Research To Practice
Cases from the Community
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Sequence and selection of treatment for metastatic castration resistant prostate cancer

Celestia (Tia) S. Higano, MD, FACP

Professor

Departments of Medicine and Urology

University of Washington

Member

Fred Hutchinson Cancer Research Center

Seattle Cancer Care Alliance

Fred Hutchinson Cancer Research Center

University of Washington School of Medicine

Children's Hospital & Regional Medical Center

Disclosures

Advisory Committee	Asana BioSciences, Astellas Pharma Global Development Inc, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Churchill Pharmaceuticals LLC, Clovis Oncology, Dendreon Pharmaceuticals Inc, Ferring Pharmaceuticals, PAREXEL International Corporation
Contracted Research	Algeta/Bayer HealthCare Pharmaceuticals, Aptevo Therapeutics, Aragon Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Dendreon Pharmaceuticals Inc, Genentech BioOncology, Medivation Inc, Pfizer Inc, Takeda Oncology
Leadership Position (spouse)	Cell Therapeutics Inc

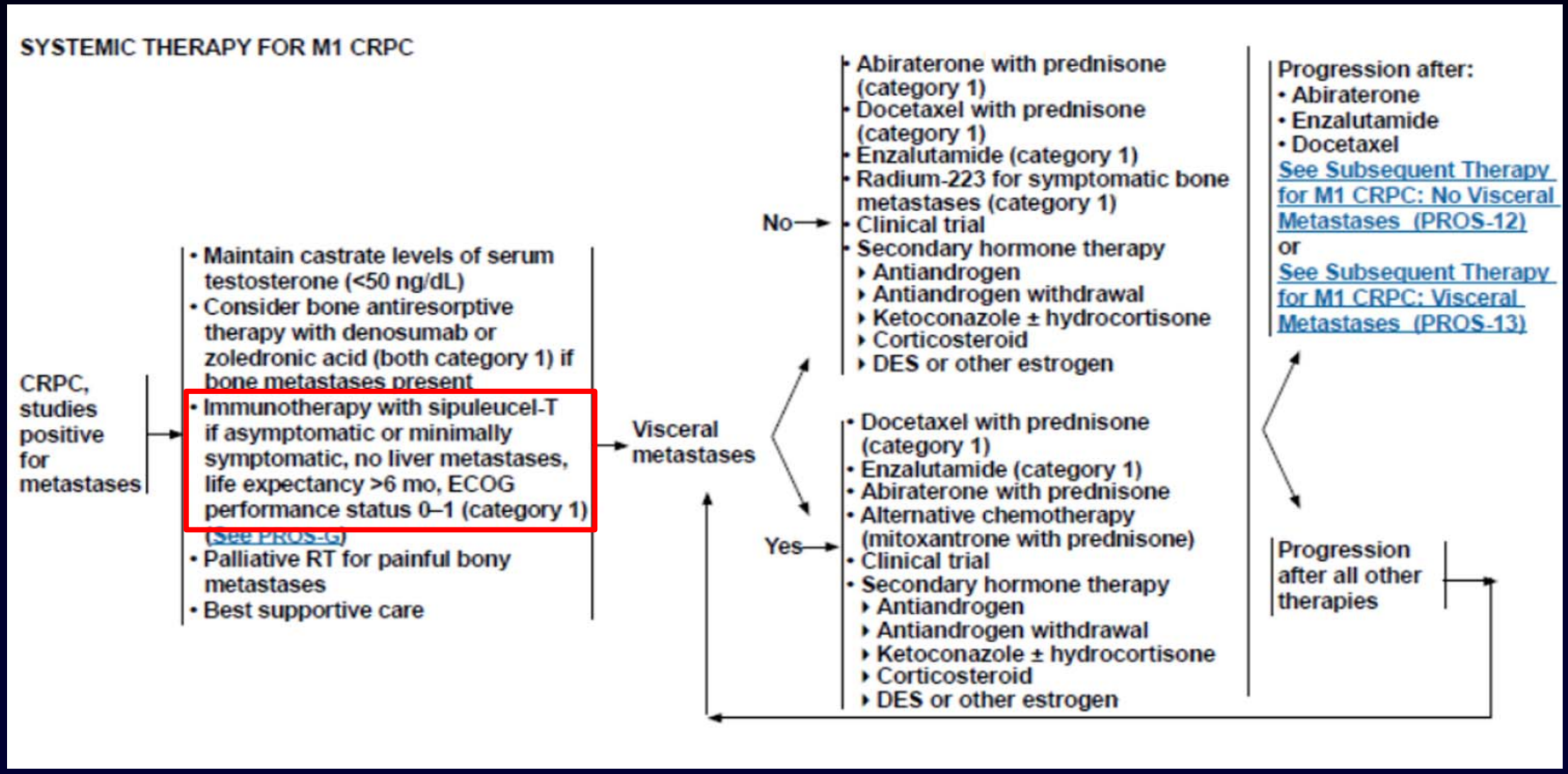
Overview

- Patient characteristics to consider
- NCCN algorithm
- AR-V7 and genomics
- Take home message

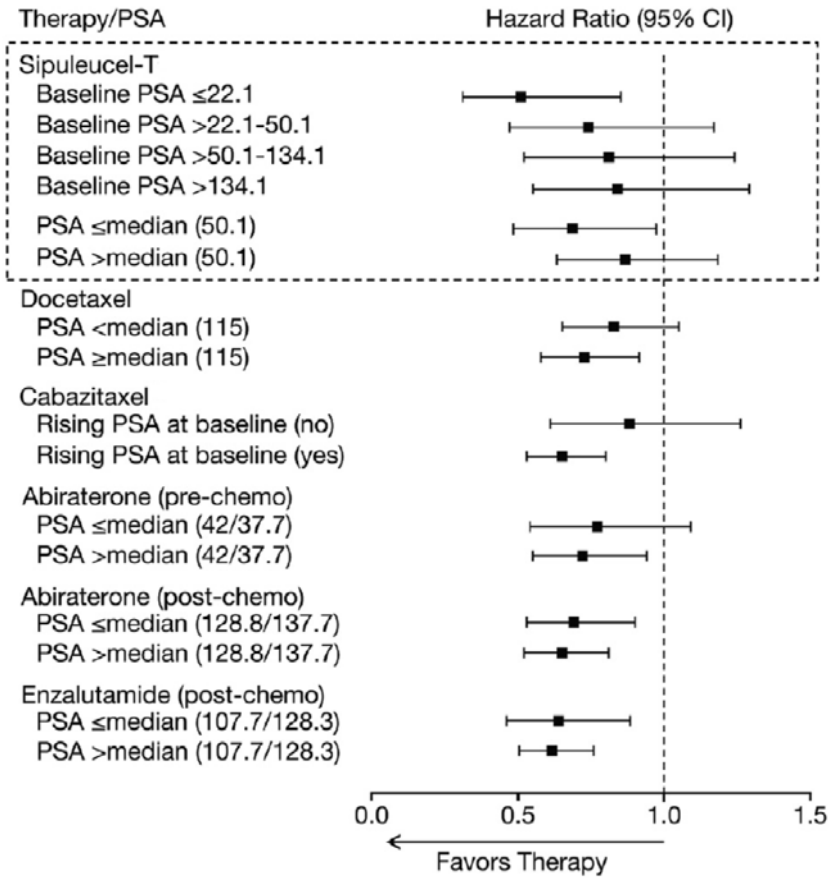
Considerations for choosing therapy

- Symptoms
- Location of metastases
- PSA-DT
- Prior therapy: docetaxel in mHSPC
- Co-morbidities
- Performance status
- Family history of cancer

NCCN schema: M1 CRPC



Post hoc analysis of IMPACT trial



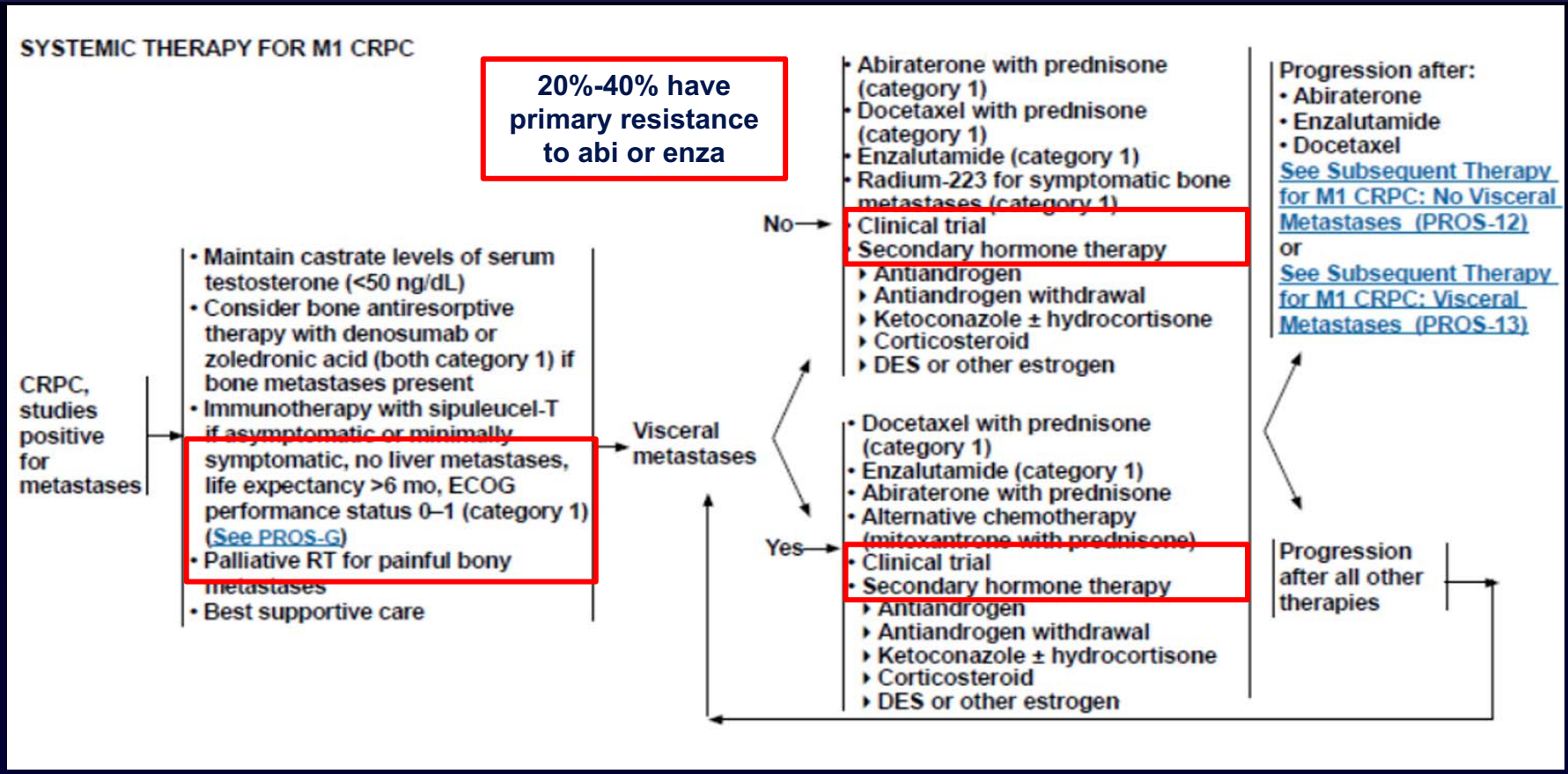
Patients in the lowest PSA quartile group in the sipuleucel-T arm had a greater OS benefit, suggesting sipuleucel-T is most beneficial when administered early in the course of mCRPC

Schellhammer PF et al. Urology 2013;81:1297-1302.

Sequencing therapies in asymptomatic mCRPC

- Sipuleucel-T can be given very early if no visceral metastases
- After sipuleucel-T, follow and treat the patient as you would have without this therapy
- No prospective data on how to sequence abiraterone and enzalutamide
- There is evidence that cross-resistance exists between abiraterone and enzalutamide — prospective data is needed

NCCN schema for M1 CRPC



- Lebdai et al World J Urol 2016: Review of 17 sequencing studies: all small retrospective
- Delanoy et al GU Cancers Symposium 2017 abstract 267: Doc-cabaz-ART: high PSA, short response to first line ADT should be considered for docetaxel early

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

- **AR splice variants lack ligand-binding domain**
- **AR-V7 is most common variant**

"AR-V7 may be associated with resistance to enzalutamide and abiraterone"

Antonarakis E et al. N Engl J Med 2014;371(11):1028.

AR-V7 testing

- CTC based
  - Only about 50% have CTCs
- Available CLIA certified tests in US
  - Johns Hopkins, cost $800
  - EPIC (only in CA at the moment)
  - No assay FDA cleared yet
  - Most insurers now cover the cost

- AR-V7 positive[1]
  - Resistance to abi, enza
  - Not predictive of response to taxane based therapy
  - Prevalence increases with additional lines of hormonal therapy
- AR-V7 negative
  - Does not guarantee response to abi, enza
  - Secondary hormonal therapy or chemotherapy about same[2]

1. Antonarakis et al NEJM 2014, Steinestel et al, Oncotarget 2015, Scher et al JAMA Oncol 2016
2. Antonarakis et al JAMA Oncol 2015

Of those with CTCs

- **Pre-abi and enza**
  - **10%-15% AR-V7 positive (5%-7.5% all comers)**
  - **Consider early taxane chemotherapy**
- **Post abi *or* enza**
  - **30%-35% AR-V7 positive (15%-17.5% all comers)**
  - **Consider taxane chemotherapy**
- **Post abi *and* enza**
  - **45%-50% AR-V7 positive (22.5%-25% all comers)***
  - **Consider AR-V7 positive trial or chemotherapy**
- **Post chemotherapy**
  - **Conversion from AR-V7 positive to negative**
  - **Consider abi or enza**

* Schweizer et al, GU Cancers Symposium 2017 abstract 264: Only 1 of 14 AR-V5-6 positive

No CTC or CTC status unknown: Timing and selection of abi or enza

- Choice of abiraterone versus enzalutamide cannot be dictated based on differences in efficacy
  - Similar OS, PFS from cross-trial comparisons
- Selection is often based on clinical factors related to toxicity
  - Enzalutamide: hypertension, seizure, and fall risk
  - Abiraterone: CV risk factors, contraindications to prednisone
- What to use after failure of first AR directed therapy?
  - The other one alone, add the other one, go on to something else?

Evolving role of genomics

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono

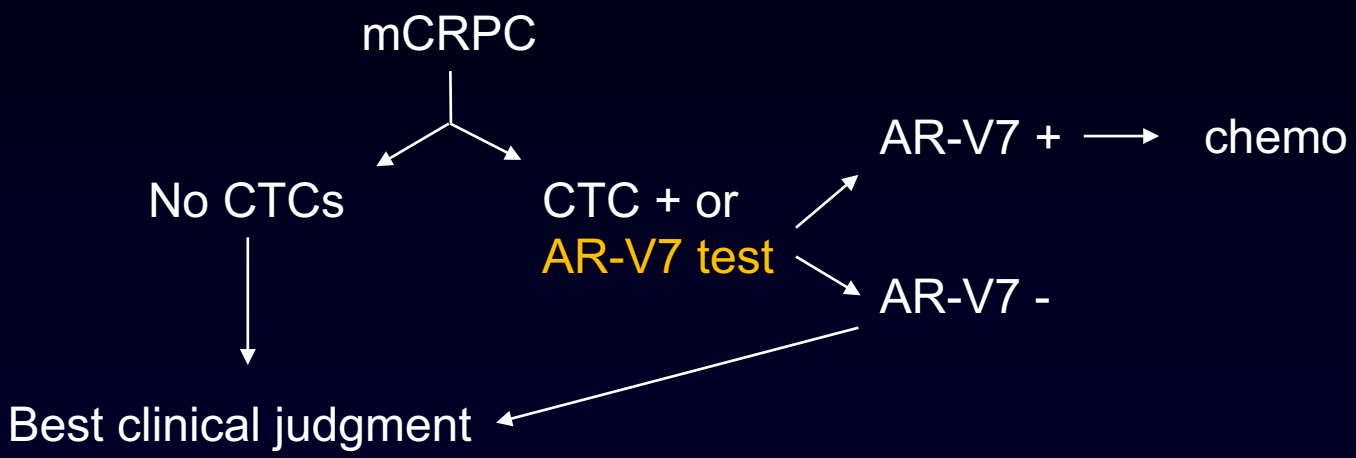
Post docetaxel, progression after standard treatment

- DNA repair alterations, 25%-30%
  - BRCA1/2, ATM, Fanconi's anemia, CHEK2
  - Biallelic somatic (tumor) — tumor biopsy, 25%
  - Germline (inherited) — saliva, 12%
- Yes, PARP inhibitor or platinum analogue (?)
  - High response rate (PSA, CTC, imaging)
  - No OS data
  - Olaparib has Breakthrough designation by FDA
- No, may still respond to PARPi
- Need for functional assay of PARPi

AR-V7, genomic testing: When?

- AR-V7 assays based on CTC but this is likely to change
- Some clinics obtain genomic testing on *all* patients
  - Feasibility
  - Cost
  - Caveat: tumor genomics change over time
- These biomarkers are still not validated for use in the clinic

Non-validated biomarkers and therapeutic options



In order to incorporate biomarkers for better treatment selection

- Analytic validation of biomarker(s)
- Prospective trials to show clinical benefit resulting from application of the biomarker(s) to decision making

Treatment options by disease state

Metastatic Castration Resistant

Asymptomatic/min sx		Chemo-naïve, symptomatic		Prior docetaxel
Antiresorptive bone therapy				
Sipuleucel-T*		**Docetaxel**		**Cabazitaxel**
Abiraterone	AR-V7 testing?	**Radium 223***	Genomic testing?	**Radium 223***
Enzalutamide	Genomic testing?	**Strontium 89**	AR-V7 testing?	**Abiraterone**
Docetaxel		**Samarium 153**		**Enzalutamide**
Second line hormonal therapy	Germline testing?	**Mitoxantrone**		**Sipuleucel-T***
				Docetaxel rechallenge
				Other chemo

Extends survival time
Pain palliation only
No evidenced based data
* No visceral disease

Final remarks

- Sipuleucel-T should be considered early in the natural history of mCRPC
- Timing and choice of next therapy require consideration of many factors
- AR-V7 testing is available, limited by CTC positivity and lack of prospective data
- Tumor genomics and germline testing will become standard over time
- New data emerging on how to sequence therapies for mCRPC

Mount Rainier seen from Seattle, Washington

Selected vaccine combination trials

- Hormone therapy
  - Sip-T + ADT vs ADT + sip-T
  - Enza +/- PROSTVAC
- Chemotherapy
  - Docetaxel +/- DCVAC
- Radiation
  - EBRT + valacyclovir +/- Adv-tk (+/- ADT)
  - SBRT + sipuleucel-T
- Other immune therapy
  - Sip-T vs sip-T + anti-PD-1 +/- CTX