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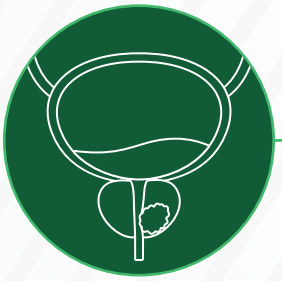
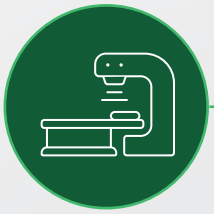
# Biomarkers for the Prediction of Disease Progression, Prognosis, and Treatment Response of Metastatic Prostate Cancer

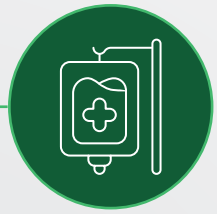


**Advances in the diagnosis and treatment of prostate cancer over the last 25 years have improved patient survival[1]**

**Radiation therapy (RT)**

- HORRAD, STAMPEDE





**Chemotherapy with docetaxel**

- CHAARTED, STAMPEDE

**In addition to androgen deprivation therapy (ADT), several other clinical trials have demonstrated the safety and efficacy of various treatments for patients with localised or metastatic hormone-sensitive prostate cancer (mHSPC)[2–11]**

**Androgen receptor (AR) signalling inhibitors**

- Abiraterone - LATITUDE, STAMPEDE
- Enzalutamide - ENZAMET, ARCHES
- Apalutamide - TITAN

**Triplet therapy (add-on to ADT + docetaxel)**

- Abiraterone - PEACE-1
- Darolutamide - ARASENS

**However, heterogeneity in the clinical features of prostate cancer has necessitated a shift towards individualising treatment approaches according to disease presentation[1]**

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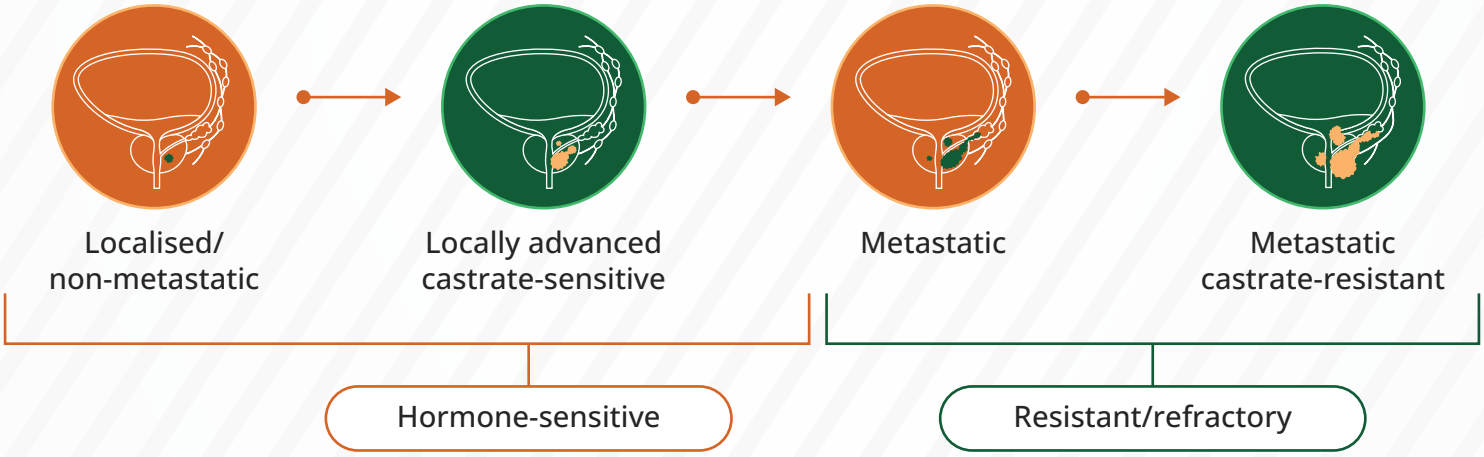
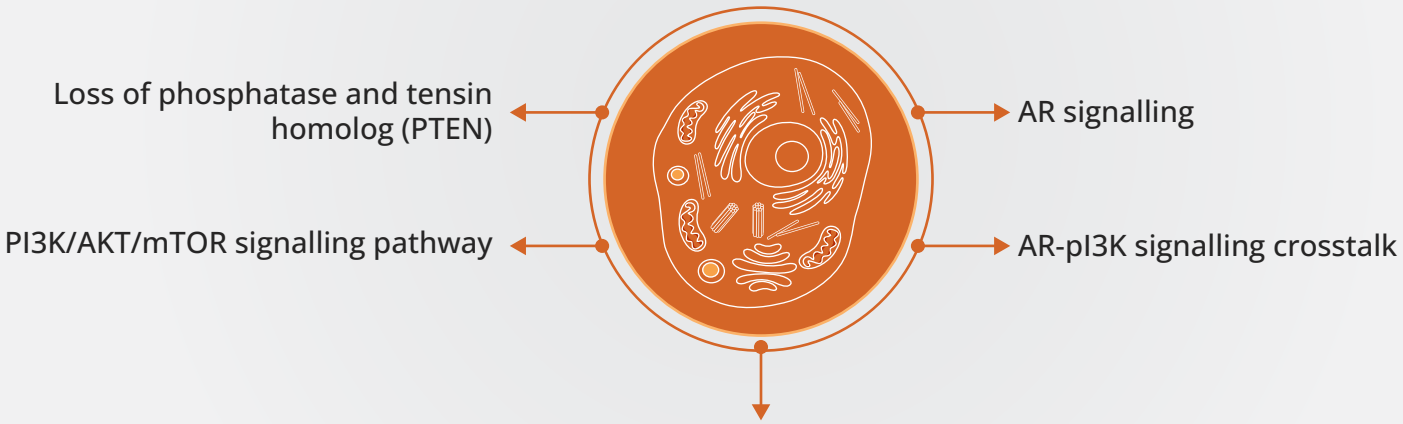
## Stages in the advancement of prostate cancer[12]




## Signalling pathways involved in prostate cancer progression[13]

Patients who initially respond well to ADT may subsequently develop resistance due to deregulation of the following pathways




**Patients with mHSPC who harbour genetic alterations have a poorer prognosis following surgery or RT[13]**

**Biomarker screening can help evaluate patient prognosis and treatment response**

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# Prognostic biomarkers

### Patient-centred factors[14]

- Age
- Haemoglobin
- Performance status
- Alkaline phosphatase

### Tumour-related factors[14]

- Gleason index
- Disease volume
- Metastases/visceral disease

### Serum factors[14,15]

- Lactate dehydrogenase
- Prostate-specific antigen (PsA)

| PSA levels ng/dL | Median overall survival (years) |
|---|---|
| ≤0.2 | 6.6 |
| 0.2–4 | 4.3 |
| ≥4 | 1.8 |

# Predictive biomarkers

### Imaging features[16,17]

Prostate-specific membrane antigen (PSMA) is over-expressed in prostate cancer cells

PSMA PET imaging is a highly specific technique used for the diagnosis of prostate cancer and metastasis

PSMA PET functions as a predictive biomarker of prognosis following RT and treatment with lutetium ($^{177}$Lu) vipivotide tetraxetan ($^{177}$Lu-PSMA-617), which targets PSMA

**Genetic alterations** such as mutations in the *BRCA* gene and loss of PTEN are associated with poorer prognosis and resistance to treatment[1,18,19]

### Transcriptomic profile[20]

- Cancers with distinct transcriptomic signatures may have variable susceptibility to specific treatments
- Docetaxel + ADT versus ADT alone has been shown to improve overall survival in the luminal B cancer subtype only

# Artificial intelligence and machine learning-based predictive models[21]

ArteraAI is a unique multimodal artificial intelligence (MMAI) biomarker test designed to analyse images from patient's biopsy and clinical data

**Advantages**

- Risk assessment and stratification of patients who are likely to benefit from short-term ADT
- Decrease in the use of intensive treatments and associated adverse effects
- Prediction of the disease's progression and likelihood of metastasis, prognosis, and treatment response

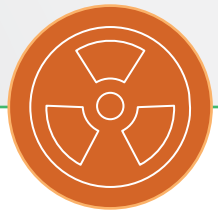
# Effect of combinatorial therapies

**Addition of docetaxel to ADT provides a 9%–11% survival benefit to patients with poorer prognosis[2,3]**

- ! Higher tumour volume
- ! >4 bone or visceral metastases

The risks of docetaxel treatment may outweigh its benefits in patients with smaller tumour volumes[2,3]

Addition of RT to docetaxel with or without abiraterone does not significantly improve patients' overall survival[11,16]



RT has been shown to benefit patients with localised cancer or *de novo* mHSPC with a low metastatic burden[11,16]

## Therapies under investigation for patients with genetic aberrations[12,13]

- pI3K inhibitors – sonolisib, buparlisib, p110 isoform-specific inhibitors
- AKT inhibitor – uprosertib, ipatasertib
- mTORC1 inhibitors – everolimus, AZD8055, INK128
- Dual pI3K/mTOR inhibitors

## Ongoing clinical trials

- KEYNOTE-991 - ADT + enzalutamide ± pembrolizumab
- CAPItello-281 - ADT + abiraterone acetate ± capivasertib
- CYCLONE-3 - ADT + abiraterone acetate ± abemaciclib
- PSMAddition - ADT ± $^{177}$Lu-PSMA-617
- TALAPRO-3 - Enzalutamide ± talazoparib
- AMPLITUDE - Abiraterone + prednisone ± niraparib

**An individualised treatment approach, which accounts for disease-specific factors, may help improve the survival of patients with mHSPC. Assessment of prognostic biomarkers can help predict the risk of progression, treatment response, and patient outcomes**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