Hormonal therapy in Carcinoma Prostate
Prostate Cancer-Burden

- 2nd most frequent cancer and 5th leading cause of cancer death in men.

- 2nd leading site of cancer among males in Indian cities like Delhi, Kolkata, Pune.²

- Hormonal therapy is the mainstay of treatment for men with prostate Ca

Global cancer statistics 2018
Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A.

Hormonal therapy - how is it effective?

Androgen Production and Action

LHRH → Anterior Pituitary → LH → Testis

90% Testosterone

5α reductase → DHT → AR → DNA → Prostate cancer cell

10% Testosterone

Adrenal gland → steroids → conversion
Hormonal therapy - how is it effective in Ca Prostate?

Androgen Deprivation

LHRH

Anterior Pituitary

LH

Testis

90% Testosterone

10% Testosterone

Prostate cancer cell

steroids

conversion

conversion

conversion
Androgen Deprivation in Ca Prostate - the discovery!

In 1940-50s Dr Charles Huggins discovered orchiectomy leads to significant reduction in Prostate Ca. Nobel Prize in 1966

Schally discovered structure of LHRH, developed LHRH agonists, demonstrated decreased testosterone levels with daily doses; Nobel Prize in 1977
Strategies of Androgen Deprivation

**SURGICAL CASTRATION**

- Orchietomy

**MEDICAL CASTRATION**

- Inhibition of LHRH / LH release
- Ablation of androgen sources
- Inhibition of androgen synthesis
- Antiandrogens
Strategies for Androgen Deprivation

- Estrogens
- LHRH Antagonists
- LHRH Agonists
- Anterior Pituitary
- LH
- Testis
- Surgical Castration
- Adrenal gland
- Steroids
- Conversion
- Nonsteroidal antiandrogen

Conversion:
- 5α Reductase
- DHT
- AR → DNA

Testosterone Levels:
- 90% T
- 10% T

Finasteride
Orchiectomy (Surgical Castration)

• Bilateral orchiectomy quickly reduces circulating testosterone levels to castration level (less than 50 ng/dL)

  ➤ Simple procedure
  ➤ Compliance not a problem
  ➤ No flare
  ➤ Nonreversible
  ➤ Carries significant psychological burden
Inhibition of LHRH / LH release

- LH-RH agonists
  - Leuprolide, Goserelin, Triptorelin, Histrelin

Desensitization of LH-RH receptor in Anterior Pituitary after chronic exposure to LHRH

**Testosterone flare** - Coadministered with antiandrogens for 2-3 weeks
LH-RH Antagonists

- Competitive inhibitors of LHRH
  - No testosterone flare (no need for antiandrogen coadministration)
  - Rapid Onset
  - Persistent suppression.
  - When rapid fall in testosterone is desired like bladder outlet obstruction, spinal cord compression, then LHRH antagonist preferred

https://www.urotoday.com/
<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Route</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goserelin acetate implant</td>
<td>Zoladex</td>
<td>S/C</td>
<td>3.6mg every month 10.8mg every 3 months</td>
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<tr>
<td>Leuprolide acetate depot</td>
<td>Lupron Depot</td>
<td>IM</td>
<td>7.5mg every month 22.5mg every 3 months 30mg every 4 months</td>
</tr>
<tr>
<td>Leuprolide acetate injectable</td>
<td>Eligard</td>
<td>S/C</td>
<td>7.5mg every month 22.5mg every 3 months 30mg every 4 months 45mg every 6 months</td>
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<tr>
<td>Histrelin implant</td>
<td>Vantas</td>
<td>S/C</td>
<td>50mg yearly</td>
</tr>
<tr>
<td>Leuprolide acetate implant</td>
<td>Viadur</td>
<td>S/C</td>
<td>65mg yearly</td>
</tr>
<tr>
<td>Triptorelin pamoate injectable</td>
<td>Trelstar Depot</td>
<td>IM</td>
<td>3.75mg every month 11.25mg every 3 months</td>
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<tr>
<td>Abarelix</td>
<td>Plenaxis</td>
<td>IM</td>
<td>100mg on Day 1,15, 29 followed by 100mg 4 weekly</td>
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<tr>
<td>Degarelix</td>
<td>Firmagon</td>
<td>S/C</td>
<td>240 mg once f/b 80 mg per month</td>
</tr>
</tbody>
</table>
• GnRH agonists vs. antagonists

(Crawford, J Urol, 2011)
Inhibition of androgen synthesis

- Aminoglutethimide
- Ketoconazole
- Abiraterone
Inhibition of androgen synthesis

- **Aminoglutethimide**
- **Ketoconazole**
- **Abiratirone**

- **Aromatase inhibitor**
  - Cholesterol $\rightarrow$ Pregnenolone
  - “Medical adrenalectomy”
  - Required glucocorticoid + mineralocorticoid Rx with high side effect profile
Inhibition of androgen synthesis

- Aminoglutethimide
- **Ketoconazole**
- Abiraterone

- **Antifungal and Cytochrome P-450 inhibitor**
  - Blocks cholesterol side chain cleavage
  - Blocks 17,20 desmolase in DHEA synthesis
- Requires hydrocortisone Rx
- AEs: GI distress, hepatotoxicity, and medication interactions
- CRPC
Inhibition of androgen synthesis

- Aminoglutethimide
- Ketoconazole
- Abiraterone

- Potent, selective inhibitor of Cytochrome P-17A
  - Inhibits 17-alpha-hydrolase and 17,20-lyase
  - Causes increased ACTH and increase in mineralocorticoids → Requires prednisone Rx

- Very effective androgen suppression (T<1ng/mL)
- AEs: Hypertension, hypokalemia, fluid retention
Antiandrogens

- Cyproterone acetate
- Flutamide
- Nilutamide
- Bicalutamide
- Enzalutamide
- Apalutamide

- Steroidal competitive AR-antagonist
- Lowers testosterone through central inhibition of GnRH via activation of progesterone receptor
- Severe cardiovascular complications (up to 10%)
Antiandrogens

- Cyproterone acetate
- Flutamide
- Nilutamide
- Bicalutamide
- Enzalutamide
- Apalutamide

- **Non-steroidal competitive AR antagonists**
  - Raise T levels by 1.5x
  - T→estradiol = gynecomastia and breast pain (up to 70%)
  - Partial agonist activity
  - Generally inferior as monotherapy to other forms of surgical or pharmaceutical castration
Antiandrogens

- Enzalutamide/Apalutamide- Non-competitive AR antagonist

1. Enzalutamide inhibits AR-testosterone binding with higher affinity than bicalutamide
2. Enzalutamide receptor inhibition blocks the activational change induced by AR-testosterone binding
3. Enzalutamide inhibits AR-testosterone nuclear translocation and DNA transcription
4. Enzalutamide lacks partial AR agonist activity that occurs with bicalutamide resistance
Adverse effects of androgen deprivation therapy (ADT). Inside the dotted line represents metabolic effects of ADT. DM, diabetes mellitus.

https://www.researchgate.net/
Adverse Effects: Osteoporosis

- Bone loss on ADT
  - Baseline ~50% osteopenic/osteoporotic
  - ADT causes increased bone turnover, decreased mineral density, increased risk of fractures
  - +21-54% RR of fracture

- Screening
  - Baseline DEXA scan

- Treatment
  - Exercise
  - Calcium + Vit D3 Supplementation
  - Bisphosphonates or denosumab (RANK-L inhibitor) if high fracture risk
Indication/Timing of ADT?

Whom to give

- **Low Risk** – No role

- **Intermediate risk** – NAHT + Conc + Adjuvant (short course 4-6 months)

- **High risk** – NAHT + Conc + Adjuvant (long course 2-3 years)

- **N1M0 disease** – EBRT + long term ADT + Abiraterone

- **Recurrence after RT or Surgery**

- **Metastatic** – Long term ADT + Abiraterone/Doce/Enzalutamide/Apalutamide
ADT for low risk localized Ca prostate

- Lu-Yao, JAMA Internal Med, 2014
  - SEER-Medicare analysis of 66,717 men
  - Diagnosed with T1-T2 CaP and started on primary ADT
  - No improved 15 years DSS or OS
ADT for intermediate risk localized Ca Prostate

• Short term ADT with RT improves OS

Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991

Michel Bolla, Philippe Maingon, Christian Carrie, Salvador Villa, Petros Kitsios, Philip M.P. Poortmans...

• 75% of the study population was intermediate risk
• Six months of concomitant and adjuvant AS improves biochemical and clinical DFS of intermediate- and high-risk cT1b-c to cT2a
# EAU guidelines

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Recommendation</th>
<th>Strength rating</th>
<th>Clinical trial</th>
<th>Drug used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate risk disease</td>
<td>For external-beam radiation therapy (EBRT), use a total dose of 76-78 Gy, in combination with short-term neoadjuvant plus concomitant androgen deprivation therapy (ADT) (four to six months).</td>
<td>Strong</td>
<td>Jones et al 2011*</td>
<td>Goserelin &amp; Leuprolide</td>
</tr>
<tr>
<td></td>
<td>In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.</td>
<td>Weak</td>
<td>Krauss et al 2010**</td>
<td>Investigator choice</td>
</tr>
</tbody>
</table>

In patients with high-risk localised disease, use external-beam radiation therapy (EBRT) with 76-78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).

**Trials:** RTOG 9202  
EORTC 22863  
RTOG 8531
RTOG 9202 Trial

- Group 1: 4 months ADT before and during RT
- Group 2: 4 months ADT before and during RT followed by 2 years of ADT
- Subgroup: GS 8-10, OS benefit

![Graphs A, B, C, and D showing disease-specific survival, distant metastasis failure, biochemical failure, and overall survival for all eligible patients. STAD, short-term androgen-deprivation therapy; LTAD, long-term androgen-deprivation therapy; RT, radiotherapy.](image-url)
EORTC 22863 trial

- Node-negative patients with clinical stage T3 disease or T1–T2 patients with high-grade disease
- Received adjuvant ADT on the first day of radiotherapy (prescribed dose of 70 Gy) and continued for 3 years.
- The 10-year overall survival was 58% versus 40% for patients treated with ADT plus EBRT and EBRT alone, respectively ($p = 0.0004$).
## Role with Radical Prostatectomy

No role of Neoadjuvant ADT prior to radical prostatectomy

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Recommendation</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx after RP</td>
<td>Only discuss adjuvant treatment in men with a post-operative prostate-specific antigen (PSA) &lt; 0.1 ng/mL</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Do not prescribe adjuvant androgen deprivation therapy (ADT) in pN0 patients</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Discuss three management options with patients with pN+ disease after an extended lymph node dissection, based on nodal involvement characteristics:</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>1. Offer adjuvant ADT for node-positive (pN+).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Offer adjuvant ADT with additional radiotherapy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA &lt; 0.1 ng/mL and absence of extranodal extension.</td>
<td></td>
</tr>
</tbody>
</table>
ADT for M0 biochemical recurrence (BCR)

• Early vs. Delayed ADT
  • Long natural history *(Pound, JAMA, 1999)*
    • BCR – *(8 years)* → Metastasis – *(5 years)* → Death
  • Unclear effect on survival
    • Delays PSA progression but ?OS effects *(Loblaw 2007; Messing 2006)*

• Timing of ADT depends on patient and prognostic factors
  • Younger patients with rapid PSA velocity → ADT
  • Older patients with slow PSA velocity → observe
Timing of ADT Summary

Adjuvant/neoadjuvant Tx for high risk CaP

Biochemical failure without metastases

Low risk CaP primary tx

Metastatic disease

Figure 109–10. Based on available clinical trial data, the hypothetical gain or loss in overall survival based on the time in the natural history of the disease that ADT is instituted, as demonstrated by the dotted line. (Concept and figure courtesy of P. Iversen.)
ADT for M1 castration naïve prostate CA

- Gold standard for patients with metastatic disease at presentation
  - Immediate ADT seems to improve DSS, but not OS
  - Decreases symptoms and potential complications

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>Immediate ADT (n/N)</th>
<th>Deferred ADT (n/N)</th>
<th>RR (random); 95% CI</th>
<th>Weight %</th>
<th>RR (random); 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byer VACURG 1</td>
<td>139/469</td>
<td>173/484</td>
<td>19.58 0.83 (0.69 to 1.00)</td>
<td>9.5%</td>
<td>0.84 (0.75 to 0.94)</td>
</tr>
<tr>
<td>Kirk MRC PR03</td>
<td>241/469</td>
<td>287/469</td>
<td>27.26 0.84 (0.75 to 0.94)</td>
<td>15.2%</td>
<td>0.84 (0.75 to 0.94)</td>
</tr>
<tr>
<td>Studer SAKK 88-08</td>
<td>23/96</td>
<td>34/92</td>
<td>6.06 0.65 (0.42 to 1.01)</td>
<td>3.5%</td>
<td>0.65 (0.42 to 1.01)</td>
</tr>
<tr>
<td>Studer EORTC 30891</td>
<td>94/492</td>
<td>99/493</td>
<td>13.87 0.95 (0.74 to 1.23)</td>
<td>9.2%</td>
<td>0.95 (0.74 to 1.23)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1,526</td>
<td>1,538</td>
<td>66.76 0.84 (0.77 to 0.92)</td>
<td>32.7%</td>
<td>0.84 (0.77 to 0.92)</td>
</tr>
</tbody>
</table>

Total events: 497 (Immediate ADT), 593 (Deferred ADT)
Test for heterogeneity: $\chi^2 = 2.25 (P = .52)$, I$^2 = 0$
Test for overall effect: $z = 3.82 (P = .0001)$

(Loblaw, 2007 ASCO Practice Guideline Meta-Analysis, JCO)
Do we need to add anything to ADT?
CHAARTED Trial

**PATIENTS**
Stratified according to:
- Age (≥ 70 vs < 70)
- PS (0-1 vs 2)
- Duration of prior adjuvant hormonal therapy (> 12 months vs ≤ 12 months)
- Concurrent bisphosphonate use (yes vs no)
- Volume of disease (low vs high)

[Diagram showing the randomization of patients into two groups: ADT + docetaxel (n=397) and ADT alone (n=393).]

790 patients randomised
July 2006 - December 2013

**Primary:**
- OS

**Secondary:**
- Time to Clinical Progression
- Time to Castration Resistant Prostate Cancer
- Proportion of Patients With PSA Complete Response (CR) at 6 Months
- Proportion of Patients With PSA Complete Response (CR) at 12 Months
- QOL

OVERALL SURVIVAL BY EXTENT OF METASTATIC DISEASE AT START OF ADT

- 17-month benefit in median OS (from 32.2 to 49.2 months) for high volume
- We projected 33 months in ADT arm with collaboration of SWOG9346 team

ADT: androgen deprivation therapy; DOC: Docetaxel 75 mg/m²
From N Engl J Med, Sweeney C, et al., Chemoendocrine Therapy in Metastatic Hormone-Sensitive Prostate Cancer, 373, 737-46
A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Total (Total</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
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<tr>
<td>CHAARTED</td>
<td>-0.4943</td>
<td>0.133</td>
<td>397</td>
<td>393</td>
<td>32.1%</td>
<td>0.61 [0.47, 0.76]</td>
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<tr>
<td>GETUG-15</td>
<td>-0.1054</td>
<td>0.1468</td>
<td>192</td>
<td>193</td>
<td>28.8%</td>
<td>0.90 [0.67, 1.20]</td>
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<tr>
<td>STAMPEDE Docetaxel</td>
<td>-0.3147</td>
<td>0.1086</td>
<td>362</td>
<td>725</td>
<td>39.1%</td>
<td>0.73 [0.59, 0.90]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>951</td>
<td>1311</td>
<td>100.0%</td>
<td>0.73 [0.60, 0.90]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02; Chi² = 3.05, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 3.03; P = 0.002

RECOMMENDATION #1
Men with high-risk metastatic prostate cancer, especially those presenting with metastases at or soon after diagnosis, who are judged fit to receive chemotherapy, should be offered 6 cycles of docetaxel in addition to ADT

STAMPEDE: ADT + Abiraterone + Prednisolone vs ADT Alone

Randomized, open-label, multiarm, multistage phase II/III trial (N = 1917)

- **OS in Patients With Metastatic Disease**
  - HR: 0.61

- **Failure-Free Survival in Patients With Metastatic Disease**
  - HR: 0.31

Similar OS and better FFS implies better salvage RX

LATITUDE: ADT + Abiraterone + Prednisone vs ADT + Dual Placebo in Metastatic Castrate-Sensitive PC

Randomized, double-blind phase III trial in patients with newly diagnosed disease (N = 1199)

- **Overall Survival (%)**
  - Abiraterone vs Placebo
  - Hazard ratio, 0.62 (95% CI, 0.51–0.76)
  - $P < 0.001$

- **Patients without PSA Progression (%)**
  - Abiraterone vs Placebo
  - Hazard ratio, 0.30 (95% CI, 0.26–0.35)
  - $P < 0.001$

ENZAMET – Study Design

- Phase III, randomized, open-label, multicenter clinical trial
- Stratified by volume of metastases (high vs low), antiresorptive therapy (yes vs no), ECOG PS (0/1 vs 2), comorbidities (ACE-27: 0/1 vs 2/3), study site, planned use of early docetaxel (yes vs no)

- Patients with metastatic prostate cancer, starting first-line ADT (max 12 wks prior to randomization); ECOG PS 0-2; cycles prior docetaxel allowed (N = 1125)
- Enzalutamide 160 mg/day + testosterone suppression (n = 563)
  - Evaluate every 12 wks
- Standard NSAA* + testosterone suppression (n = 562)
  - Evaluate every 12 wks
  - Follow for time to progression and OS

- Primary endpoint: OS
- Secondary endpoints: PSA PFS (including clinical progression if occurring first), clinical PFS, AEs, HRQoL

* Bicalutamide, nilutamide, or flutamide

Presented By Christopher Sweeney at 2019 ASCO Annual Meeting
ENZAMET – Results

Primary endpoint: OS

Proportion alive at 36 months (95% CI)

<table>
<thead>
<tr>
<th>NSAA</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.72 (0.68 to 0.76)</td>
<td>0.80 (0.75 to 0.83)</td>
</tr>
</tbody>
</table>

Hazard ratio = 0.67 (95% CI: 0.52 to 0.86)
Log-rank p = 0.002

Number at risk

<table>
<thead>
<tr>
<th>NSAA</th>
<th>Enzalutamide</th>
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<tbody>
<tr>
<td>562</td>
<td>563</td>
</tr>
<tr>
<td>551</td>
<td>558</td>
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<td>541</td>
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<td>189</td>
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<td>86</td>
<td>106</td>
</tr>
<tr>
<td>32</td>
<td>45</td>
</tr>
</tbody>
</table>

Secondary endpoint: PFS (PCWG2)

Proportion event-free

Hazard ratio = 0.39 (0.33 to 0.47)
Log-rank p < 0.001

Number at risk

<table>
<thead>
<tr>
<th>NSAA</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
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<td>44</td>
<td>77</td>
</tr>
<tr>
<td>17</td>
<td>34</td>
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</tbody>
</table>

Hazard ratio = 0.40 (0.33 to 0.49)
Log-rank p < 0.001

Number at risk

<table>
<thead>
<tr>
<th>NSAA</th>
<th>Enzalutamide</th>
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</thead>
<tbody>
<tr>
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<tr>
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<td>96</td>
<td>156</td>
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<tr>
<td>50</td>
<td>84</td>
</tr>
<tr>
<td>17</td>
<td>36</td>
</tr>
</tbody>
</table>
ENZAMET – Conclusions

- Enzalutamide demonstrated improved survival compared with standard NSAA in patients with mHSPC
  - 36-mo OS: 80% for enzalutamide vs 72% for NSAA (HR: 0.67; \( P = .002 \))
  - Similar OS benefit in patients with low and high volume of metastases
- Increased toxicity was shown with the addition of enzalutamide, as expected
  - Patients who were also treated with docetaxel experienced more chemotherapy-related toxicity
- The study investigators concluded that enzalutamide is an appropriate option for men with mHSPC starting on ADT

Davis et al NEJM 2019
TITAN – Study Design

- International, randomized, double-blind, placebo-controlled phase III trial
  - Gleason score ($\leq 7$ vs $>7$), region (NA/EU vs other), prior docetaxel (yes vs no)

Patients with metastatic castration-sensitive prostate cancer; ECOG PS 0/1; prior ADT $\leq 6$ mos for mCSPC or $\leq 3$ yrs for local disease ($N = 1052$)

- Apalutamide 240 mg QD + ADT ($n = 525$)
- Placebo + ADT ($n = 527$)

Primary endpoints: OS, radiographic PFS
Secondary endpoints: time to pain progression, time to SRE, time to chronic opioid use, time to cytotoxic chemotherapy
Exploratory endpoints including: time to PSA progression, PFS2

Presented By Kim Chi at 2019 ASCO Annual Meeting
TITAN – Results

Blinded independent central imaging review confirmed investigator assessment of radiographic progression (concordance, 85%)

Apalutamide significantly reduced risk of rPFS or death by 52%

Apalutamide significantly reduced risk of death by 33%

Modified By Kim Chi at 2019 ASCO Annual Meeting
HOW TO CHOOSE BETWEEN UP-FRONT TREATMENTS IN mHSPC

<table>
<thead>
<tr>
<th></th>
<th>DOCETAXEL</th>
<th>ABIRATERONE</th>
<th>ENZALUTAMIDE APALUTAMIDE</th>
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<tbody>
<tr>
<td>Duration of treatment</td>
<td>Short term treatment</td>
<td>Long term treatment</td>
<td>Long term treatment</td>
</tr>
<tr>
<td>Toxicities</td>
<td>Peripheral neuropathy, hair loss</td>
<td>Liver enzymes, electrolytes</td>
<td>CNS (seizure), falls</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Use of corticosteroids</td>
<td>Use of corticosteroids</td>
<td>No use of corticosteroids</td>
</tr>
<tr>
<td>Setting</td>
<td>High volume</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

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- RT to the prostate no improvement in OS in unselected patients.
- RT did improve overall survival & FFS in those with a low metastatic burden without compromising on side effect profile.
- Can be a standard treatment in this subgroup.
- Extrapolating results from these findings-
  1. RT may improve survival in pelvic node-positive disease
  2. for prevention of symptomatic local events
# EAU Guidelines for the first-line treatment of metastatic disease

## Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
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<tbody>
<tr>
<td>Offer immediate systemic treatment with androgen deprivation therapy (ADT) to</td>
<td>Strong</td>
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<tr>
<td>palliate symptoms and reduce the risk for potentially serious sequelae of</td>
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<td>advanced disease (spinal cord compression, pathological fractures, ureteral</td>
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<tr>
<td>obstruction) to M1 symptomatic patients.</td>
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<tr>
<td>Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to</td>
<td>Weak</td>
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<tr>
<td>patients with an impending spinal cord compression or bladder outlet obstruction.</td>
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<tr>
<td>Do not offer AR antagonists monotherapy to patients with M1 disease.</td>
<td>Strong</td>
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<tr>
<td>Offer ADT combined with chemotherapy (docetaxel) to patients whose first</td>
<td>Strong</td>
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<tr>
<td>presentation is M1 disease and who are fit for docetaxel.</td>
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<tr>
<td>Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or</td>
<td>Strong</td>
</tr>
<tr>
<td>enzalutamide to patients whose first presentation is M1 disease and who are</td>
<td></td>
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<tr>
<td>fit enough for the regimen.</td>
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<tr>
<td>Offer ADT combined with prostate radiotherapy to patients whose first</td>
<td>Strong</td>
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<tr>
<td>presentation is M1 disease and who have low volume of disease by CHAARTED</td>
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<tr>
<td>criteria.</td>
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<tr>
<td>Do not offer ADT combined with any local treatment</td>
<td>Strong</td>
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<tr>
<td>(radiotherapy/surgery) to patients with high volume (CHAARTED criteria) M1</td>
<td></td>
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<tr>
<td>disease outside of clinical trials (except for symptom control).</td>
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</table>

[https://uroweb.org/guideline/prostate-cancer/#6](https://uroweb.org/guideline/prostate-cancer/#6)
ADT use in COVID era: NCCN Recommendation

1. First level

- Prophylactic whole pelvic radiation therapy (WPRT) should be avoided during this time due to the increased risk of grade IV lymphopenia.

What is to be avoided

- Patients with very low, low, and favorable intermediate risk (IR) disease should not undergo further staging, active surveillance, confirmatory testing/monitoring, and treatment until deemed safe.

- For patients with non-metastatic disease, avoid initiating androgen deprivation therapy (ADT) for patients with a prostate-specific antigen (PSA) doubling time of >9 months.

- Once ADT is initiated or intermittent ADT is started, consider remote telehealth visits and PSA/testosterone and other laboratory monitoring to avoid clinic exposures.
Patients with asymptomatic unfavorable intermediate risk (UIR), high risk, and very high risk (HR) prostate cancer can defer further staging and radical treatment until deemed safe.

Neoadjuvant ADT should be considered in asymptomatic UIR and HR patients planning to receive definitive radiation therapy (RT). This may safely be given for up to 4-6 months as necessary.

Individuals who have received definitive treatment for their cancer with either radiation or surgery could defer initial post-treatment monitoring (PSA-based testing and digital rectal exam [DRE]) until deemed safe.

Data from Johns Hopkins suggest delaying surgical treatment for UIR and HR patients upwards of 6 months from biopsy diagnosis will not negatively impact their outcome.
**Shorten or reduce**

- **Consideration to use 3-, 4-or 6-month formulations of ADT should be preferred over 1-month injections.**

- **For symptomatic patients, conservative measures should be prioritized (e.g., medical therapy, ADT, clean intermittent catheterization). If necessary, surgical intervention or RT may be considered.**

- **If it is deemed safe for patients to receive RT, the shortest safe external beam RT (EBRT) regimen should be used. This can consist of 5 to 7 fractions, consistent with current NCCN Guidelines.**
Conclusion

• Hormonal therapy is a highly effective initial systemic therapy for Prostate cancer

• It is a low toxicity treatment but there are impacts on QOL

• ADT shows benefit in all 3 stages of prostate cancer (localized, locally advanced, metastatic) with an extensive safety and efficacy data

• Choice of drug depends on treatment cost, dosing, speed of onset, safety and tolerability, clinician experience and patient’s wish
THANK YOU