



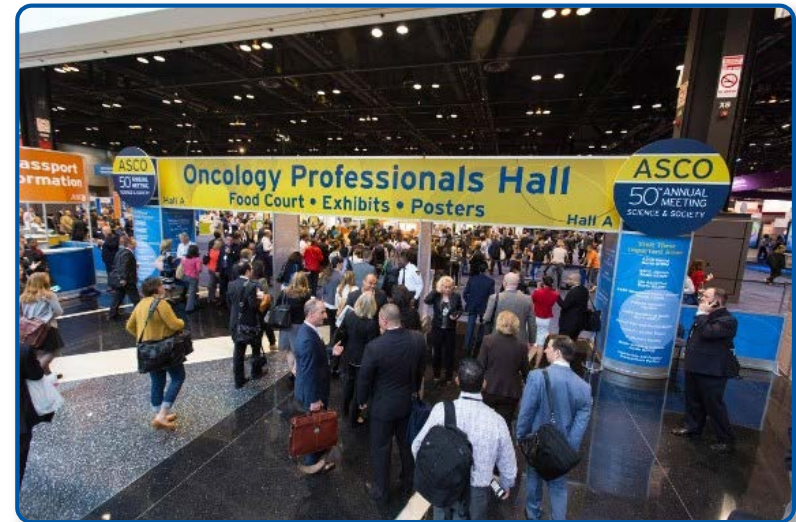
2015 ASCO Conference Highlights for PCa Patients: May 29-June 2 – Chicago, IL

Howard R. Soule, PhD

- **Theme: Illumination and Innovation — Transforming Data Into Learning**

“We are in an information age and there is a lot of data coming at us. We need to become smarter and more nimble about how we look at data and derive knowledge, and then that drives actual decision-making that improves patient outcomes.”

— *ASCO President Peter Yu, MD*



- **~37,000 attendees**
- **Abstracts Submitted: 5,945**
- **Accepted for Presentation: 2,391**
- **Program included 97 sessions in 17 tracks**

Highlights from the 2015 ASCO Annual Meeting relevant for patients:

- 1. Earlier chemotherapy may be better:** First survival results from STAMPEDE demonstrate that upfront therapy with docetaxel prolongs overall survival in men with hormone-naïve metastatic prostate cancer commencing ADT by 10 months on average.
- 2. Neoadjuvant chemotherapy should be considered for localized high-risk prostate cancer patients:** Neoadjuvant docetaxel combined with ADT and IMRT shows a 10% increase in 6-year survival benefit in RTOG 0521 trial.
- 3. New recommendations for castration-resistant prostate cancer clinical trial design and patient treatment:** Consensus from the Prostate Cancer Working Group 3.
- 4. New genomic classifier for lethal disease subset:** An 81-gene classifier that can identify the aggressive neuroendocrine subset of treatment-resistant prostate cancer was created.

- 5. Stronger and earlier suppression of the androgen receptor may be better:**
The addition of neoadjuvant abiraterone to ADT had superior anti-tumor activity vs. ADT alone in localized high-risk prostate cancer. More may be better for higher-risk patients with higher Gleason grades and PSAs.

- 6. Copy number gains or losses may mediate enzalutamide resistance:**
Genomic analysis of circulating cell-free DNA identifies mechanisms of primary and acquired resistance to enzalutamide (Xtandi®) in metastatic castration-resistant prostate cancer (mCRPC).

- 7. Distinguishing who should receive more therapy:** A DNA-based genomic classifier was validated to distinguish biochemically recurring patients for whom salvage radiotherapy is likely sufficient, from those who have a high risk for metastasis and should consider additional therapy.

- 8. A potential benefit for statins:** Statin use at the time of initiation of ADT was associated with delayed time to PSA progression in patients with hormone-sensitive prostate cancer by 10 months on average.



**APPENDIX I:
2015 ASCO CONFERENCE
HIGHLIGHTS FOR PCa PATIENTS –
DETAIL**

1

Upfront Therapy with Docetaxel Prolongs Overall Survival in Men with Hormone-Naïve Metastatic Prostate Cancer Commencing ADT: First survival results from STAMPEDE



Nicholas James, MD, PhD
University of Warwick and
Queen Elizabeth Hospital
Birmingham

- Prostate cancer patients who present with primary metastatic disease or relapse with metastases after definitive local treatment with prostatectomy or radiotherapy (RT) typically receive androgen deprivation therapy (ADT) with or without RT as the standard of care.
- When tumors develop resistance to ADT, taxane chemotherapy or 2nd generation anti-androgen medications will likely be prescribed. However, it is hypothesized that earlier administration of these therapies may extend patient lives.
- **Dr. Nicholas James** presented the first survival results released from the **STAMPEDE** clinical trial, which tested the outcome of adding various therapies to standard of care (SOC) consisting of androgen deprivation therapy (ADT) with or without radiotherapy (RT), in hormone-naïve patients either presenting with metastatic disease or relapsing after prostatectomy or RT.
- Results were presented from four randomized study arms: SOC (1184 patients), SOC + zoledronic acid (593 patients), SOC + docetaxel + prednisolone (592 patients), and SOC + zoledronic acid + docetaxel + prednisolone (593 patients).
- No benefits to failure free survival (FFS) or overall survival (OS) were observed with addition of zoledronic acid, a bisphosphonate that reduces bone fractures and pain from bone metastases.
- The addition of docetaxel + prednisolone to SOC extended median FFS from 21 months to 37 months and extended median OS from 67 months to 77 months.
- These results support previous results from the CHARTED trial where a median overall survival (OS) improvement from 44 to 57.6 months with the addition of docetaxel to ADT in hormone-sensitive metastatic prostate cancer patients was observed.
- Collectively, these results support a paradigm change in clinical practice. Docetaxel in combination with ADT should now be considered much earlier in the treatment regimen for men with hormone-naïve metastatic prostate cancer.

1

Upfront Therapy with Docetaxel Prolongs Overall Survival in Men with Hormone-Naïve Metastatic Prostate Cancer Commencing ADT: First survival results from STAMPEDE

Docetaxel: Survival

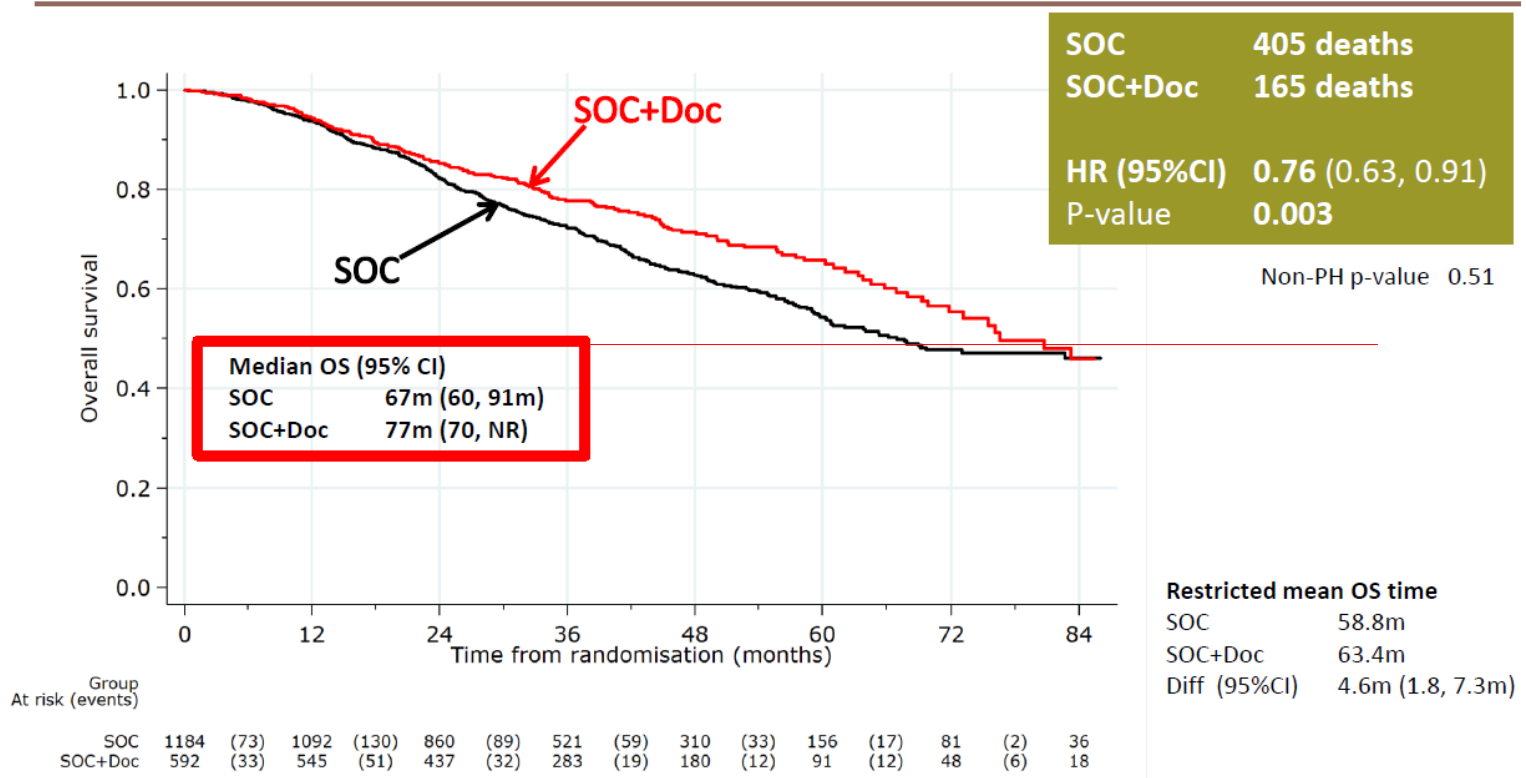
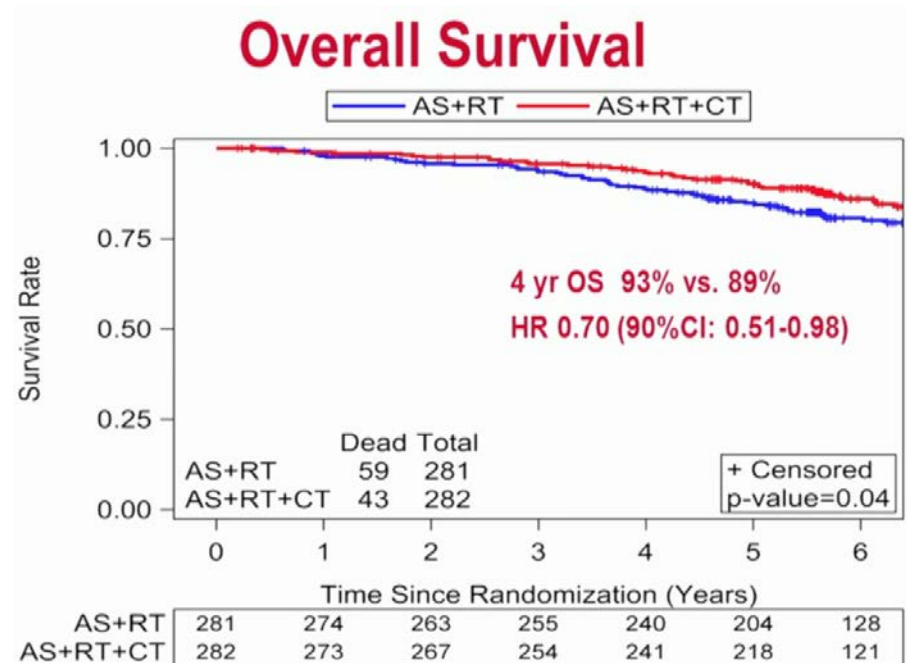


Figure: The addition of docetaxel + prednisolone (Doc) to standard of care (SOC, androgen deprivation therapy +/- radiotherapy) extended median overall survival (OS) from 67 to 77 months.

2

Neoadjuvant Chemotherapy Combined with ADT and IMRT Shows Survival Benefit in Localized High-Risk Prostate Cancer Patients: Results from RTOG 0521

- A patient diagnosed with localized high-risk prostate cancer will typically receive androgen deprivation therapy (ADT) + radiotherapy (RT) as their first line of treatment.
- Neoadjuvant chemotherapy is a common treatment option for many types of cancers, but has not previously been demonstrated to benefit prostate cancer patients.
- **Dr. Howard Sandler** (Cedars-Sinai Medical Center) presented results from **RTOG 0521**, a Phase III trial testing the addition of docetaxel + prednisone to ADT+ Intensity-Modulated RT (IMRT) in treatment-naïve high-risk localized prostate cancer.
- At a median of 6 years of follow up, 563 patients were evaluable. The addition of docetaxel + prednisone to ADT + IMRT improved the 4-year overall survival (OS) rate from 89% to 93% of patients and improved 6-year disease-free survival rates from 55 to 65%.
- These studies indicate that neoadjuvant chemotherapy in combination with ADT and IMRT may benefit patients with localized high-risk prostate cancer and should be considered as the first line of therapy.



3

The Prostate Cancer Working Group 3 (PCWG3) Defines New Consensus for Castration-Resistant Prostate Cancer (CRPC) Clinical Trial Design and Patient Treatment Recommendations (ctd.)

- The **Prostate Cancer Working Group (PCWG)** is a committee of prostate cancer experts who periodically create a consensus report for clinical trial design and patient treatment recommendations to promote the alignment of clinical trials research and clinical practice.
- In 2008, the PCWG2 proposed a set of clinical practice principles for castrate resistant prostate cancer (CRPC). PCWG2 principles were designed for pre- and post-chemotherapy settings when docetaxel was the only therapy approved for CRPC patients.
- Since then, 5 additional life-extending therapies have been FDA-approved, new disease manifestations of prostate cancer have been described, new biomarkers for treatment response or resistance have been identified, molecular imaging advancements have improved diagnosis and prognosis, and much has been learned about how to optimally design clinical trials.
- PCWG3 was convened in 2012 to improve upon and update the recommendations for clinical trial design and treatment strategies set forth by the PCWG2.
- PCWG3 is headed by **PCF-funded Dr. Howard Scher** (Memorial Sloan Kettering Cancer Center), who discussed the recommendations outlined by PCWG3.
- Key objectives of PCWG3 include identifying patient subsets for whom specific agents are either most appropriate or contraindicated, developing intermediate endpoints and new outcomes measures for clinical trials, assessing tumor biology before and after treatments to understand treatment sensitivity and resistance, and determining the best sequencing, timing, and combinations of treatments.

3

The Prostate Cancer Working Group 3 (PCWG3) Defines New Consensus for Castration-Resistant Prostate Cancer (CRPC) Clinical Trial Design and Patient Treatment Recommendations (ctd.)

- Because patients can now receive a number of life-prolonging therapies in addition to docetaxel, clinical practice models have been revised to consider the treatments and order of treatments that an individual patient has received.
- New recommended practices include re-biopsy of lesions to assess changing tumor biology and consideration of blood-based diagnostics utilizing circulating tumor DNA or circulating tumor cells (CTCs).
- Improved imaging technologies have allowed better understandings of the effects of disease status on prognosis. New imaging technologies will continue to refine these indications.
- Imaging of bone lesions has been difficult because traditional technetium bone scans are not able to differentiate between metastatic bone lesions and “flare,” an inflammatory healing reaction that occurs during therapeutic responses.
- PCWG2 outlined a 2+2 rule for determining metastatic bone progression, in which two additional scans must be used to confirm the appearance of at least two new lesions observed in an initial post-treatment scan. PCWG3 maintained these recommendations and extended them to definitively define progression from non-metastatic to metastatic CRPC.
- Outcomes and endpoints measures are recommended to include measures of clinical benefit and the appearance of new symptomatic bone metastases.
- Adequate drug exposure is important for obtaining therapeutic responses. Treatment should continue through early changes in PSA and/or pain in the absence of other measures of disease progression.
- These recommendations will be used to guide the design of new clinical trials and therapeutic conduct for non-metastatic and metastatic CRPC patients.

3

The Prostate Cancer Working Group 3 (PCWG3) Defines New Consensus for Castration-Resistant Prostate Cancer (CRPC) Clinical Trial Design and Patient Treatment Recommendations (ctd.)

The PCWG2 Control/Relieve – Delay/Prevent Framework Aligns With the Indications and/or Uses of the Available Agents That Have Transformed Management

Early (Response)
Control, Relieve, Eliminate

Approved to Control of Pain or *Indicated for Patients With Symptoms**

- Radiopharmaceuticals
- Mitoxantrone + prednisone
- *Radium-223 (symptoms from bone metastases – no other organs)

No approvals for other control, relieve, eliminate endpoints

- PSA declines
- Tumor shrinkage
- Change in a bone scan
- Circulating tumor cells

Late (Progression – Time to Event)
Delay, Prevent

Approved or Shown to Delay SREs

- Zoledronic acid (SRE)
 - Denosumab (SRE)
 - Radium-223 (SSE)
 - Abiraterone
 - Enzalutamide
- SRE: Skeletal related events;
SSE: Symptomatic skeletal events*

Approved for Delay of Death

- Docetaxel
- Sipuleucel-T
- Cabazitaxel
- Abiraterone
- Enzalutamide
- Radium-223

4

Creation of an 81-gene Classifier that Can Identify the Aggressive Neuroendocrine Subclass of Treatment-Resistant Prostate Cancer (ctd.)

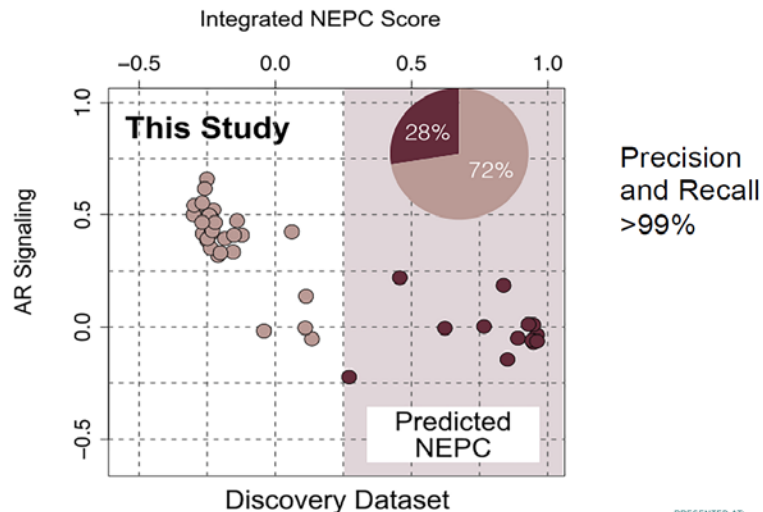
- Tumor cells are continuously evolving to adapt to selective pressures introduced by changing host factors and the administration of new therapies.
- Following the administration of the second-generation anti-androgen therapies abiraterone and enzalutamide, prostate tumors inevitably develop resistance and progress to lethal disease.
- Anti-androgen therapy-resistant prostate cancers can either manifest as a gradually progressive disease with bone and lymph node metastases and a rising PSA or as a rapidly progressing disease with liver and brain metastases and a low or non-rising PSA. This indicates that at least two evolutionary paths of resistance to androgen-targeting therapy can occur.
- Aggressive PSA-low/negative tumors commonly exhibit a neuroendocrine phenotype, in which tumor cells express neurodevelopmental markers. However, the expression of these markers and the pathologic morphology of these tumors is heterogeneous, making it a challenge for clinicians to diagnose.
- **PCF-funded Dr. Himisha Beltran** (Weill Cornell Medical College) presented results from a study which assessed whether molecular characteristics including genetic alterations, gene expression, and epigenetic signatures could differentiate CRPC tumors with a neuroendocrine phenotype from those with a typical adenocarcinoma phenotype.
- Significant overlap was observed in the genomic profiles of these tumor types. Genomic differences included loss of the tumor suppressor RB1 and mutation or deletion of p53, which occurred in ~70% of neuroendocrine tumors compared with ~30% of adenocarcinoma tumors. Alterations in the androgen receptor (AR), including point mutations and amplification were characteristic of adenocarcinoma but not neuroendocrine tumors.
- Analysis of serial biopsies taken from patients who progressed from adenocarcinoma to neuroendocrine phenotypes indicated that these morphologically different tumors arose from divergent clonal evolution rather than linear evolution or independent clonal evolution.

4

Creation of an 81-gene Classifier that Can Identify the Aggressive Neuroendocrine Subclass of Treatment-Resistant Prostate Cancer (ctd.)

- Overall, genomic alterations did not fully explain the transition from adenocarcinoma to neuroendocrine phenotypes. The epigenetic signatures of these tumors however, could almost entirely differentiate these tumor subtypes.
- Epigenetic signatures are non-mutational but heritable alterations, in which the structure of a genomic region is changed by the addition or subtraction of molecules that regulate whether or not genes in that region can be expressed.
- Dr. Beltran identified an 81-gene classifier consisting of key distinguishing genomic, gene expression and primarily epigenetic features, which could classify neuroendocrine tumors with over 99% precision and recall. This molecular classifier was validated using datasets from four other prostate cancer cohorts.
- This classifier will allow clinicians to diagnose neuroendocrine phenotypes and study clinical outcomes and therapeutic responses. This research will lead to new treatments and clinical strategies for this aggressive prostate cancer subtype.

Development of a NEPC Classifier



5

The Addition of Neoadjuvant Abiraterone Acetate to LHRHa May Have Superior Anti-Tumor Activity vs. LHRHa Alone in Localized High-Risk Prostate Cancer

- The androgen receptor (AR) is the primary driver of prostate cancer, and is therefore the primary therapeutic target. However, resistance to androgen-deprivation therapy (ADT) is common and these patients inevitably progress to lethal metastatic disease.
- Recent studies have found that alterations in the AR pathway are a common mechanism of ADT-resistance. Stronger second generation AR-targeting therapies can slow disease progression and prolong survival of castrate resistant prostate cancer (CRPC) patients. These observations have led to the hypothesis that stronger upfront inhibition of the AR pathway may improve patient outcomes.
- **PCF-funded Dr. Eleni Efstathiou** (The University of Texas MD Anderson Cancer Center) presented results from a randomized clinical trial in 65 localized high-risk prostate cancer patients that tested the addition of the second generation androgen-targeting therapy abiraterone acetate + prednisone (AA) to standard neoadjuvant ADT (LHRH agonists). Following 3 months of therapy, patients underwent radical prostatectomy and any remaining tumor tissue was molecularly and morphologically characterized.
- No new safety concerns were identified in the combination therapy arm.
- The AA+ADT arm exhibited superior clinical activity by three measurements of residual tumor size in prostatectomy specimens: tumor volume, tumor cell density, and tumor epithelium volume (tumor volume x tumor cell density).
- Resistance to AA+ADT, as indicated by a larger residual tumor size, was associated with higher expression of the constitutively active AR variant, AR-V7, and the glucocorticoid receptor (GR). Both of these molecules are able to induce expression of AR-targeted genes in an androgen-independent fashion and are known androgen-therapy resistance mechanisms.
- Longer follow up will allow determination of the effects of AA+ADT on metastasis and overall survival, but these early trial results indicate that earlier & stronger androgen-axis suppression may benefit patients.

5

The Addition of Neoadjuvant Abiraterone Acetate to LHRHa May Have Superior Anti-Tumor Activity vs. LHRHa Alone in Localized High-Risk Prostate Cancer

Residual Tumor Quantification

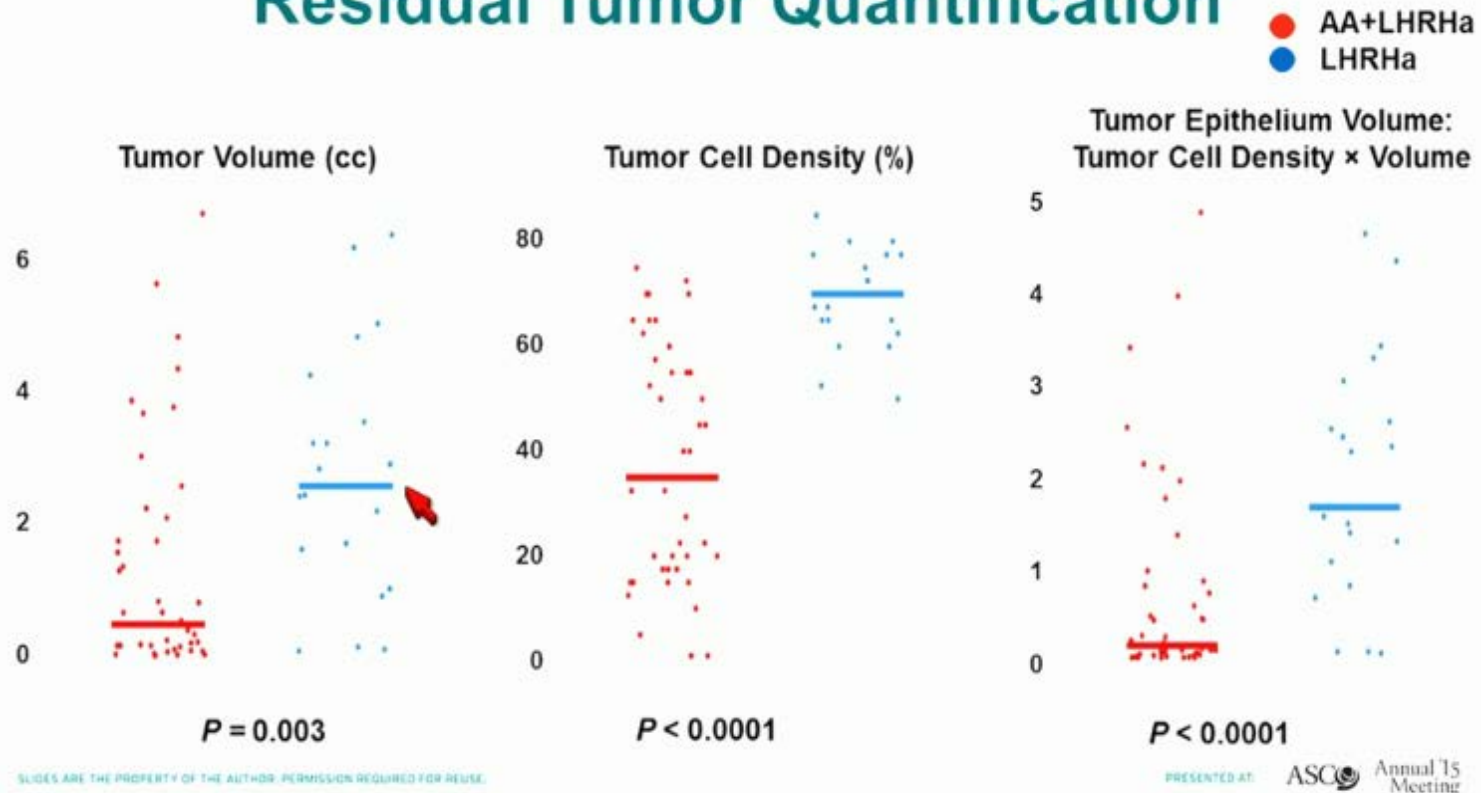


Figure: AA+ADT arm exhibited superior clinical activity vs. ADT alone by three measurements of residual tumor size in prostatectomy specimens: tumor volume, tumor cell density, and tumor epithelium volume.

6

Genomic Analysis of Circulating Cell-free DNA Identifies Mechanisms of Primary and Acquired Resistance to Enzalutamide in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

- Understanding the mechanisms underlying therapeutic resistance is critical for designing new therapies and treatment strategies for prostate cancer patients.
- Cell-free tumor DNA (cfDNA) can be obtained from patient blood as a minimally-invasive strategy for recurrently profiling the genomic alterations that occur as tumors progress.
- **Dr. Arun Azad** (BC Cancer Agency, Vancouver, Canada) and colleagues assessed genomic alterations in cfDNA from metastatic castrate resistant prostate cancer (mCRPC) patients prior to and following the development of resistance to treatment with enzalutamide.
- Poorer median progression-free survival (mPFS) in response to enzalutamide was associated with pre-existing copy-number amplifications of the oncogenes AR, MYC and MET, mutations in AR, or copy-number losses of the tumor-suppressor gene RB1.
- Ten of 44 patients acquired new copy-number changes during enzalutamide treatment. Acquired AR or MYC amplifications or RB1-loss were associated with poorer mPFS during treatment with enzalutamide. Five patients acquired new AR mutations during enzalutamide treatment and also had significantly reduced mPFS.
- Ongoing studies are assessing tumor genomic alterations in patients enrolled in clinical trials with other therapies. These studies will lead to the establishment of Precision Medicine treatment models, in which tumor genomic profiles are used to select treatments most likely to provide benefit and avoid treatments for which benefit is unlikely.

6

Genomic Analysis of Circulating Cell-free DNA Identifies Mechanisms of Primary and Acquired Resistance to Enzalutamide in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

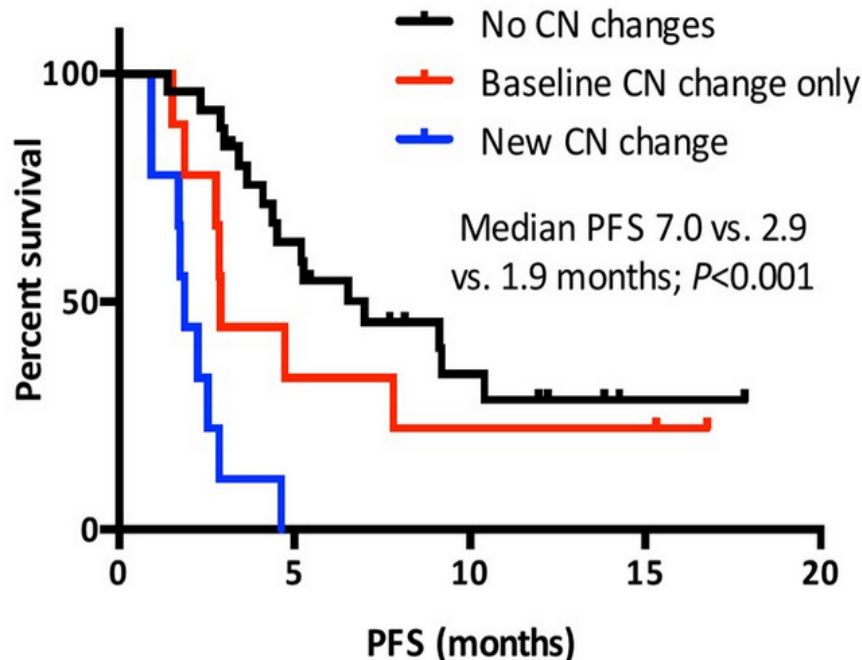


Figure 2: Kaplan-Meier analysis of clinical +/- radiographic PFS on ENZ stratified by CN status

Figure: Copy number (CN) changes (baseline or acquired) were associated with poorer mPFS during treatment with enzalutamide.

7

Validation of a Genomic Classifier that can Distinguish Patients for Whom SRT is Likely Sufficient from Those Who Have a High Risk for Metastasis and Should Consider Additional Therapy

- Biochemical recurrence of prostate cancer following prostatectomy (rising PSA levels) could indicate either local or metastatic recurrence. While salvage radiation therapy (SRT) may be sufficient to treat local recurrence, the addition of androgen deprivation therapy (ADT) provides better outcomes for patients who develop metastatic recurrences.
- Various risk-stratification tools have been developed to identify patients who are at a greater risk for recurrence and are more likely to benefit from ADT.
- The **Decipher Genomic Classifier** (GC) is a validated metastasis risk prediction test that analyses the expression of 22 genes in prostate tumor tissue and derives a score for the risk of developing metastases within 5 years of radical prostatectomy.
- **PCF Young Investigator Dr. Robert Den** (Thomas Jefferson University) and colleagues compared GC with two other risk-classification tools (CAPRA-S and Briganti) for their ability to predict which patients will vs. won't develop metastases from a cohort that received SRT following radical prostatectomy.
- The GC was superior to the CAPRA-S and Briganti methods in sensitivity and specificity for identifying patients at risk for metastatic recurrences. Patients with a low GC score had an excellent prognosis with SRT alone, while patients with a high GC score had a high likelihood of metastasis and SRT failure.
- In summary, these results indicate that the Decipher Genomic Classifier is an effective tool that will enable clinicians to distinguish patients for whom SRT is likely sufficient from those who have a high risk for metastasis and are most likely to benefit from SRT plus additional therapy.

7

Validation of a Genomic Classifier that can Distinguish Patients for Whom SRT is Likely Sufficient from Those Who Have a High Risk for Metastasis and Should Consider Additional Therapy

c. Genomic Classifier (GC)

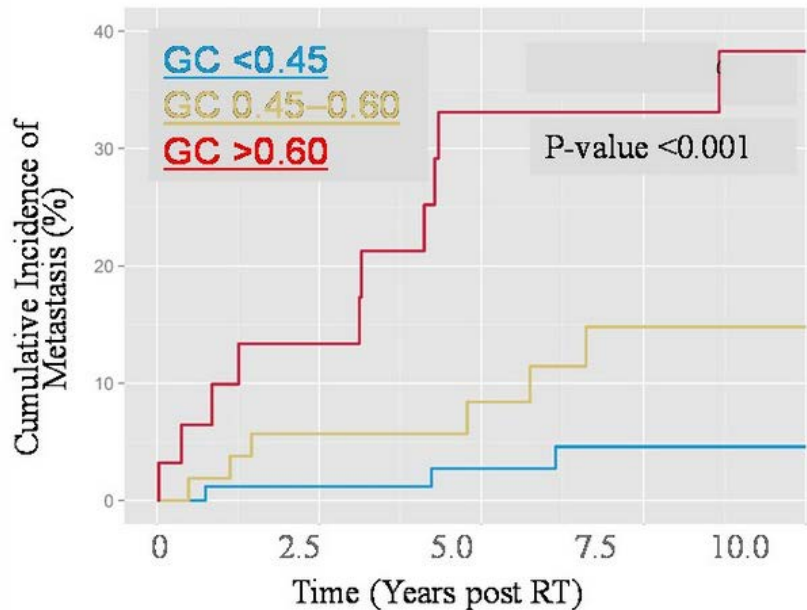


Figure: Patients with a low GC score had an excellent prognosis with SRT alone, while patients with a high GC score had a high likelihood of metastasis and SRT failure.

GC > 0.60	31	14	5
GC 0.45-0.60	53	27	11
GC < 0.45	86	50	21
		Patients at risk	

Cumulative incidences of metastasis for GC low, average and high groups 5 years post-RT: 2.7%, 8.4% and 33.1%, respectively

8

Statin Use at the Time of Initiation of Androgen Deprivation Therapy Delays Time to Progression in Patients with Hormone-Sensitive Prostate Cancer

- The cell membrane transport molecule SLCO2B1 enables cells to take up a variety of compounds including statins and the androgen precursor DHEAS.
- Expression of SLCO2B1 increases as prostate tumors progress and genetic variants of SLCO2B1 have been associated with time to progression. These studies indicate that uptake of DHEAS by cells via SLCO2B1 plays an important role in prostate cancer progression.
- **PCF Young Investigator Dr. Lauren Harshman** (Dana-Farber Cancer Institute, Harvard Medical School) and colleagues hypothesized that the use of **statins** may boost the efficacy of androgen deprivation therapy (ADT) by competing with DHEAS for SLCO2B1 uptake and thereby further limiting the amount of androgens available to fuel prostate cancer cells.
- In a retrospective analysis of 926 analyzable patients who initiated ADT between 1996 and 2013, statin use at the time of ADT initiation was associated with a significantly increased median time to progression on ADT (27.5 months for statin users vs. 17.4 months for non-statin users). These differences were observed regardless of whether patients had radiographic evidence of metastasis or only biochemical relapse at the time of ADT initiation.
- ***These results require validation in a prospective study and further studies are needed to definitively define the mechanisms involved. Nevertheless, statins have an established safety profile and may be an effective anti-cancer therapeutic in combination with ADT***

