

Follow Up on ADT Alone versus ADT “Plus”

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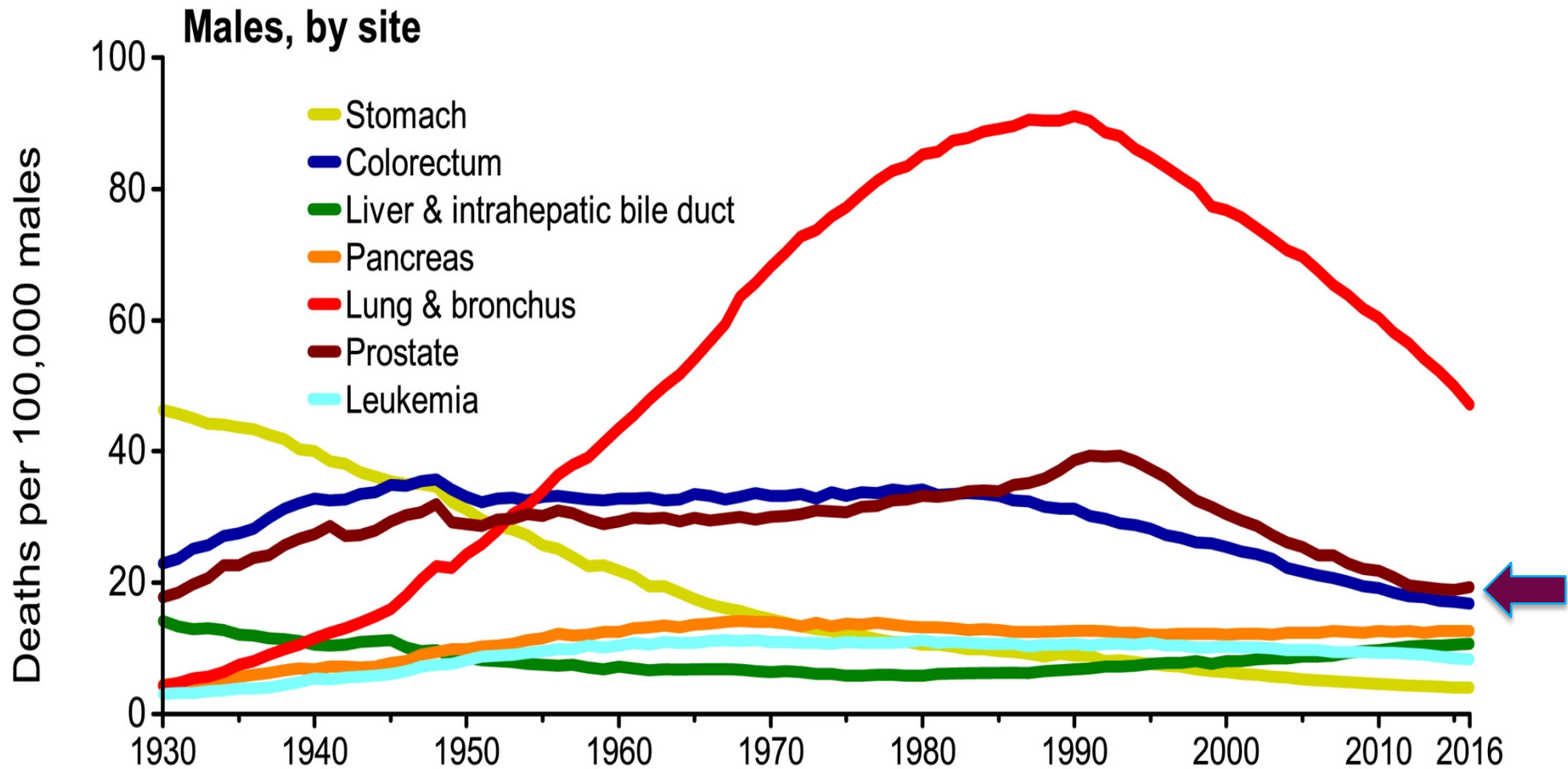
**Mount
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Disclosures

Consultant/SAB: Amgen, Astellas, Bayer, Astra-Zeneca, Genzyme-Sanofi, Janssen, CPS Diagnostics, Bellicum Pharmaceuticals, Sema4

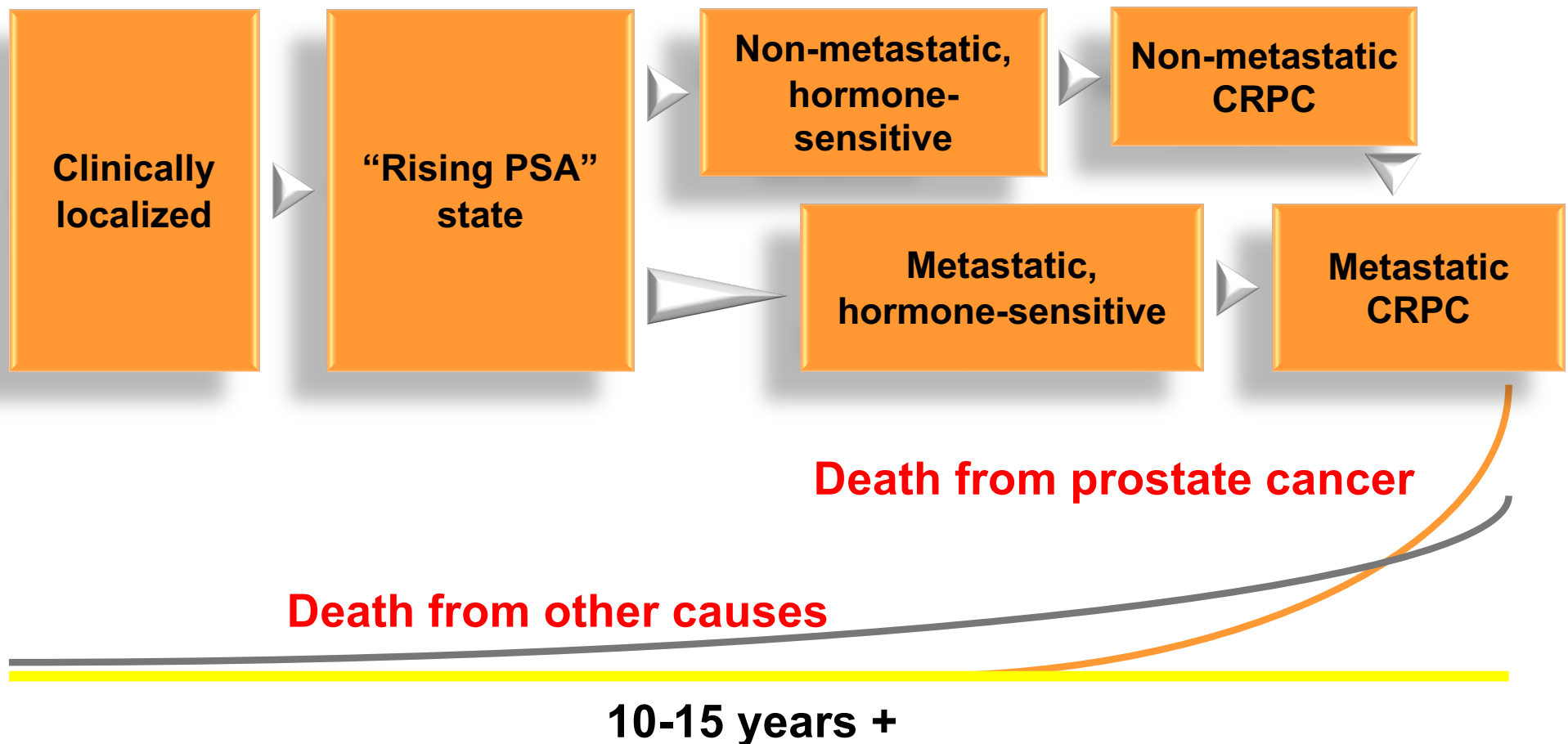


Cancer Death Rates Among Men, US, 1930-2016

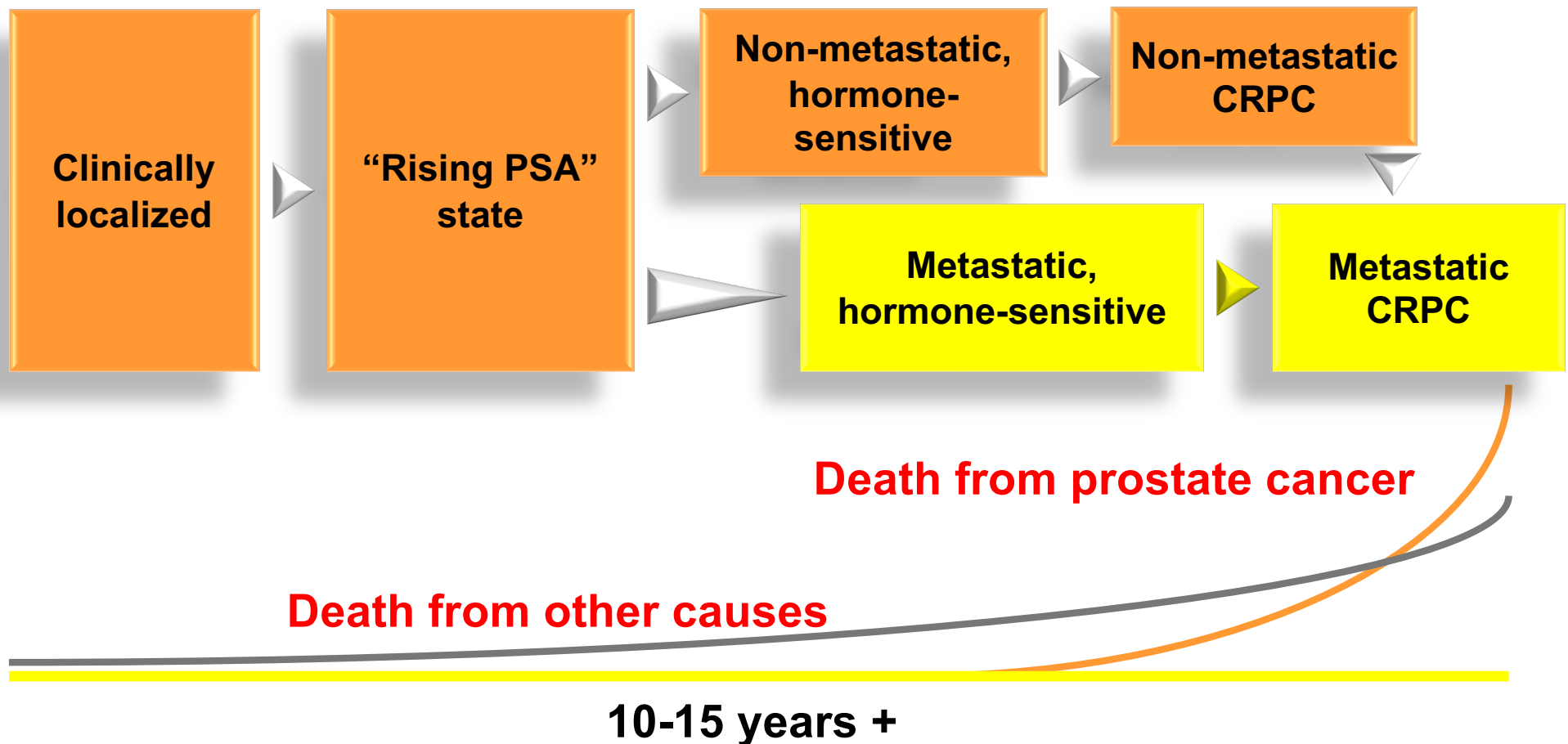


American Cancer Society 2019

Clinical States of Prostate Cancer



Clinical States of Prostate Cancer

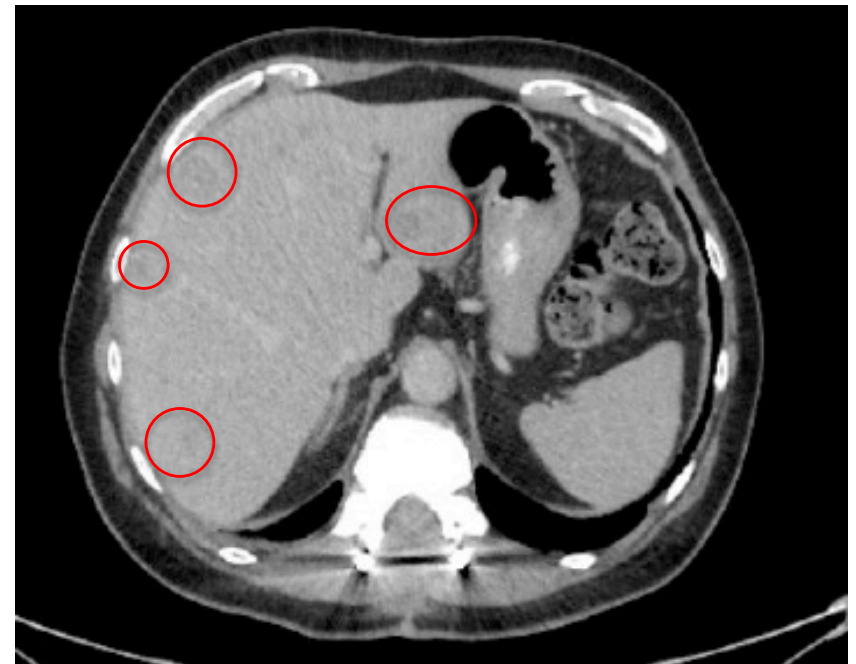
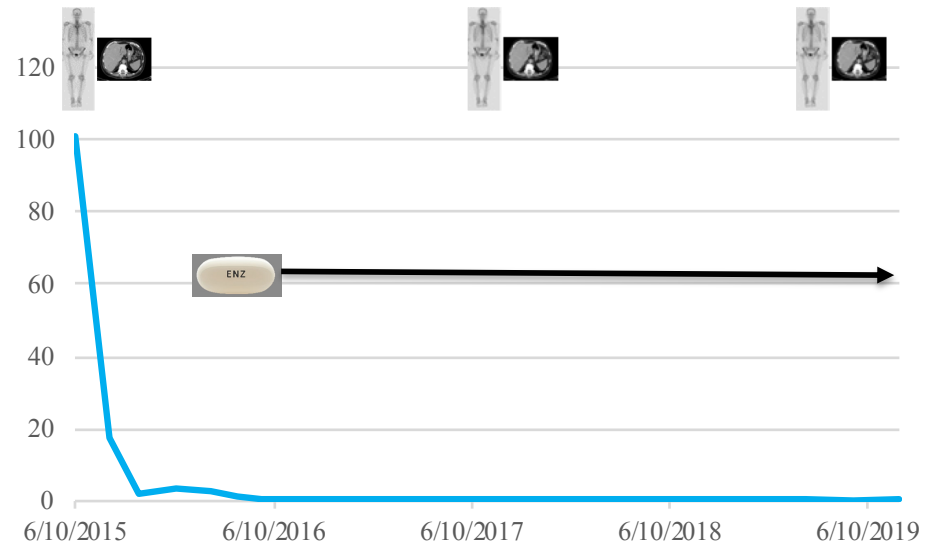


Patient #1: 65 yo mHSPC on Enzalutamide

- 65 yo M presented 2015 with pain and bone mets
- Biopsy: Gleason 9 with intraductal features
- PSA 101 ng/ml
- Bone scan with extensive bone mets, CT with pelvic LNs
- Starts ADT and completes docetaxel x 5 cycles
- PSA declines to 2.6 ng/ml
- Started on enzalutamide for persistently elevated PSA

Patient #1: 65 yo mHSPC on Enzalutamide

- PSA continued to slowly decline x 3 years
 - Asymptomatic, traveling
 - Normal LFTs
-
- Routine CT CAP showed multiple new liver lesions up to 2 cm



How Closely Should We Be Monitoring Patients on Therapy?

CLOSELY

- Potential to improve disease control by switching early to a more effective therapy
- Reduce the risks of treatment-related AEs from ineffective therapy
- Reduce costs from ineffective therapy

NOT SO CLOSELY

- Premature abandonment of effective therapy
 - False positive imaging
 - Disease flare
 - Insignificant progression
- Reduce costs of imaging
- ***Still no strong evidence that detecting treatment failure early is beneficial***

A Clinician's Guide to Next Generation Imaging in Patients With Advanced Prostate Cancer (RADAR III)

E. David Crawford,*† Phillip J. Koo,‡ Neal Shore,§ Susan F. Slovin,¶
Raoul S. Concepcion,|| Stephen J. Freedland,** Leonard G. Gomella,††
Lawrence Karsh,‡‡ Thomas E. Keane,§§ Paul Maroni, David Penson,¶¶
Daniel P. Petrylak,||| Ashley Ross,*** Vlad Mouraviev,†††
Robert E. Reiter, Chaitanya Divgi and Evan Y. Yu‡‡‡
for the RADAR III Group

Repeat imaging using traditional scans (bone scan and/or CT) is indicated when at least one of the following occurs:

- Every doubling of PSA since the previous image was taken
- Change in symptomatology
- Change in performance status
- Every six to nine months in the absence of a PSA rise

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PRINCIPLES OF IMAGING

- Bone scans are helpful to monitor metastatic prostate cancer to determine the clinical benefit of systemic therapy. However, new lesions seen on an initial post-treatment bone scan, compared to the pre-treatment baseline scan, may not indicate disease progression.
- New lesions in the setting of a falling PSA or soft tissue response and in the absence of pain progression at that site may indicate bone scan flare or an osteoblastic healing reaction. For this reason, a confirmatory scan is recommended to determine true progression. Lesions favoring progression may lead to treatment reasonably, but initiation of new hormonal therapy in the first half of patients treated with abiraterone. Similar modalities, such as PET/CT, may be helpful.
- Bone scans and soft tissue imaging may be obtained to determine clinical benefit.
- Bone scans should be performed every 6–12 mo to monitor disease progression. The need for soft tissue imaging remains unclear. In CRPC, 8- to 12-week imaging intervals appear reasonable.
- PET/CT for detection of bone metastatic disease with greater sensitivity but less specificity than standard bone scan imaging.
 - ▶ F-18 sodium fluoride PET/CT or PET/MRI may be used to detect bone metastatic disease with greater sensitivity but less specificity than standard bone scan imaging.
 - ▶ Plain films, CT, MRI, F-18 sodium fluoride PET/CT or PET/MRI, C-11 choline PET/CT or PET/MRI, or F-18 fluciclovine PET/CT or PET/MRI can be considered for equivocal results on initial bone scan.
- Earlier detection of bone metastatic disease may result in earlier use of newer and more expensive therapies, which may not improve oncologic outcomes or overall survival.

Computed Tomography

- CT provides a high level of anatomic detail, and may detect gross extracapsular disease, nodal metastatic disease, and/or visceral metastatic disease.
- CT is generally not sufficient to evaluate the prostate gland.
- CT may be performed with and without oral and intravenous contrast, and CT technique should be optimized to maximize detection of disease.

• Bone scans should be performed for symptoms and as often as every 6–12 mo to monitor ADT. The need for soft tissue images remains unclear. In CRPC, 8- to 12-week imaging intervals appear reasonable.

- MRI may be considered in patients after RP when PSA fails to fall to undetectable levels or when an undetectable PSA becomes detectable and increases on 2 or more subsequent determinations, or after RT for rising PSA or positive DRE if the patient is a candidate for additional local therapy. MRI-US fusion biopsy may improve the detection of higher grade (Grade Group ≥ 2) cancers.
- Multiparametric MRI (mpMRI) can be used in the staging and characterization of prostate cancer. mpMRI images are defined as images acquired with at least one more sequence in addition to the anatomical T2-weighted images, such as DWI or dynamic contrast-enhanced (DCE) images.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

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.

[Continued](#)

PROS-B
2 OF 3

ORIGINAL ARTICLE

Radiographic progression with nonrising PSA in metastatic castration-resistant prostate cancer: *post hoc* analysis of PREVAIL

AH Bryce¹, JJ Alumkal², A Armstrong³, CS Higano⁴, P Iversen⁵, CN Sternberg⁶, D Rathkopf⁷, Y Loriot⁸, J de Bono⁹, B Tombal¹⁰, S Abhyankar^{11,15}, P Lin¹², A Krivoshik¹³, D Phung¹⁴ and TM Beer²

- 872 patients randomized to receive enzalutamide
- 265 radiographic progression events
 - 65 (24.5%) had a non-rising PSA
 - Median rPFS 8.3 months
 - 200 (75.5%) had a rising PSA
 - Median rPFS 11.1 months

| <i>Characteristic</i> | <i>Non-rising PSA group (n=65)</i> | <i>Rising PSA group (n=200)</i> |
|--|--|-------------------------------------|
| Age, median, years | 73 (68–79) | 71 (65–75) |
| ECOG PS 0, n (%) | 46 (70.8) | 143 (71.5) |
| Hemoglobin, median, g l ⁻¹ | 131 (124–137) | 129 (123–137) |
| Alkaline phos, median, U l ⁻¹ | 80 (66–114) | 92 (70–141) |
| LDH, median, U l ⁻¹ | 183 (167–203) | 183 (162–215) |
| PSA, median, ng ml ⁻¹ | 82.2 (26.4–189.1) | 61.3 (22.4–111.5) |
| Gleason score, median | 7 (7–8) | 7 (7–9) |
| Gleason score ≥8, n (%) | 26 (41.9) | 86 (45.3) |
| <i>Type of disease progression at study entry, n (%)</i> | | |
| PSA progression only | 27 (41.5) | 69 (34.5) |
| Radiographic and PSA | 33 (50.8) | 87 (43.5) |
| Radiographic without PSA | 3 (4.6) | 41 (20.5) |
| No disease progression p | 2 (3.1) | 3 (1.5) |
| Measurable disease, n (%) | 46 (70.8) | 106 (53.0) |

| <i>Disease localization at screening and at progression</i> | <i>Non-rising PSA group (n=65)</i> | <i>Rising PSA group (n=200)</i> |
|---|--|-------------------------------------|
| <i>Bone only at screening, n (%)</i> | <i>n=16</i> | <i>n=61</i> |
| Bone-only progression | 10 (62.5) | 36 (59.0) |
| Soft-tissue progression | 6 (37.5) | 22 (36.1) |
| Soft-tissue and bone | 0 | 3 (4.9) |
| <i>Soft-tissue only at scr., n (%)</i> | <i>n=8</i> | <i>n=37</i> |
| Bone-only progression | 1 (12.5) | 2 (5.4) |
| Soft-tissue progression | 7 (87.5) | 34 (91.9) |
| Soft-tissue and bone | 0 | 1 (2.7) |
| <i>Both bone and soft tissue</i> | <i>n=41</i> | <i>n=100</i> |
| Bone-only progression | 17 (41.5) | 29 (29.0) |
| Soft-tissue progression | 24 (58.5) | 69 (69.0) |
| Soft-tissue and bone | 0 | 2 (2.0) |

Summary: Imaging in Metastatic Disease

- No consensus regarding frequency and type of imaging in mHSPC
- Data from early mCRPC suggests we may be overreliant on PSA to determine progression
 - 25% may progress on scans without PSA rise
 - Routine CT and bone scans? How often?
- Is the biology of recurrence being altered by the earlier use of novel AR targeted therapies?



Patient #2: 65 yo with mHSPC

- 65 yo M with rectal pain, PSA 2→7 ng/ml in 1 yr
- Gleason 8 in all cores
- Mets to multiple bones, pelvic nodes
- PMH: HTN on 2 meds, distant h/o sz disorder
- Started ADT and abiraterone/prednisone, PSA declines
- After 6 months, developed chest spasms
 - Multivessel coronary disease noted
 - 3 cardiac stents placed
- PSA rises again, resumes half-dose abiraterone/pred

Phase 3 Trials of ART Therapies in mHSPC

| Trial | Treatment | Overall Survival HR (95% CI) | P Value | Median Duration of ART Therapy |
|----------|---------------------------------|---------------------------------|---------|--------------------------------|
| STAMPEDE | Abiraterone + ADT v. ADT | 0.63 (0.52-0.76) | 0.001 | 33.2 mo |
| LATITUDE | Abiraterone + ADT v. ADT | 0.62 (0.51-0.76) | 0.001 | 24 mo |
| ENZAMET | Enzalutamide + ADT v. ADT | 0.67 (0.52-0.86) | 0.002 | >36 mo |
| TITAN | Apalutamide + ADT v. ADT | 0.67 (0.51-0.89) | 0.005 | 23 mo |

Side Effects of ADT

- Fatigue
- Hot flashes
- Sexual dysfunction
- Weight gain
- Decreased muscle mass
- Falls
- Increased glucose intolerance
- Anemia
- Altered lipids
- Increased CV risk
- Cognitive changes
 - Dementia?
- Osteoporotic fractures



Side Effects of ADT

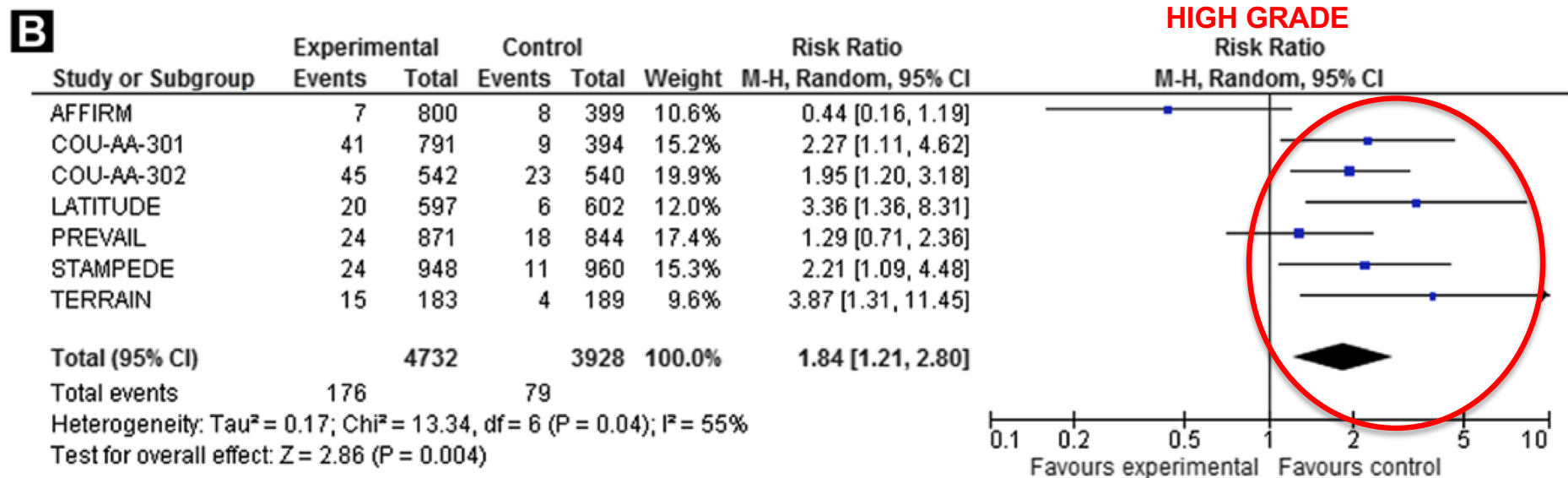
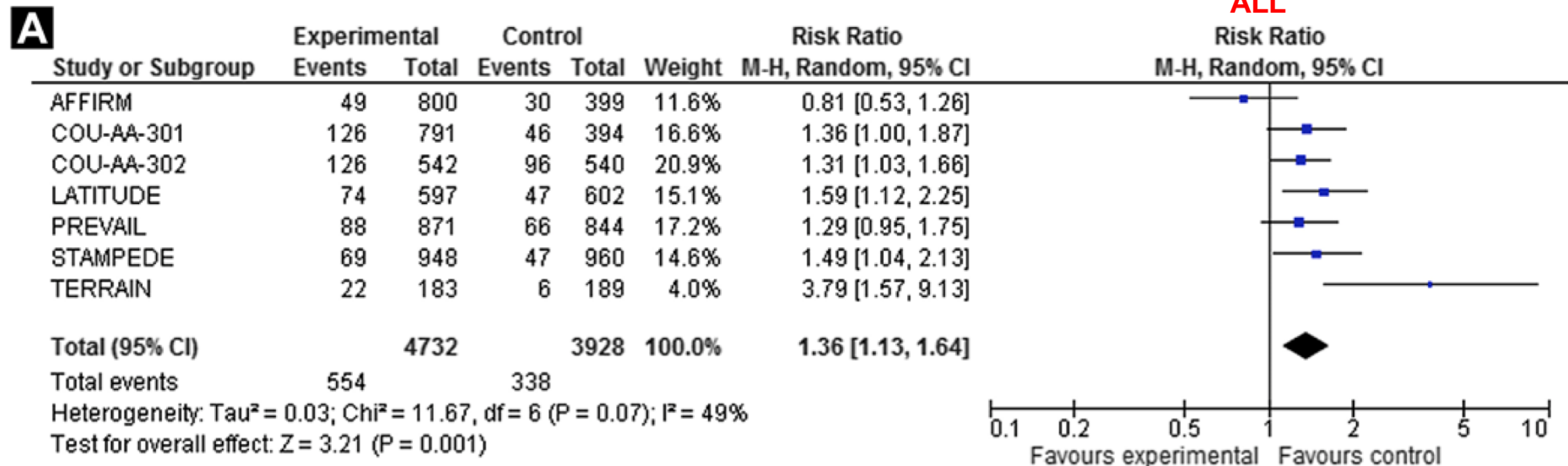
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- **Increased CV risk**
- **Cognitive changes**
 - **Dementia?**
- **Osteoporotic fractures**

Complications of ART Therapies

- Enzalutamide has **8x** the binding affinity to AR compared with bicalutamide
- What does that do to the known long-term complication rate with ADT alone?
- What's the impact of duration of therapy?
- What happens in the real world?



Cardiovascular Toxicity with ART Therapies



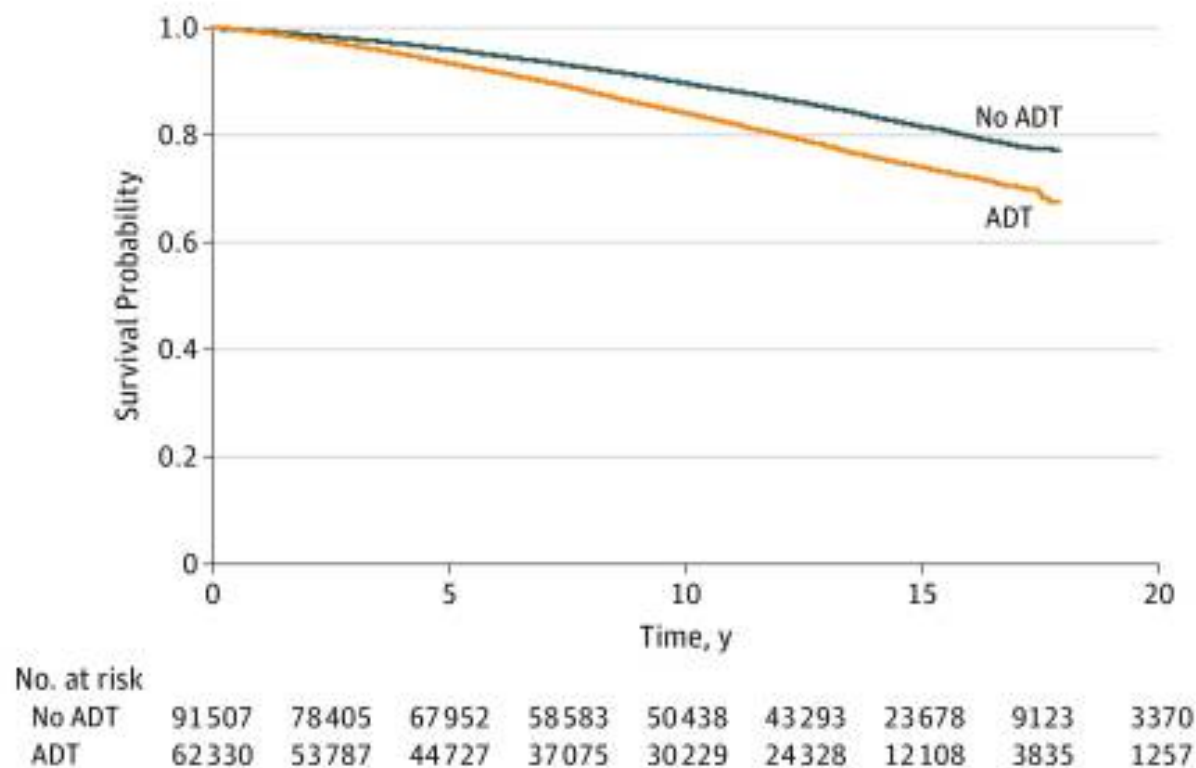
Do ART Therapies Increase Dementia?



Original Investigation | Oncology

Association Between Androgen Deprivation Therapy Use and Diagnosis of Dementia in Men With Prostate Cancer

Ravishankar Jayadevappa, PhD; Sumedha Chhatre, PhD; S. Bruce Malkowicz, MD; Ravi B. Parikh, MD, MPP; Thomas Guzzo, MD, MPH; Alan J. Wein, MD, PhD (Hons)

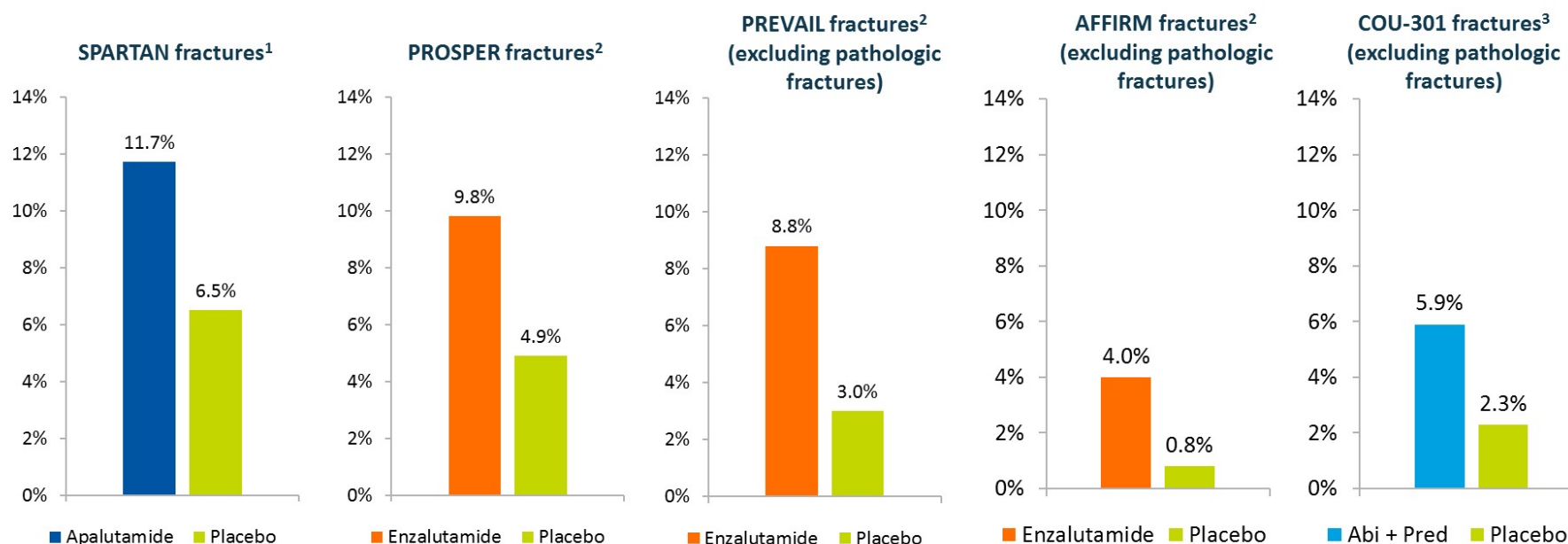


Osteoporotic Fractures are More Frequent with ART Therapies in mCRPC



The future of cancer therapy

Fractures are commonly reported in the investigational arm of phase III studies with new AR pathways inhibitors



USPI, U.S. prescribing information.

1. Smith MR *et al.* *N Engl J Med* 2018; doi:10.1056/NEJMoa1715546 [Epub ahead of print]. 2. Xtandi (enzalutamide) [prescribing information]. Astellas Pharma US, Inc., Northbrook, IL. July 2018. 3. Zytiga (abiraterone acetate) [prescribing information]. Janssen Biotech, Inc., Horsham, PA. February 2018. 4. Erleada (apalutamide) [prescribing information]. Janssen Products, LP, Horsham, PA. February 2018.

Mini Review

Revisiting Intermittent Therapy in Metastatic Prostate Cancer: Can Less Be More in the “New World Order”?

Jeffrey Shevach^a, Matthew R. Sydes^b, Maha Hussain^{a,c,}*

^a Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; ^b MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London, UK; ^c Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

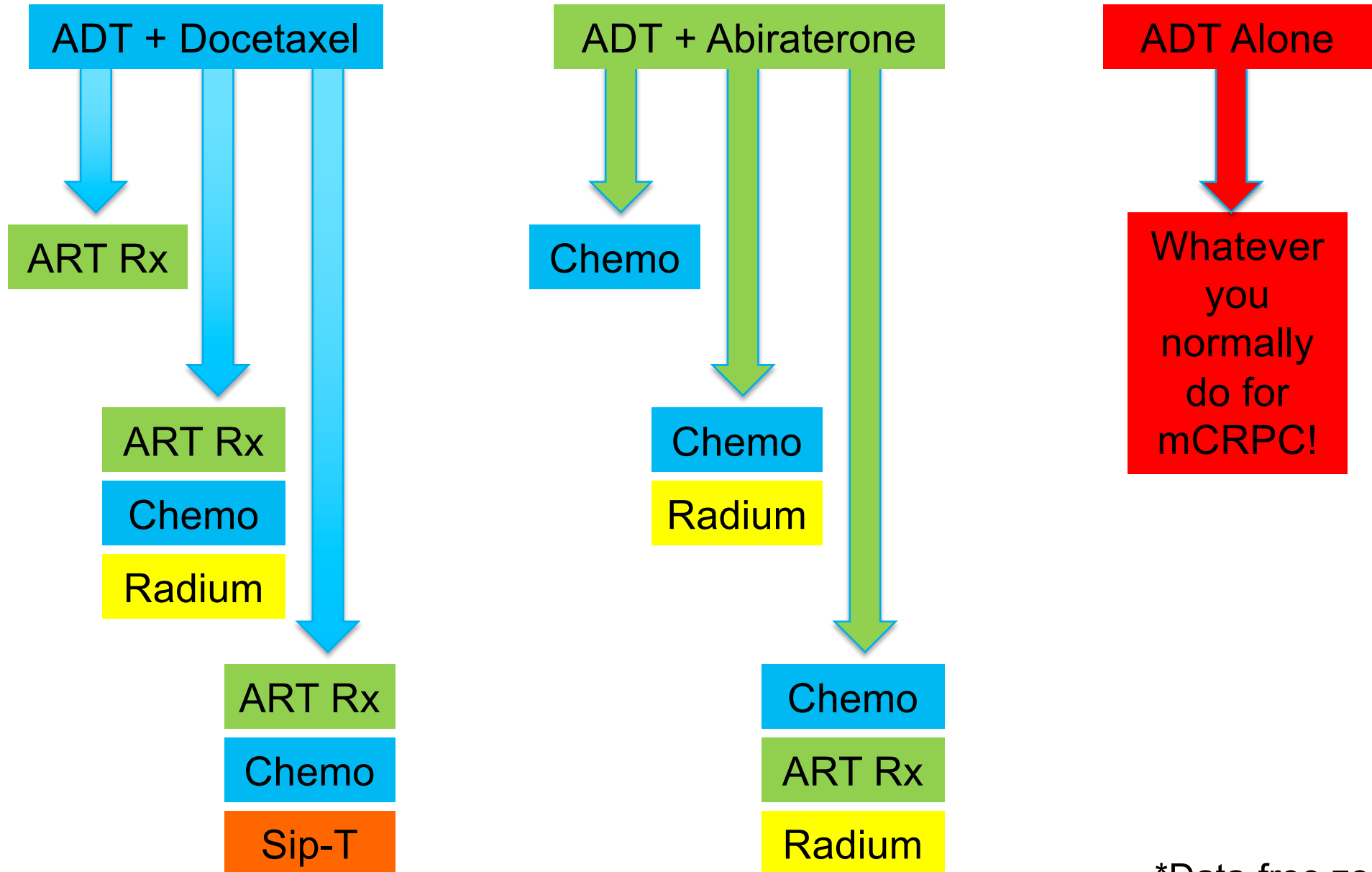
“IAD...is not the standard of care, particularly in the era where we have seen unprecedented survival impact from combination ADT + docetaxel or abiraterone”

Summary: Complications of ART Therapies

- AR targeted therapy has moved earlier
 - mHSPC, M0 CRPC
- Patients are being exposed to longer durations of ADT + ART therapies
 - Cost, toxicity
- How can complications be managed while maintaining the benefits of therapy?



Finally, what treatment next?*



*Data-free zone

