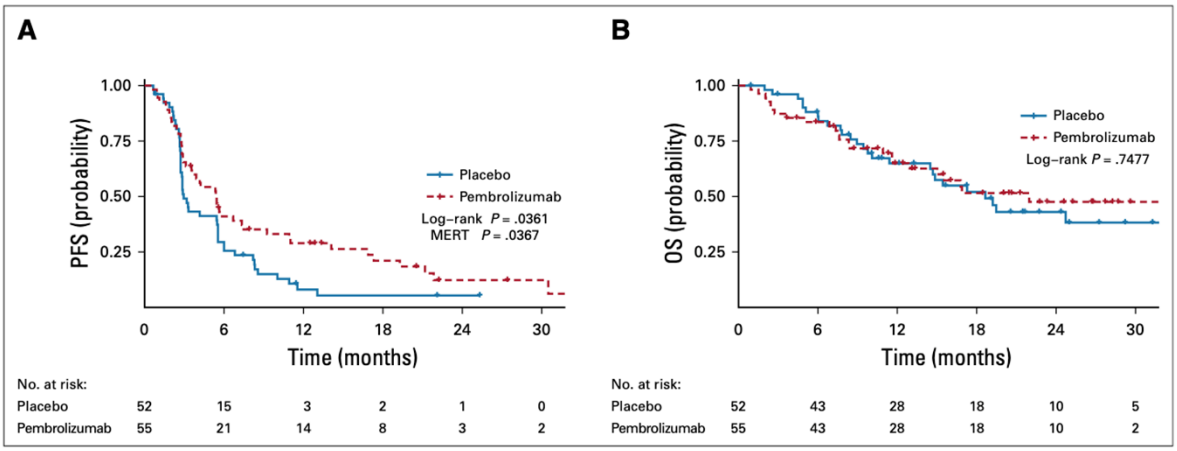
OS in the overall population



OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

Journal of Clinical Oncology 38, no. 18_suppl

Pembrolizumab Maintenance



J Clin Oncol 38:1797-1806.

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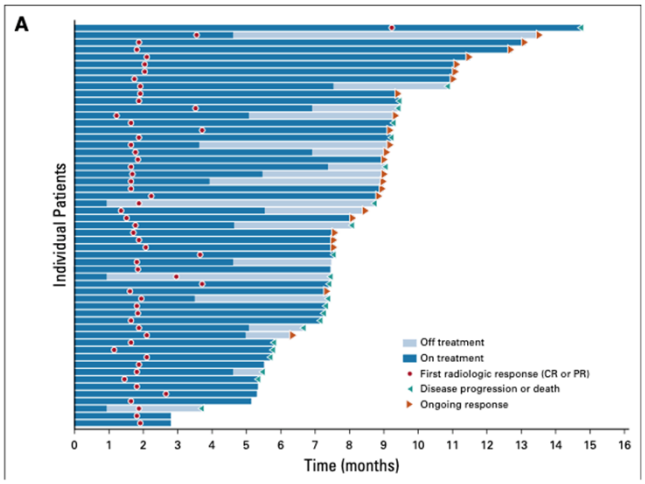
Enfortumab Vedotin

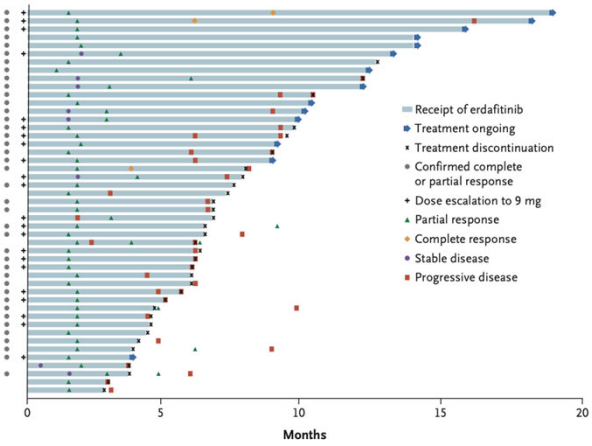
- Nectin-4 targeted Antibody-drug conjugate using a microtubule-disrupting agent, MMAE
- 44% objective response rate in patients after chemotherapy and immunotherapy



J Clin Oncol 37:2592-2600.

Erdafitinib

- Tyrosine kinase inhibitor of FGFR1–4
- Objective tumor response rate: 40%
- Median duration of PFS was 5.5 months



N Engl J Med 2019; 381:338-348

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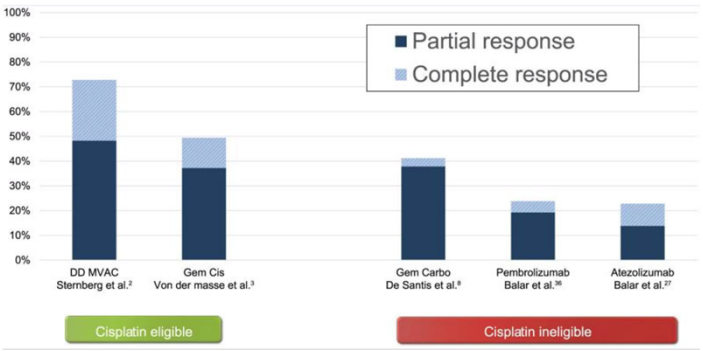
Locally Advanced, Metastatic Bladder Cancer

- Cisplatin Ineligible
  - Gemcitabine + Carboplatin
  - Atezolizumab
  - Pembrolizumab
  - Others: Gemcitabine, Gem + Paclitaxel
- Second-line Treatment
  - Pembrolizumab
  - Atezolizumab
  - Nivolumab
  - Durvalumab
  - Avelumab
  - Others



Response rates to first-line therapy for metastatic urothelial carcinoma.

Ghatalia et. al. Ther Adv Med Oncol 2018;10

Adverse Events

Treatment-related adverse events of FDA-approved PD-1/PD-L1 inhibitors in patients with urothelial carcinoma.

Target	Inhibitor name	Treatment-related adverse events	Immune-related adverse events
PD-1	Nivolumab	Fatigue, decreased appetite, nausea, musculoskeletal pain, diarrhea, rash	Pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, renal dysfunction, encephalitis, rash
	Pembrolizumab	Fatigue, decreased appetite, nausea, musculoskeletal pain, diarrhea, rash, pruritus, constipation	Pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, renal dysfunction
	Atezolizumab	Fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, constipation	Pneumonitis, hepatitis, colitis, endocrinopathies (thyroid disease, adrenal insufficiency, hypophysitis, type 1 diabetes), meningitis/encephalitis, pancreatitis, dermatitis/rash
PD-L1	Durvalumab	Fatigue, decreased appetite, nausea, urinary tract infection, diarrhea, musculoskeletal pain, constipation, peripheral edema	Pneumonitis, hepatitis, colitis, endocrinopathies (thyroid disease, adrenal insufficiency, hypophysitis, type 1 diabetes), nephritis
	Avelumab	Fatigue, decreased appetite, nausea, urinary tract infection, musculoskeletal pain	Pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, renal dysfunction

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Conclusions:

- There is a growing importance to the multidisciplinary management of bladder cancer do to new and expanding drug approvals
- An emphasis on quality of life may provide more opportunities for bladder preservation
- The treatment of metastatic bladder cancer has been transformed by new treatment paradigms

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Q&A

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