# RTP at AUA 2017: Prostate Cancer:

## Sunday, May 14th 2017, Boston, MA

### Sequence and Selection of Systemic Therapy for Patients with mCRPC


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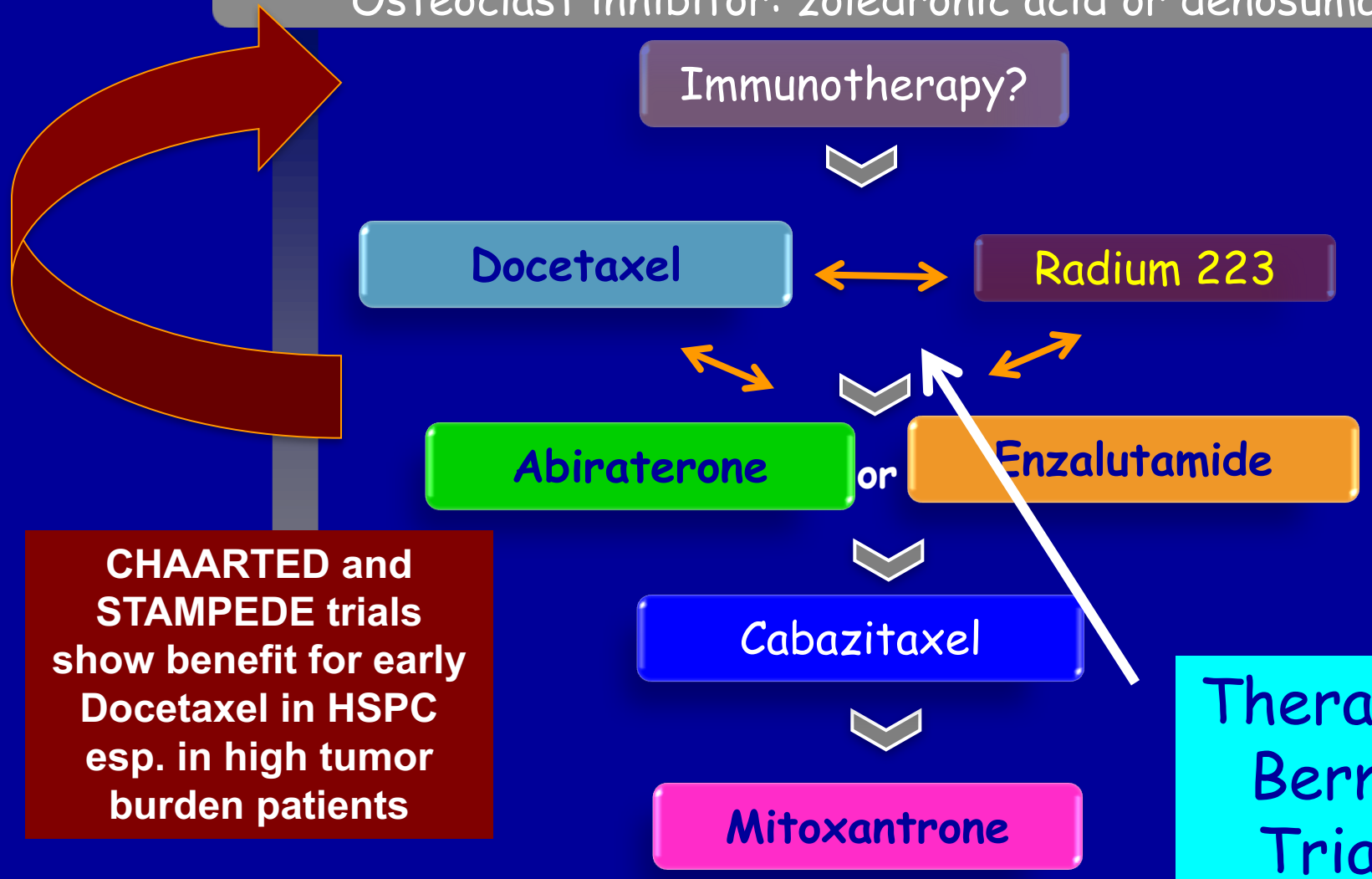
# Faculty Disclosure

| Company | Nature of Affiliation | Unlabeled Product Usage |
|---|---|---|
| Pfizer/Astellas | Advisory board, compensated | Enzalutamide in CRPC |
| Bayer | Advisory board, compensated | Radium 223 in CRPC |
| Sanofi | Advisory board, compensated | Cabazitaxel in CRPC |
| AstraZeneca | Advisory board, compensated | Olaparib in CRPC |
| Dendreon | Advisory board, compensated | Sipuleucel-T in CRPC |

# Preferred Therapeutic Sequencing For Metastatic CRPC possible changes for 2017

Baseline: Androgen Deprivation, Calcium, Vitamin D,
Osteoclast inhibitor: zoledronic acid or denosumab




**CHAARTED and STAMPEDE trials show benefit for early Docetaxel in HSPC esp. in high tumor burden patients**

Therapeutic Bermuda Triangle

# Long-term safety and efficacy data with secondary hormonal agents in chemotherapy-naïve and pretreated CRPC

- We have long-term follow-up in the trials done in the early CRPC setting with enzalutamide and abiraterone (Rathkopf D et al. *Eur Urol*;66:815-25, 2014; Higano CS et al. *Eur Urol*;68:795-801,2015)
- They typically show very few emergent adverse events with longer follow-up
- However, these studies are not designed to assess longer term bone, frailty, cardiac and musculoskeletal issues of prolonged AR pathway blockade
- We need extended pharmacovigilance to assess this
- Earlier usage in the HNPC setting has potential to make these issues worse

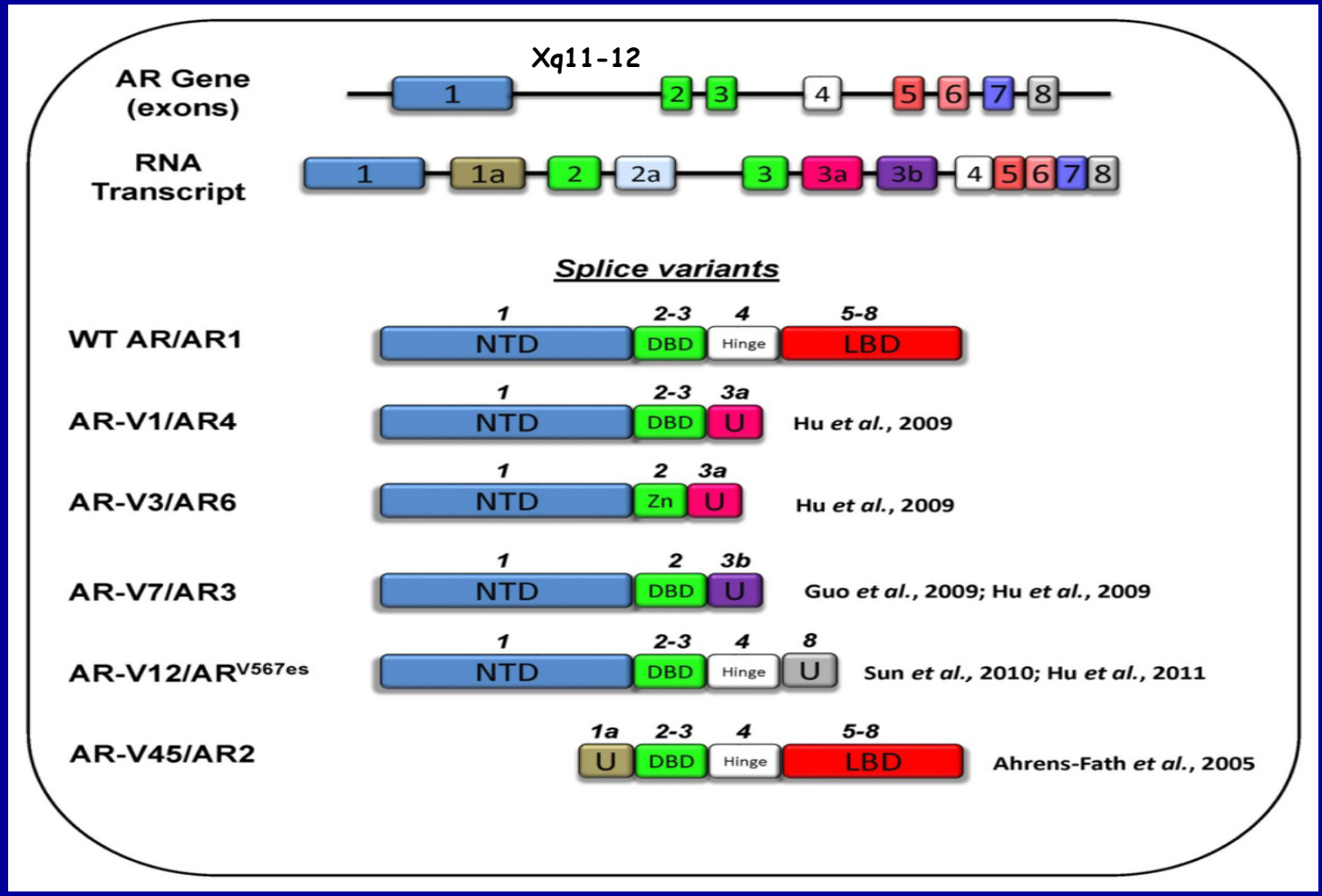
# Resistance, Biomarkers, Therapy selection and sequencing?

# Available research information and ongoing evaluation of androgen-receptor splice variant 7 (AR-V7) as a biomarker to predict resistance to secondary hormonal therapy: summary

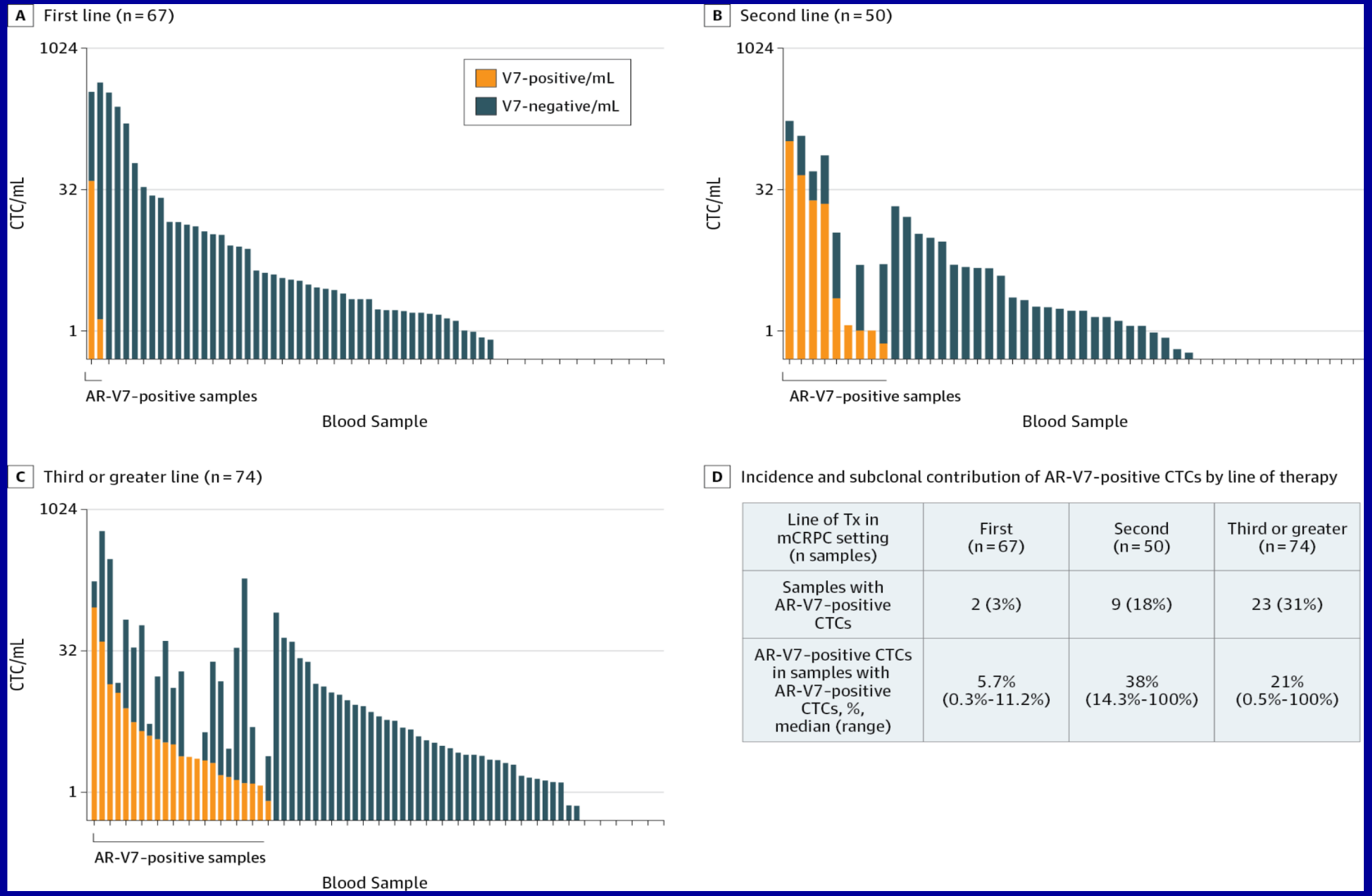
- Patients detectable AR-V7 variant in circulating tumor cells by PCR or IHC are less responsive to abiraterone and enzalutamide[1,2]
- Expression of nuclear AR-V7 is associated with worse ORR, rPFS and OS with the use of abiraterone / enzalutamide[2]
- No significant association between AR-V7 expression and response to taxane chemotherapy[2]
- Patients harboring pre-therapy AR-V7-positive CTCs experienced better OS with taxanes than with abiraterone or enzalutamide after adjusting for other variables[2]
- Assays for full length AR in CTC measure amplification: response to second line AR inhibition are best in patients with no detectable increase in ARFL and worse in cases where it increasingly present[3]


1. Antonarakis et al. N Engl J Med 2014; 371:1028-1038
2. Scher et al. JAMA Oncol. 2016;2(11):1441-1449. 3. Silberstein J et al GU ASCO 2017

# ANDROGEN RECEPTOR (AR) SPLICE VARIANTS MAY BE IMPORTANT IN THE DEVELOPMENT OF CASTRATION RESISTANCE AND CROSS RESISTANCE TO ANDROGEN PATHWAY INHIBITORS



# Prevalence and Frequency of AR-V7 CTC Positivity by Line of Therapy: The burden of intact, non-apoptotic CTCs

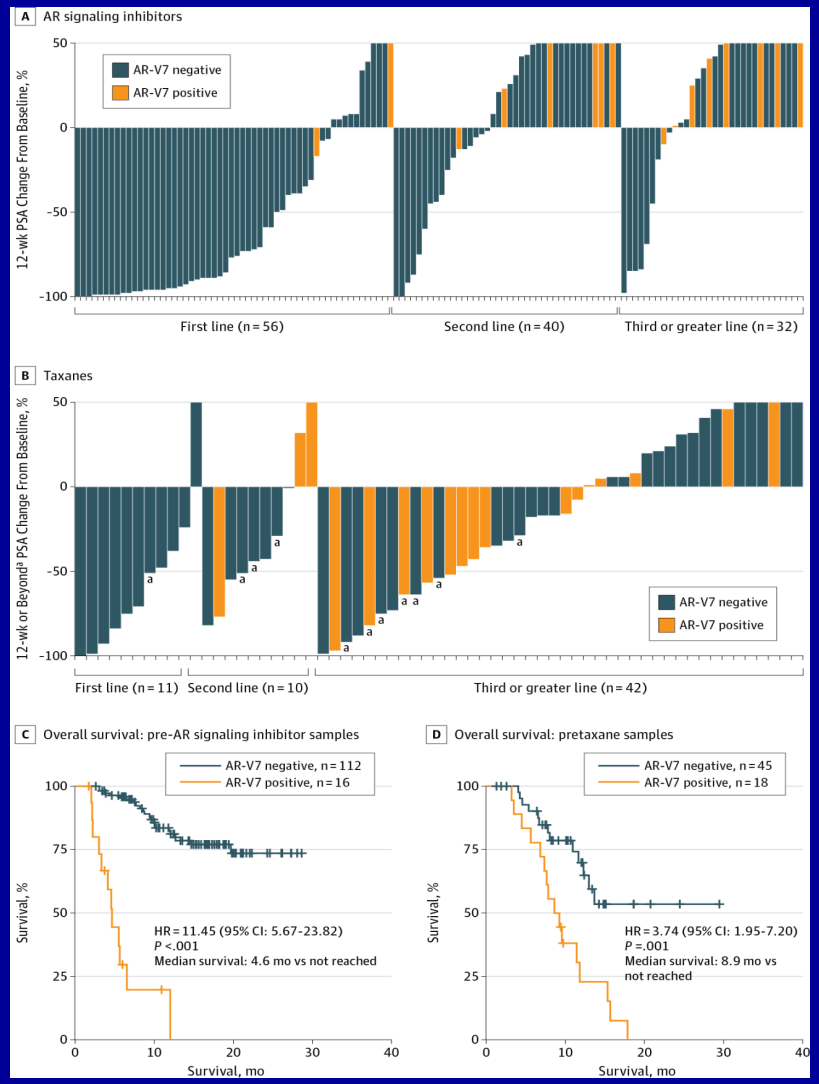



D Incidence and subclonal contribution of AR-V7-positive CTCs by line of therapy

| Line of Tx in mCRPC setting (n samples) | First (n = 67) | Second (n = 50) | Third or greater (n = 74) |
|---|---|---|---|
| Samples with AR-V7-positive CTCs | 2 (3%) | 9 (18%) | 23 (31%) |
| AR-V7-positive CTCs in samples with AR-V7-positive CTCs, %, median (range) | 5.7% (0.3%-11.2%) | 38% (14.3%-100%) | 21% (0.5%-100%) |

**Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer.** ***JAMA Oncol*** **2016;2(11):1441-9.**

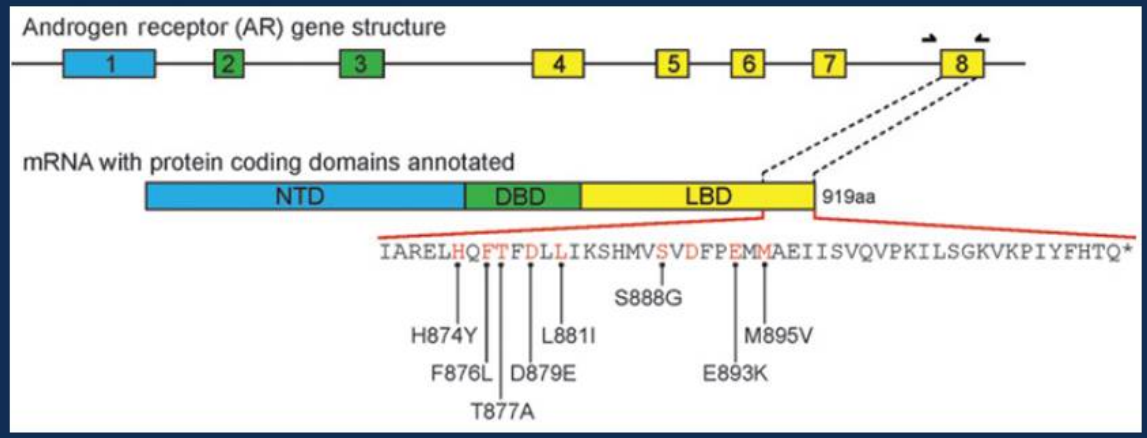
# Presence of AR-V7–Positive CTCs and Response to AR Signaling Inhibitors

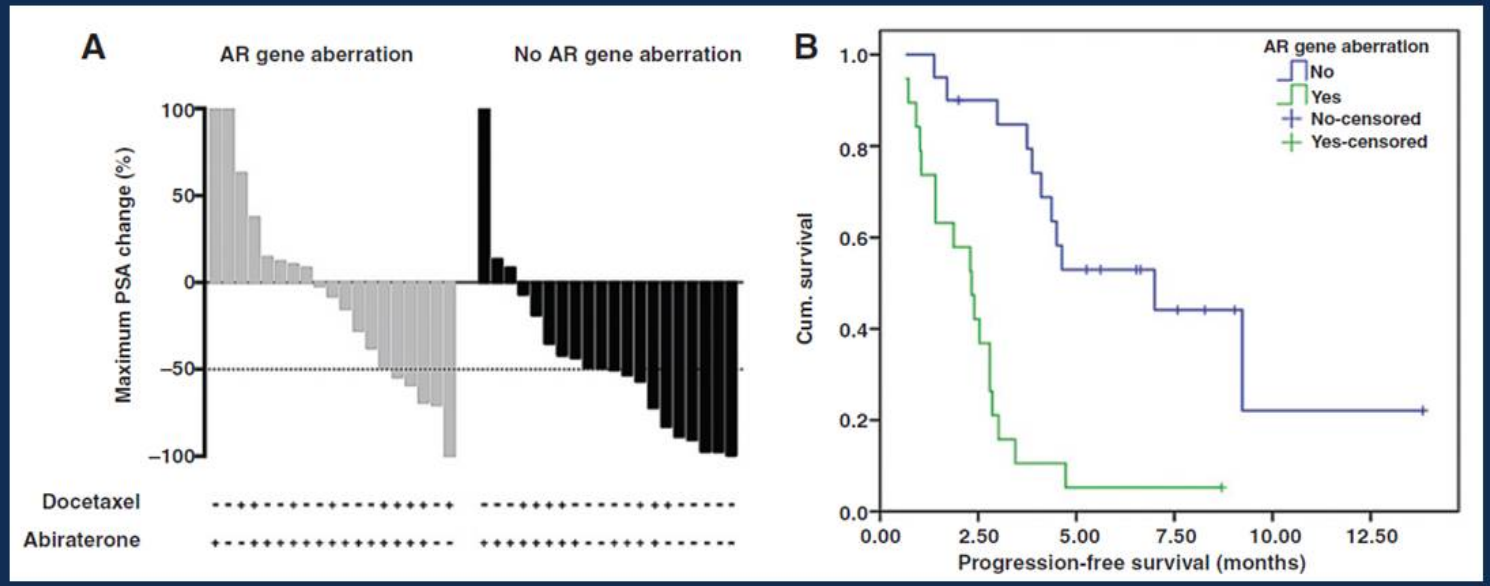



Waterfall plots, colored by presence of AR-V7–positive CTCs, show the percent PSA change from baseline at
(A) 12 weeks on ARS inhibitors
(B) 12 weeks (or best decline if after 12 weeks) on taxanes
(C) Overall survival is shown, separated by AR-V7 status, for samples from patients receiving (C) ARS inhibitors or (D) taxanes.

Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer. *JAMA Oncol* 2016;2(11):1441-9.

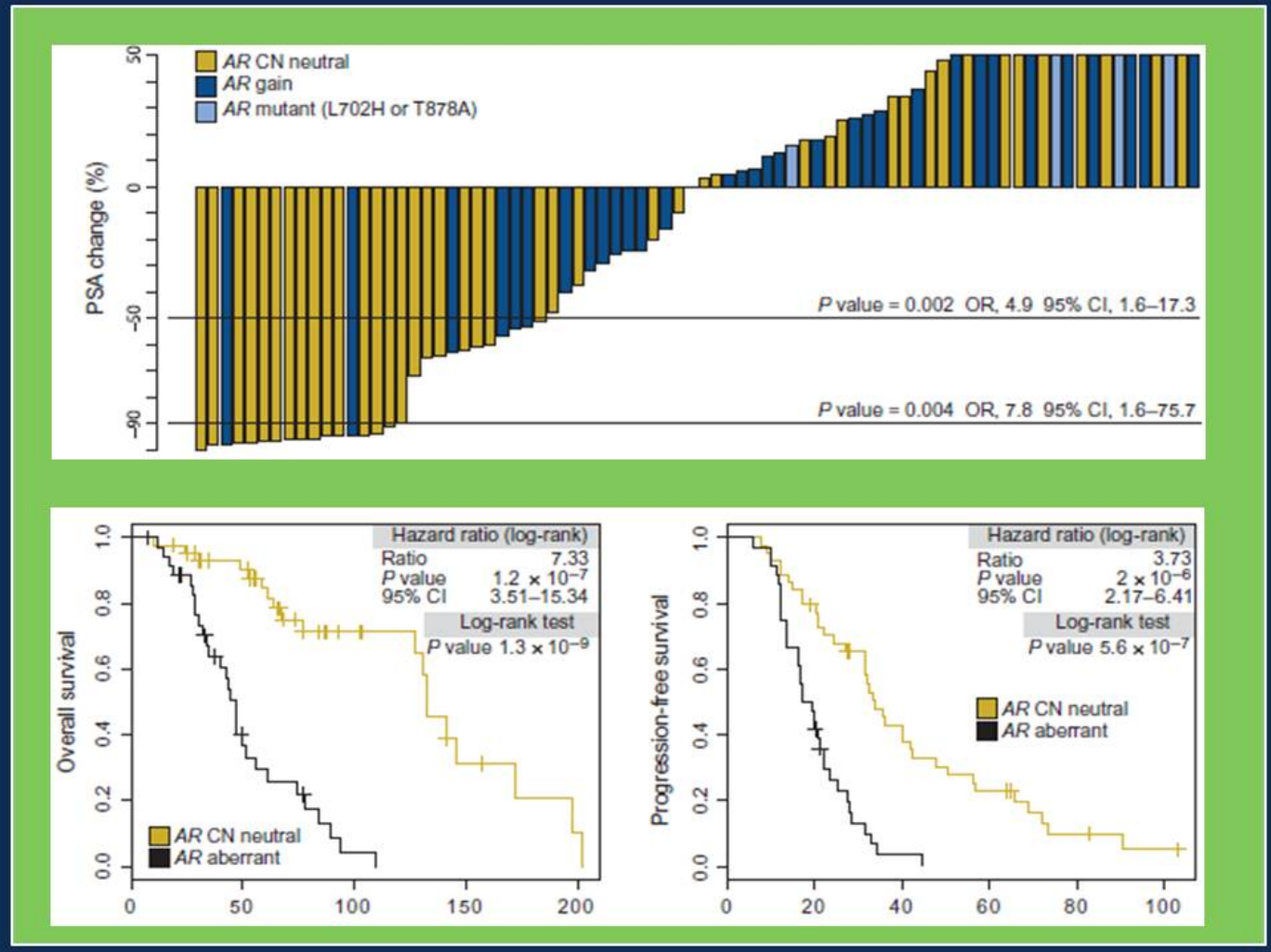
# Enza: ctDNA analysis for AR amp/mut




Azad AA et al. *Clin Cancer Res* 2015;21:2315-24; Silberstein J et al. GU Cancers Symposium 2017;Abstract 132.

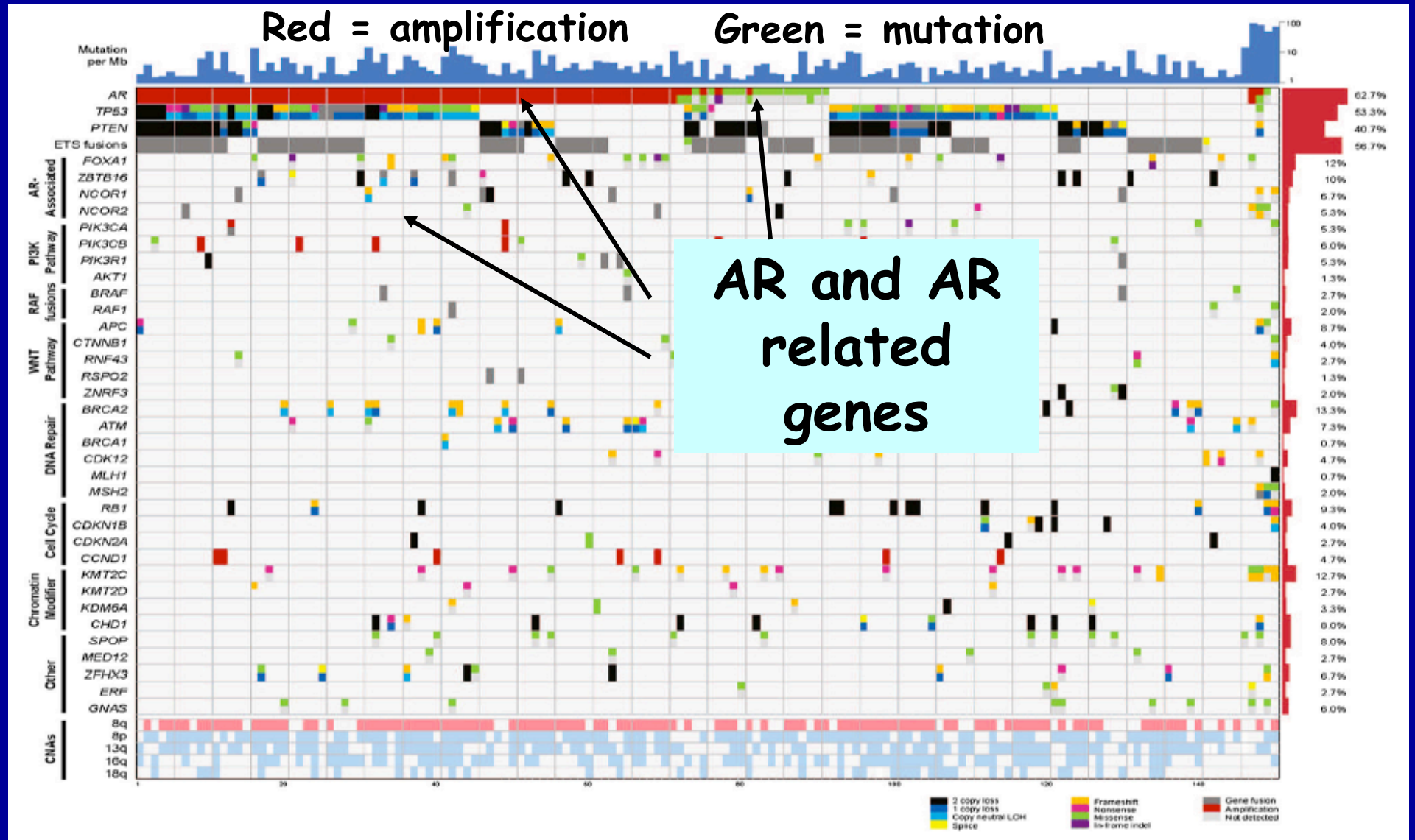
# Abi: ctDNA analysis for AR amp/mut




Romanel A et al. *Sci Trancl Med* 2015;7:312re10; Silberstein J et al. GU Cancers Symposium 2017;Abstract 132.

# Androgen receptor and other molecular variants: TCGA and 2U2C

Robinson et al. Cell 2015



AR full length: increased expression

# Results

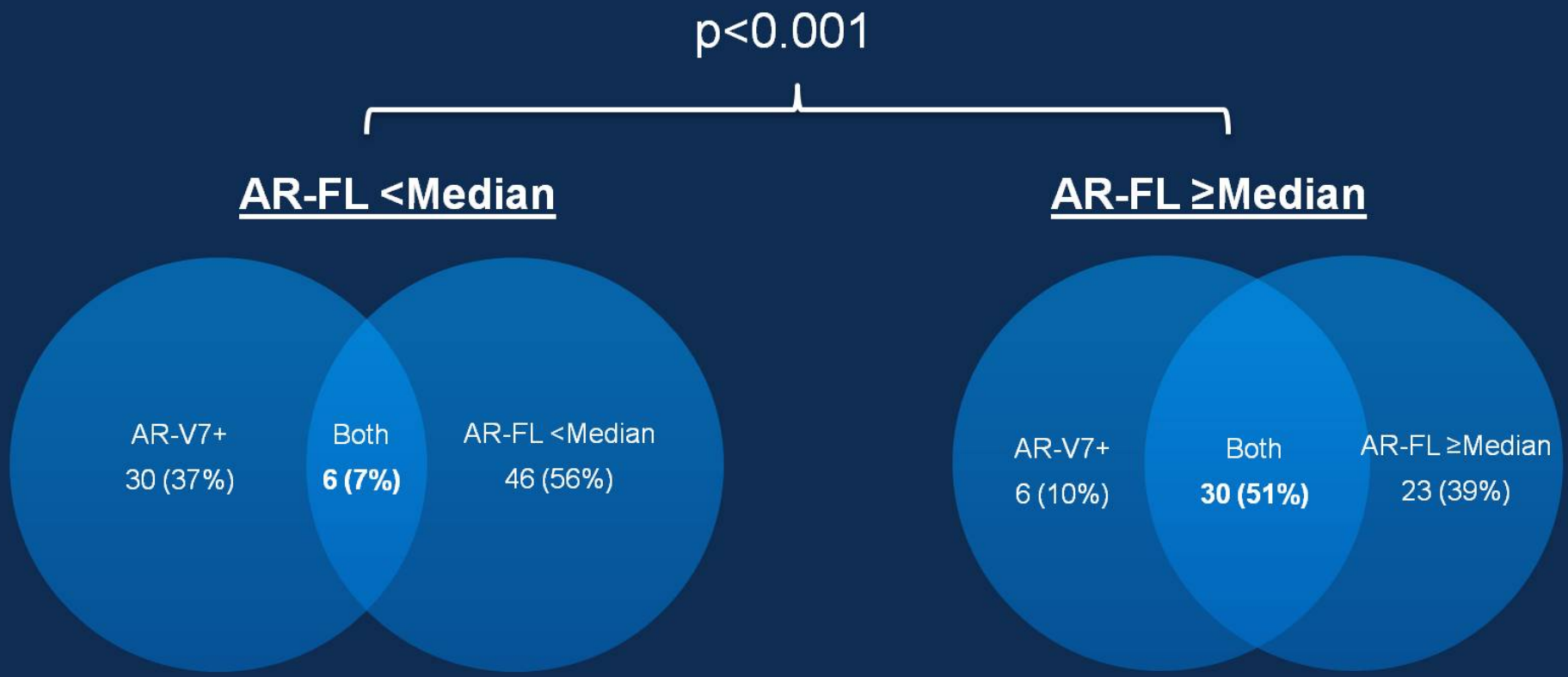
202 men were enrolled, prior to starting Abi/Enza

AR-FL status was considered as 3 groups:

- AR-FL Negative (undetectable): 97/202 = 48%
- AR-FL Positive (<Median): 52/202 = 26%
- AR-FL Positive (≥Median): 53/202 = 26%

Silberstein J et al. Genitourinary Cancers Symposium 2017;Abstract 132.

# Interplay Between AR-FL and AR-V7

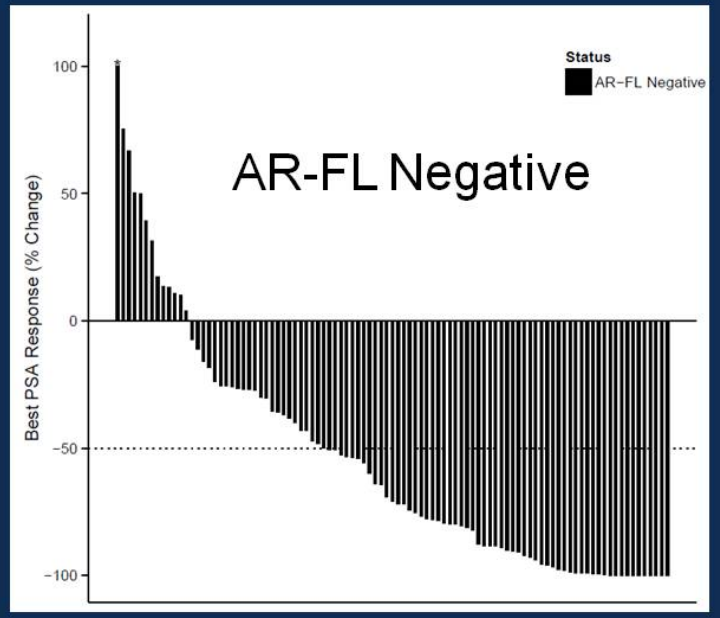



Silberstein J et al. Genitourinary Cancers Symposium 2017;Abstract 132.

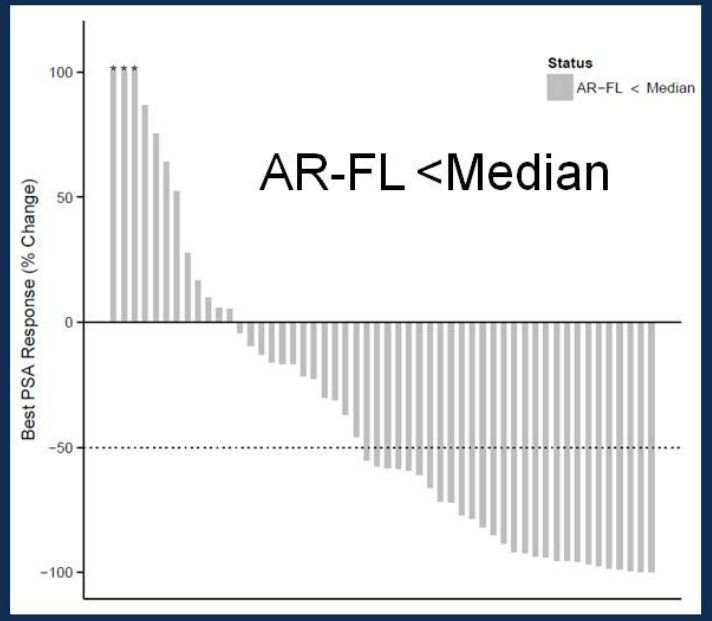
# Best PSA Response

p<0.001

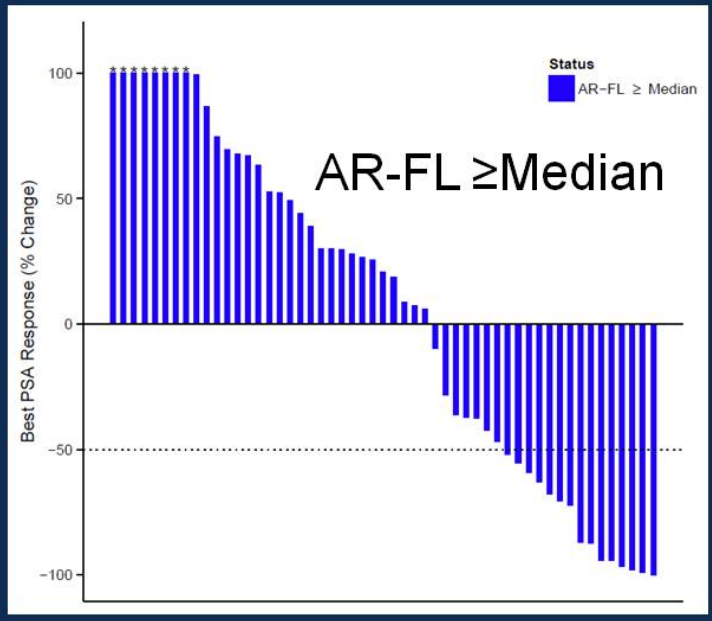
60/97 = **62%**




28/52 = **54%**




15/53 = **28%**




Silberstein J et al. Genitourinary Cancers Symposium 2017;Abstract 132.

# Summary

- CTC-based liquid biopsy allows AR-FL mRNA quantification
- Higher AR-FL levels correlate with AR-V7 positivity
- Higher AR-FL correlated with inferior clinical outcomes (table), and generally remained significant in multivariable models

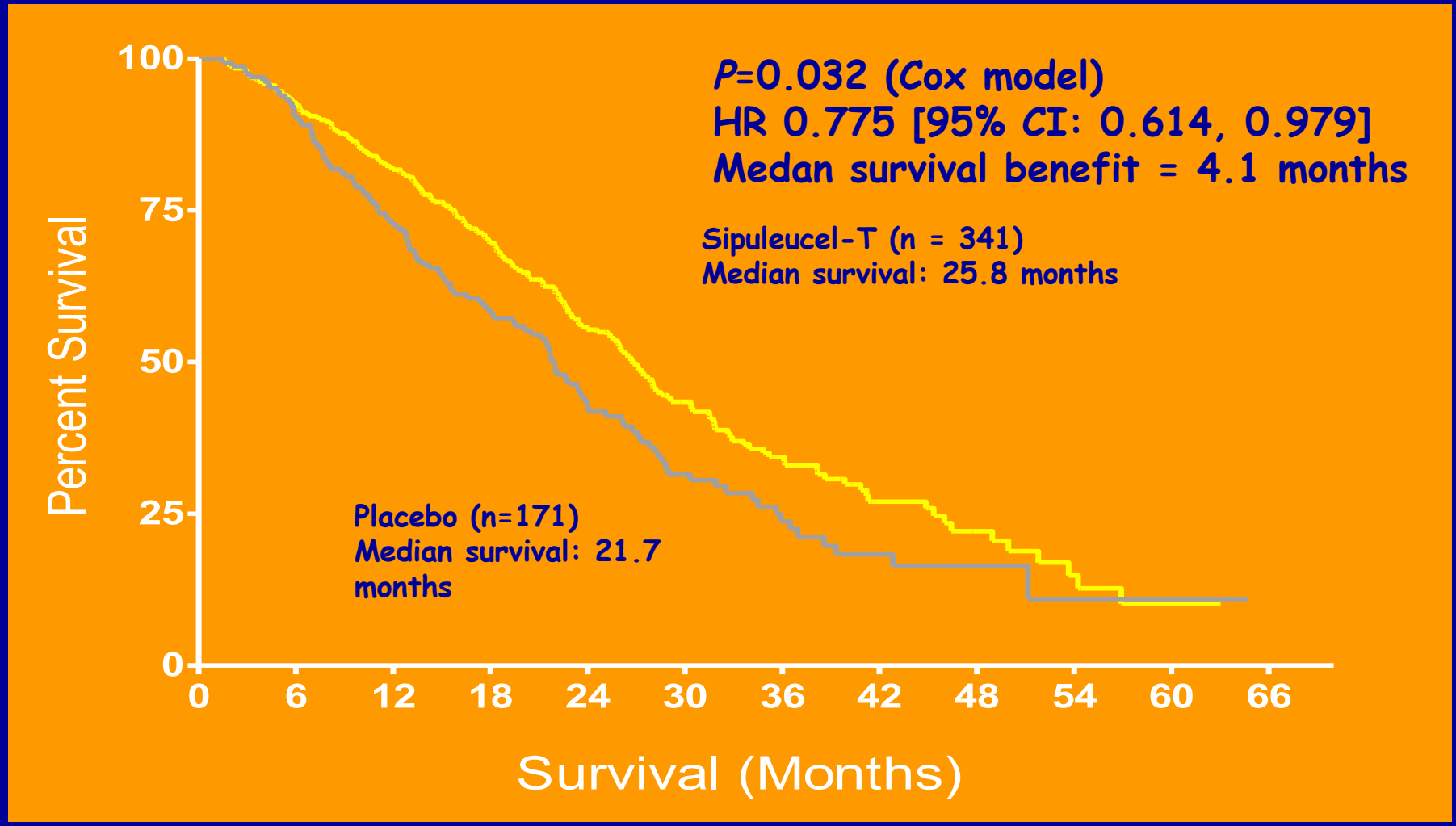
| | AR-FL negative (N=97) | AR-FL <median (N=52) | AR-FL ≥median (N=53) | *P*-value |
|---|---|---|---|---|
| **PSA-PFS (mo)** | 9.6 | 6.2 | 2.5 | **<0.001** |
| **PFS (mo)** | 11.1 | 8.7 | 3.2 | **<0.001** |
| **OS (mo)** | 33.3 | 18.0 | 11.3 | **<0.001** |

- AR-V7 remained independently prognostic for all outcomes in multivariable analyses

Silberstein J et al. Genitourinary Cancers Symposium 2017;Abstract 132.

# Patient selection for sipuleucel-T in clinical practice; Effects of tumor burden/extent of disease on its clinical utility

# Sipuleucel-T Vaccine




**Approved by FDA: April 2010**

Adapted from Penson D, et al. Presented at American Urological Association (AUA) 2009 Annual Meeting. April 25-30, 2009; Chicago, IL.

# Sipuleucel-T - Overall Survival by PSA Quartiles: great OS benefit to earlier therapy, likely with a lower disease burden

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 , months | | | | |
| Sipuleucel-T | 41.3 | 27.1 | 20.4 | 18.4 |
| Control | 28.3 | 20.1 | 15.0 | 15.6 |
| Difference | 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) |

P. Schellhammer et al. 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. Urology Vol.81, Issue 6, June 2013;1297-1302

## Rapidity of response associated with the use of second-generation androgen inhibitors and sipuleucel-T; use of these therapies versus chemotherapy for symptomatic disease

- Early PSA non-response and LDH increase is an important predictor of longer term benefit with anti-androgens
- SipT does not produce a symptomatic or PSA response.
- The bias is to treat a symptomatic patient with chemotherapy but the best evidence from cross trial comparisons is that hormonal agents produce response as quickly as chemotherapy

# Early (28 days) PSA Response is an Independent Prognostic Factor in Patients with mCRPC Treated with Next-generation Androgen Pathway Inhibitors. N=118

| Variable | Multivariate analysis for rPFS | | | Multivariate analysis for OS | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| PSA decline ≥50% vs <50% | 0.33 | 0.2-0.5 | $7x10^{-6}$ | 0.5 | 0.3-0.8 | 0.009 |
| LDH >ULN vs NL | 1.56 | 0.9-2.5 | 0.08 | 1.6 | 0.9-2.8 | 0.08 |
| Albumin <LLN vs NL | 3.8 | 1.9-7.8 | 0.0001 | 2.7 | 1.3-5.8 | 0.008 |
| Visceral dx Yes vs No | 1.5 | 0.8-2.7 | 0.16 | 2.1 | 1.1-3.9 | 0.02 |

Median OS was 32.2 months if PSA declined by ≥ 50% at 28 days of therapy vs 15.9 months if <50%

Fuerea A. et al. European Journal of Cancer 61(2016) 44-51