

EMJ

European Medical Journal

Volume 12 Supplement 2
October 2024
emjreviews.com

Symposium Review

The Androgen Deprivation Therapy Landscape in 2024 – Co-navigating the Available Options with Prostate Cancer Patients

This promotional article was funded by Accord Healthcare Ltd.
and it is intended for healthcare professionals only.

EUR-Onc-Org-01413 | October 2024



Urology
Supplement



The Androgen Deprivation Therapy Landscape in 2024 – Co-navigating the Available Options with Prostate Cancer Patients

This industry symposium took place on 5th April 2024 during the 39th Annual European Association of Urology (EAU) Congress in Paris, France

Chairpersons:	Eva Hellmis, ¹ Amit Bahl ²
Speakers:	Amit Bahl, ² Andrew Gabriel, ³ Romain Mathieu ⁴
	<ol style="list-style-type: none"> 1. Urologicum Duisburg, Germany 2. Bristol Cancer Institute, University Hospitals Bristol, UK 3. Hampshire, UK 4. Centre Hospitalier Universitaire (CHU) Pontchaillou, Rennes, France
Disclosure:	Hellmis has received honoraria for consultancy or participation in advisory boards from Accord Healthcare, Apogepha, Astellas Pharma, AstraZeneca, Bayer Vital, Bristol Myers Squibb, Eisai, Hexal, Ipsen, Janssen (now Johnson & Johnson Innovative Medicine), Merck, MSD, Novartis, Orion Pharma, Pfizer, Roche, and Takeda Pharmaceuticals. Bahl has received honoraria and sponsorship for attending meetings and advisory boards from Accord Healthcare, Advanced Accelerator Applications (AAA), Amgen, Astellas Pharma, Bayer, Ipsen, Janssen (now Johnson & Johnson Innovative Medicine), MSD, Novartis, and Sanofi Genzyme; and research grants (paid to institution) from Bayer, Janssen, and Sanofi Genzyme. Gabriel is a consultant to Accord Healthcare. Mathieu has received honoraria for consultancy, conferences, or participation in advisory boards from Accord Healthcare, AAA, Astellas Pharma, AstraZeneca, Bayer, Ferring Pharmaceuticals, Ipsen, Janssen (now Johnson & Johnson Innovative Medicine), MSD, Pfizer, and Viatrix; and institutional funding for work in clinical trials/contracted research from Astellas Pharma and Janssen (now Johnson & Johnson Innovative Medicine).
Acknowledgements:	Medical writing assistance was provided by Jennifer Taylor, London, UK.
Disclaimer:	The opinions expressed in this article belong solely to the named speakers. ORGOVYX (relugolix) is indicated for the treatment of adult patients with advanced hormone-sensitive prostate cancer. If you are a HCP in the EU, prescribing information can be found here . If you are a GB HCP, prescribing information can be found here .
Keywords:	Adverse events, androgen deprivation therapy (ADT), prehabilitation, prostate cancer (PCa), prostate-specific antigen (PSA).
Citation:	EMJ Urol. 2024;12[Suppl 2]:2-11. https://doi.org/10.33590/emjurol/JVPT6691 .
Support:	The publication of this article was funded by Accord Healthcare. The views and opinions expressed are exclusively those of the speakers.



Adverse events should be reported. For UK healthcare professionals, reporting forms, and information can be found at <https://yellowcard.mhra.gov.uk/>.

Adverse events should also be reported to Accord-UK LTD on 01271 385257 or email medinfo@accord-healthcare.com.

For non-UK/EU healthcare professionals, you can report side effects directly via the national reporting system listed in Appendix V of the EU SmPC.



Meeting Summary

This symposium convened during the 2024 European Association of Urology (EAU) Congress in Paris, France, focusing on the multifaceted aspects of prostate cancer (PCa) treatment from the patient's perspective. The session delved into the nuanced needs, expectations, and treatment experiences encountered by individuals diagnosed with this condition. A pivotal aspect of the discussion centred on the imperative of ensuring patient awareness and informed consent, particularly concerning androgen deprivation therapy (ADT), given its array of potential side effects. ADT, a cornerstone in advanced PCa management, encompasses a spectrum of side effects including both physical and psychological dimensions. These include, but are not limited to, body hair loss, weight fluctuations, mood alterations, decreased libido, cognitive impairments, muscle atrophy, and bone density loss. Effective management of these side effects requires comprehensive support to be provided to patients to mitigate complications and optimise quality of life. The options for ADT were discussed, with their comparative strengths and challenges. ADT strategies take effect over different time periods (from 12 hours up to 4 weeks), exert varying effects on testosterone levels, and carry different side effect profiles. Selecting the optimal course of treatment for localised or locally advanced PCa requires consideration of whether the patient is at intermediate-, high-, or very high-risk of biochemical recurrence, and whether the intermediate-risk disease is classified as favourable intermediate-risk (FIR) or unfavourable intermediate-risk (UIR). While continuous ADT is the standard of care, intermittent ADT has been associated with significantly better quality of life scores for hot flashes, desire for sexual activity, and urinary symptoms, with a trend toward improvement in the level of fatigue. Furthermore, the interplay between PCa, ADT, and cardiovascular disease (CVD) was discussed to underscore the imperative for clinicians to assess the cardiovascular risks associated with ADT, particularly in patients with heightened cardiovascular vulnerability. Mitigating the adverse skeletal effects of ADT mandates a multifaceted approach encompassing nutritional supplementation, exercise regimens, and lifestyle modifications including alcohol cessation and smoking cessation. Integrating a prehabilitation checklist into clinical practice emerges as a pragmatic strategy to facilitate informed discussions regarding the potential adverse effects of ADT, enabling proactive support provision to optimise patient outcomes.

Introduction

Amit Bahl, Eva Hellmis

The objectives of this symposium were to improve attendees' knowledge on ADT, including the different therapeutic options available; to allow attendees

to gain a deeper understanding of the patient perspective on treatment, including patient needs and expectations, and the importance of empowerment; and to help attendees communicate more effectively with their patients to facilitate decision-making.

ADT in 2024: What Do Our Patients Expect?

Andrew Gabriel

Gabriel described his experience of being diagnosed and treated for PCa. In 2018, aged 56, with no symptoms or family history of the condition, he underwent a prostate-specific antigen (PSA) test at a local charity. It took nearly 6 months to receive a full diagnosis of PCa (Gleason score 3+4; Stage T3aN0M0), during which he underwent ADT with bicalutamide to pause progression during diagnosis.

In 2019, Gabriel chose to undergo radiotherapy (RT) in the form of a high-dose-rate boost comprising a combination of external beam RT and one session of high-dose-rate brachytherapy. His ADT was changed to a gonadotropin-releasing hormone (GnRH) agonist, which he took for nearly 2 years. PSA levels were nearly 58 ng/mL at diagnosis, dropping to 0.12 ng/mL after 5 months of neoadjuvant GnRH agonist ADT, and remaining <0.01 ng/mL from the RT until after testosterone recovery. Testosterone levels remained <0.4 nmol/L (<11 ng/dL) during GnRH agonist therapy. Approximately 1 year after completing the course of GnRH agonist, testosterone levels returned to within the normal range while PSA rose slightly to 0.03–0.04 ng/mL.

Gabriel believes that ADT can be a complicated treatment for some patients to understand, and often there is a lack of patient awareness and informed consent. He outlined that a comprehensive list of questions would include: 1) Why is this treatment recommended? 2) What are the benefits? 3) What are the drawbacks? 4) What are the side effects? 5) Do I have a choice? 6) Can I stop if I don't like the side effects? However, discussing all of these questions would require a lengthy conversation that would generally be too long for a clinic consultation. Consequently, he questioned whether patients have genuinely provided informed consent for ADT, considering the depth and breadth of information typically required for such a decision.

ADT is associated with a number of potential side effects, ranging from physical to psychological manifestations. These include common discomforts such as hot flushes, night sweats, and loss of libido, alongside more pronounced challenges like fatigue, erectile dysfunction, and breast tissue growth or tenderness.^{1,2} Metabolic disturbances, typified by weight gain, elevated blood pressure, blood glucose, and cholesterol levels, also frequently accompany ADT administration.^{1,2} Moreover, patients may contend with cognitive and emotional fluctuations, including memory impairment, mood disturbances, and depression. Additional side effects encompass osteopenia/osteoporosis, dry skin, brittle fingernails, itching, anaemia, and dyspnoea.^{1,2}

Hot flushes are a predominant symptom reported by patients undergoing ADT, albeit they are typically manageable. A range of prescribed medications and complementary therapies exist to alleviate this discomfort, underscoring the importance of open discussion with a physician regarding available options.³ By proactively addressing hot flushes through tailored interventions, clinicians can enhance patient comfort and quality of life amidst ADT treatment.

Effective support mechanisms are indispensable for navigating the side effects associated with ADT. Often, patients are unaware of proactive measures they can undertake to safeguard their health, such as engaging in regular exercise. Peer support groups offer a valuable platform for exchanging strategies aimed at mitigating potential complications like gynaecomastia, osteoporosis, and metabolic syndrome, as well as preserving penile health in the absence of natural erections. Additionally, intimacy and relationship support services can provide vital assistance to individuals contending with the impact of ADT on their personal lives, fostering coping strategies, and bolstering overall well-being.

Maintaining penile health in the absence of natural erections is paramount, particularly given that only approximately 20% of men undergoing ADT can achieve erections on demand.⁴ The lack of testosterone

and regular erections may precipitate the deterioration of penile smooth muscle and nerves, potentially leading to fibrosis of the corpus cavernosum.⁵ While the changes can be irreversible, they may be prevented with penile rehabilitation during ADT to achieve regular erections (Gabriel A, personal communication). A vacuum erection device can be used to induce erections, while medications should be discussed with a healthcare professional.

Gynaecomastia is most common with anti-androgen-only ADT, may manifest with mastodynia, and can also occur with GnRH analogue medications.² Breast gland growth is avoidable in most cases, but usually irreversible afterwards. Healthcare providers (HCP) should communicate preventative options with patients to mitigate concerns.

Regarding the metabolic syndrome, a lack of testosterone often causes rises in blood pressure, glucose, and cholesterol, with reduced function of high-density lipoprotein cholesterol.^{1,2} In addition, there can be an increase in body fat, including visceral fat.^{1,2} Gabriel suggested that patients undergoing ADT should receive regular monitoring of metabolic factors, with potential adjustments to medications, and lifestyle guidance such as the benefits of physical activity, but said that this is rarely done.

Challenges frequently encountered in patient support groups encompass the increasing reliance on telephone appointments, which limit opportunities to discuss questions and concerns; a lack of proactive follow-up, e.g., regarding sexual function and continence; difficulty in scheduling ADT injections; difficulty/delays in obtaining test results; limited availability of certain treatments in specific regions; infrequent provision of specialist diagnoses and treatments not offered locally; and injection site reactions from certain ADT injections (Gabriel A, personal communication).

Gabriel concluded that there is far too much essential information to cover in a clinic consultation. He advocates for supplementary educational avenues such as workshops and classes to

empower patients with the requisite knowledge to maintain optimal health. In the UK, for example, the EAU's ADT Educational Programme, Life on ADT, is offered at select hospitals.⁶ He believes that knowledge is power. By fostering greater patient understanding and awareness through educational initiatives such as workshops and classes, individuals are empowered to take charge of their treatment journey. This enhanced knowledge instils a sense of control, alleviating anxieties and dispelling concerns associated with ADT.

ADT in 2024: What Do We Offer Our Patients?

Romain Mathieu

Mathieu opened by explaining that understanding the intricacies of data, treatment options, strengths, and challenges necessitates a comprehensive grasp of the patient's profile, including their medical history, treatment preferences, and the characteristics of their cancer. This holistic approach enables clinicians to tailor treatment plans to individual needs while identifying suitable co-navigators to support patients throughout their journey. By selecting the most appropriate treatment strategy and enlisting supportive co-navigators, healthcare professionals can effectively mitigate potential side effects and optimise patient outcomes. This personalised approach underscores the importance of patient-centred care in addressing the complexities of PCa treatment.

Hence, having a comprehensive understanding of key patient characteristics at the initiation of ADT is paramount. Data reveals that the median age of patients commencing ADT is typically around 75 years.⁷ Moreover, more than half of these patients have a history of CVD,⁷ underlining the significance of considering cardiovascular (CV) risk factors in treatment planning. Additionally, over 80% of individuals undergoing ADT exhibit osteopenia or osteoporosis,⁸ emphasising the importance of vigilance regarding bone

health. Furthermore, cognitive impairment affects up to half of patients undergoing ADT, highlighting the necessity for cognitive screening and support measures throughout treatment.⁹ Acknowledging and addressing these key patient characteristics are pivotal in tailoring treatment approaches and optimising patient care outcomes.

When evaluating the cancer, Mathieu outlined that it is not just one cancer; hence, it is imperative to utilise a classification system widely adopted for accurate stratification. The EAU employs a classification framework categorising PCa into low-, intermediate-, and high-risk groups based on the likelihood of biochemical recurrence in cases of localised and locally advanced PCa.¹⁰ In addition to the established risk classifications, recent advancements such as those observed in the STAMPEDE study, have introduced a novel risk stratification specifically tailored for newly diagnosed patients categorised as very high risk, which encompasses patients who are node-positive or, if node-negative, present with at least two of the following criteria: tumour Stage T3 or T4; Gleason sum score of 8, 9, or 10; and PSA levels ≥ 40 ng/mL.¹¹ In the context of metastatic prostate cancer, distinctions can be made between *de novo* and metachronous presentations, as well as between low- and high-volume disease. This comprehensive classification scheme facilitates precise risk stratification, guiding treatment decisions, and optimising patient management strategies.

There are several modalities of castration, which take effect over different time periods and come with a variety of limitations, as outlined in the French Association of Urology guidelines.¹² Orchiectomy and pulpectomy achieve castration testosterone levels within 12 hours; however, these procedures are irreversible. GnRH antagonists, such as degarelix and relugolix, are effective in 48–72 hours. Relugolix is administered orally, while degarelix has the disadvantage of requiring monthly injections. GnRH agonists, such as goserelin, leuprorelin, and triptoreline, are effective in 2–4 weeks, and a few patients may experience primary resistance or flare due to an initial surge in testosterone, which is exceptionally symptomatic.

While ADT modalities have the same therapeutic goal, they exert different effects on testosterone levels. As stated in the EAU guidelines, “the level of testosterone is reduced much faster with orchiectomy and GnRH antagonist.”¹⁰ The HERO trial, comparing 48-week treatment with relugolix (120 mg orally once daily) or leuprolide (22.5 mg injections every 3 months) in patients with advanced PCa, demonstrated that testosterone suppression to castrate levels (< 50 ng per decilitre) occurred rapidly in patients randomised to relugolix ($n=622$), with a mean testosterone level of 38 ng/dL on Day 4.¹³ Testosterone was then maintained at castrate levels throughout the treatment period.¹³ In the leuprolide group ($n=308$), a surge in testosterone levels from baseline led to a mean testosterone level of 625 ng/dL at Day 4, before decreasing to castrate levels at Day 29 and remaining at this level during the remainder of treatment.¹³ In the subgroup followed for testosterone recovery, mean testosterone levels at 90 days after treatment discontinuation were 288.4 ng/dL in the relugolix group ($n=137$) and 58.6 ng/dL in the leuprolide group ($n=47$).¹³

ADT modalities also come with different side effect profiles. EAU guidelines recommend: “At the start of ADT offer GnRH antagonists or orchiectomy to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.”¹⁰ In addition, the guidelines state: “Other adverse effects such as decreased libido, hot flushes, erectile dysfunction, weight gain, and injection site reactions are seen less often with the agonists.”¹⁰ An analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus GnRH agonists ($n=1,925$) found that overall, there were fewer joint-related signs and symptoms, musculoskeletal events, and urinary tract events in the degarelix group.¹⁴

The differing effects of ADTs extend to significant clinical outcomes. Based on data such as the HERO trial, the EAU advocates that the use of GnRH antagonist is associated with significantly lower overall mortality and CV events as compared with agonists.¹⁰ A meta-analysis of 11 randomised

controlled trials evaluating GnRH antagonists (n=2,655) versus agonists (n=1,593) demonstrated that GnRH antagonists were associated with a lower risk of major adverse CV events (MACE; relative risk [RR]: 0.57, 95% credible interval: 0.37–0.86) and a nonsignificant decreased mortality risk compared with GnRH agonists.¹⁵

Selecting the optimal course of treatment for localised or locally advanced PCa requires consideration of whether the patient has an intermediate-, high-, or very high-risk of biochemical recurrence.^{10,11} Multiple studies have demonstrated that the combination of ADT and RT reduced disease progression and improved survival compared with RT alone, and reduced recurrence and improved survival compared with ADT alone.^{10,12,16–23,24,25}

EAU guidelines recommend the combination of RT and ADT for various categories of patients.¹⁰ Intermediate-risk disease is subdivided into FIR and UIR, with unfavourable features including International Society of Urological Pathology (ISUP) Grade 3, and/or >50% positive biopsy cores and/or ≥ 2 intermediate-risk factors.¹⁰ RT and ADT are recommended for patients with intermediate-risk disease.¹⁰ A study in patients with intermediate-risk PCa demonstrated that only those with UIR received benefit from RT and ADT for 6 months regarding metastases and survival, compared with FIR patients.²⁶ Moreover, studies by D'Amico et al.^{27,28} have demonstrated that intermediate-risk patients with a history of CVD did not benefit from a combination of RT and ADT for 6 months.

In patients with high-risk disease, a study in 630 patients found no difference in the 10-year overall survival rate when comparing RT combined with either 36 or 18 months of ADT (hazard ratio [HR]: 1.024; 95% CI: 0.813, 1.289; $p=0.8411$).²⁹ Mathieu highlighted that the duration of ADT can be reduced based on this study. In very high-risk, locally advanced PCa, an analysis from the STAMPEDE investigators (n=1,974) compared ADT alone versus combination therapy with ADT plus abiraterone and prednisolone with or without enzalutamide.¹¹ Results showed that 6-year metastasis-free survival was significantly longer with combination

therapy (82%) compared with ADT alone (69%), with an HR of 0.53 (95% CI: 0.44, 0.64; $p<0.0001$).¹¹ Six-year overall survival was significantly longer with combination therapy (86%) compared with ADT alone (77%), with a HR of 0.60 (95% CI: 0.48, 0.73; $p<0.0001$).¹¹ Local radiotherapy was used in 85% (1,684/1,974) of these patients and thus these compelling findings underscore the potential benefits of utilising triplet therapy (RT plus ADT plus abiraterone) regimens in patients with very high-risk localised disease, to optimise treatment outcomes.¹¹

In metastatic disease, ADT has remained the backbone treatment for decades. However, in the past 10 years, several randomised clinical trials have demonstrated that the use of ADT alone was no longer sufficient. Doublets (ADT + neo-adjuvant hormone therapy) or even triplet therapy regimens with chemotherapy or RT should now be considered as standards of care. Specifically, the EAU guidelines state: “Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease and who are fit for the regimen” and “Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease and who are fit for docetaxel.”¹¹

Is there still a place for intermittent ADT? There is no data using doublet or triplet therapy in the metastatic setting to answer this question, and Mathieu said that the answer is probably no for *de novo* and metastatic disease. The SWOG 9346 trial, which enrolled 3,040 patients with metastatic hormone-sensitive PCa, yielded inconclusive results when comparing continuous versus intermittent ADT (HR for death with intermittent therapy: 1.10; 95% CI: 0.99, 1.23).³⁰ EAU guidelines state: “The use of intermittent ADT has been superseded as continuous ADT has become standard of care.”¹⁰ The question may still be relevant in males with rising PSA after primary or salvage RT for localised PCa and no metastases. In this population, a study in 1,386 patients demonstrated that, compared with continuous ADT, intermittent ADT was associated with significantly better scores for hot flushes ($p<0.001$), desire for sexual activity ($p<0.001$), and urinary

symptoms ($p=0.006$), with a trend toward improvement in the level of fatigue ($p=0.07$), without compromising overall survival.³¹

Mathieu concluded that this data helps inform tailored treatment decisions for patients undergoing ADT (intermittent or continuous). However, he emphasised that the critical skill clinicians require lies in effectively preventing and managing the adverse events associated with ADT, thus highlighting the holistic approach necessary for optimising patient care during ADT.

ADT in 2024: What Do We Say To Our Patients?

Amit Bahl

Bahl commenced his presentation by delineating the diverse spectrum of potential side effects associated with ADT that can impact physical appearance (skin problems, loss of body hair, weight gain), thoughts and feelings (mood changes, low libido, memory, and concentration problems), sexual function (erectile dysfunction, less intense orgasms, reduced semen production, changes to size of penis and size/shape of testicles), and muscle and bone changes (loss of muscle strength, bone thinning).³² Subsequently, he delved into a detailed examination of specific adverse events, elucidating their clinical manifestations, underlying mechanisms, and management strategies.

The associations between PCa, ADT, and CVD have been extensively investigated. An observational competing risk analysis in patients with cancer in the USA demonstrated that patients with PCa were more likely to die from CVD than from their primary cancer, and were at elevated risk of dying from CVD compared to the general USA population.³³ A meta-analysis of eight observational studies reported a consistent positive association between ADT and the risk of CVD.³⁴ The RR of any type of nonfatal CVD was 1.38 (95% CI: 1.29, 1.48) for men with PCa on GnRH agonists, compared with men not treated with ADT.³⁴ By incorporating CVD status into treatment decision-making, clinicians can minimise potential adverse CV outcomes.

In a meta-analysis of eight randomised trials including 4,141 men with unfavourable-risk, non-metastatic PCa, intermittent ADT was not associated with an increased risk of fatal CVD (compared to control; RR: 0.93; 95% CI: 0.79, 1.10; $p=0.41$).³⁵ Among the 4,805 patients in 11 trials, which included overall death data, ADT was associated with lower PCa-specific mortality (RR: 0.69; 95% CI: 0.56, 0.84; $p<0.001$) and lower all-cause mortality (RR: 0.86; 95% CI: 0.80, 0.93; $p<0.001$) compared to a control group of patients receiving no immediate ADT.³⁵

In a meta-analysis of six randomised clinical trials in 2,328 men with pre-existing CVD and PCa, the risk of cardiac events within 1 year of initiating therapy was significantly lower among men treated with a GnRH antagonist compared with GnRH agonists (HR: 0.44; 95% CI: 0.26, 0.74; $p=0.002$).³⁶ A prespecified safety analysis of the HERO trial indicated a 54% lower risk of MACE in patients receiving relugolix (2.9%, 18/622) compared with patients receiving leuprolide (6.2%, 19/308) (HR: 0.46; 95% CI: 0.24, 0.88).¹³ The analysis suggested that in the subgroup of patients with a history of MACE, the odds of MACE during treatment was 4.8 times as high with leuprolide (17.8%, 8/45) as with relugolix (3.6%, 3/84).¹³

Bahl underscored the primary importance of ensuring the appropriate use of ADT and emphasised the necessity of considering potential complications, particularly at the initiation of treatment in men with PCa who are at increased CV risk. He highlighted the well-documented evidence indicating that ADT leads to increased fat mass and decreased insulin sensitivity, thereby heightening the susceptibility to metabolic disturbances.³⁷ Consequently, Bahl stressed it is imperative for physicians to recognise these risks and proactively counsel patients on adopting a healthy lifestyle.

Turning to guidelines, the EAU acknowledges cardiac morbidity but makes no recommendations,¹⁰ while the UK National Institute for Health and Care Excellence (NICE) also declines to provide recommendations.³ The American Heart Association (AHA)/American Cancer Society (ACS)/American Urological Association

(AUA) Science Advisory on CV risk in ADT for PCa states that the benefits of ADT should be weighed against potential risks, with close monitoring of patients with CVD or risk factors.³⁸ European Society of Cardiology (ESC) guidelines on cardio-oncology recommend CV risk assessment before starting ADT and annual assessment during ADT.³⁹ They also recommend considering a GnRH antagonist in patients with pre-existing symptomatic coronary artery disease who require ADT.³⁹

Regarding bone health, patients with PCa are at increased risk of osteoporosis and fragility fractures due to ADT.^{8,40-42} In fact, Morote et al.⁸ found that the proportion of patients with osteoporosis was 81% after 10 or more years of ADT.⁸⁸ Fractures have been commonly reported in the investigational arm of Phase III studies with new androgen receptor pathway inhibitors.⁴³⁻⁴⁶ Measures can be taken to improve bone mineral density (BMD) in patients on ADT. In patients with non-metastatic PCa, denosumab was associated with improvements in BMD and a reduction in osteoporotic fractures, and zoledronic acid was shown to increase BMD during ADT.^{47,48}

EAU guidelines recommend daily calcium (>500 mg) and vitamin D (>400 international unit [IU] equivalent) in all patients with metastatic castration-resistant PCa, except in cases of hypercalcaemia.¹⁰ Bahl advised HCPs to consider assessing fracture risk in patients with PCa taking ADT by measuring BMD with dual-energy X-ray absorptiometry, in line with NICE guidelines.⁴⁹

Research has shown that regular sports activities can reduce the risk of fractures in older men.⁵⁰ The Endocrine Society suggests that men at risk of osteoporosis participate in weight-bearing activities for 30–40 minutes per session, three to four sessions per week, and that men at risk of osteoporosis who consume ≥ 3 units of alcohol per day reduce their alcohol intake.⁵¹ The society also recommends that men at risk of osteoporosis cease smoking.⁵¹ Rather than providing generic exercise recommendations, clinicians should tailor their advice to the individual patient's needs, preferences, and physical capabilities. Bahl

recommends 30 minutes, five times a week, including balance exercises to improve the risk of falls and boost cognitive function. By proactively addressing bone health through comprehensive assessment and targeted interventions, clinicians can mitigate the risk of fractures and optimise the overall well-being of patients undergoing ADT.

The benefits of physical activity in patients with PCa have been demonstrated in several studies. The CaPSURE study (n=1,455) found that men with localised PCa who walked briskly (≥ 3 mph) for ≥ 3 hours per week had a 57% lower rate of progression than men who walked at an easy pace (<3 mph) for <3 hours per week (HR: 0.43; 95% CI: 0.21, 0.91; p=0.03).⁵² The health professionals follow-up study (n=2,705) reported that men with nonmetastatic PCa who walked ≥ 90 minutes per week at a normal to very brisk pace had a 46% lower risk of all-cause mortality (HR: 0.54; 95% CI: 0.41, 0.71) compared with those who walked for shorter durations at an easy pace.⁵³ Men with ≥ 3 hours versus <1 hour per week of vigorous activity had a 49% reduction in all-cause mortality (HR: 0.51; 95% CI: 0.36, 0.72). In addition, men with ≥ 3 hours per week of vigorous activity had a 61% lower risk of PCa death (HR: 0.39; 95% CI: 0.18, 0.84; p=0.03), compared with men with <1 hour per week of vigorous activity.⁵³

HCPs should discuss the potential detrimental effects of ADT prior to treatment initiation so that support can be provided (prehabilitation).⁵⁴ A recently published prehabilitation checklist can support this process to cover all topics with patients including bone health, metabolic changes, sexual dysfunction, and other physical, psychological, and cognitive effects.⁵⁴

In his conclusion, Bahl underscored the significance of comprehensive care in the long-term management of PCa, highlighting the importance of assessing and managing CV risk factors, bone health, and cognitive function. He emphasised the incorporation of exercise medicine as a crucial component of this holistic approach to care. Bahl advocated for the utilisation of a prehabilitation checklist to systematically address these aspects, ensuring that

patients receive comprehensive support tailored to their individual needs. By implementing such a checklist, clinicians can proactively address CV health, bone density, cognitive function, and overall well-being, thereby optimising the long-term care and outcomes of patients with PCa undergoing ADT.

HCPs taking a proactive approach to gather information from patients about sensitive issues they may be hesitant to discuss openly. Mathieu stressed the role of HCPs in guiding patients through the PCa treatment journey, providing support and assistance along the way. Lastly, Bahl recommended the adoption of a prehabilitation checklist as a valuable tool to ensure that patients embarking on ADT receive comprehensive and tailored advice to address their specific needs and concerns. These take-home messages collectively underscored the importance of patient-centred care and proactive support in optimising outcomes for individuals undergoing treatment for PCa.

Concluding Remarks

The session concluded with each speaker offering their key takeaway messages. Gabriel emphasised the importance of

EU Orgovyx SmPC

References

- European Medicines Agency (EMA). Orgovyx: EPAR - Product Information. Summary of Product Characteristics. 2023. Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/orgovyx>. Last accessed: 3 April 2024.
- Prostate Cancer UK. How hormone therapy affects you. 2024. Available at: <https://prostatecanceruk.org/prostate-information-and-support/living-with-prostate-cancer/how-hormone-therapy-affects-you>. Last accessed: 3 April 2024.
- National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and manage malest. NICE guideline [NG131]. 2021. Available at www.nice.org.uk/guidance/ng131. Last accessed: 27 March 2024.
- Mazzola CR, Mulhall JP. Impact of androgen deprivation therapy on sexual function. *Asian J Androl*. 2012;14(2):198-203.
- Traish AM. Androgens play a pivotal role in maintaining penile tissue architecture and erection: a review. *J Androl*. 2009;30(4):363-9.
- European Association of Urology (EAU). The androgen deprivation therapy educational programme. 2023. Available at: <https://www.lifeonadt.com/how-to-register-uk-europe>. Last accessed: 3 April 2024.
- George G et al. Risk of cardiovascular disease following gonadotropin-releasing hormone agonists vs antagonists in prostate cancer: real-world evidence from five databases. *Int J Cancer*. 2021;148(9):2203-11.
- Morote J. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. *Urology*. 2007;69(3):500-4.
- Gonzalez BD et al. Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: a controlled comparison. *J Clin Oncol*. 2015;33(18):2021-7.
- EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on prostate cancer. 2023. Available at: <https://d56bochluxqnz.cloudfront.net/documents/pocket-guidelines/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Pocket-on-Prostate-Cancer-2023.pdf>. Last accessed: 25 March 2024.
- Attard G et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet*. 2022;399(10323):447-60.
- Ploussard G et al. French AFU Cancer Committee guidelines - update 2022-2024: prostate cancer - management of metastatic disease and castration resistance. *Prog Urol*. 2022;32(15):1373-419.
- Shore ND et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med*. 2020;382(23):2187-96.
- Klotz L et al. Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. *Eur Urol*. 2014;66(6):1101-8.
- Nelson AJ et al. Cardiovascular effects of GnRH antagonists compared with agonists in prostate cancer: a systematic review. *JACC CardioOncol*. 2023;5(5):613-24.
- Pilepich MV et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma-long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys*. 2005;61(5):1285-90.
- Pilepich MV et al. Phase III radiation therapy oncology group (RTOG)

- trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys.* 2001;50(5):1243-52.
18. Bolla M et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol.* 2010;11(11):1066-73.
 19. Bolla M et al. Short androgen suppression and radiation dose escalation in prostate cancer: 12-year results of EORTC Trial 22991 in patients with localized intermediate-risk disease. *J Clin Oncol.* 2021;39(27):3022-33.
 20. Denham JW et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. *Lancet Oncol.* 2011;12(5):451-9.
 21. Jones CU et al. Adding short-term androgen deprivation therapy to radiation therapy in men with localized prostate cancer: Long-term update of the NRG/RTOG 9408 randomized clinical trial. *Int J Radiat Oncol Biol Phys.* 2022;112(2):294-303.
 22. Dubray BM et al. Does short-term androgen depletion add to high dose radiotherapy (80 Gy) in localized intermediate risk prostate cancer? Final analysis of GETUG 14 randomized trial (EU-20503/NCT00104741). *J Clin Oncol.* 2016;34(15_suppl):5021.
 23. Widmark A et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet.* 2009;373(9660):301-8.
 24. Mason MD et al. Final report of the intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. *J Clin Oncol.* 2015;33(19):2143-50.
 25. Mottet N et al. Addition of radiotherapy to long-term androgen deprivation in locally advanced prostate cancer: an open randomised phase 3 trial. *Eur Urol.* 2012;62(2):213-9.
 26. Zumsteg ZS et al. A new risk classification system for therapeutic decision-making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol.* 2013;64(6):895-902.
 27. D'Amico AV et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA.* 2008;299(3):289-95.
 28. D'Amico AV et al. Long-term follow-up of a randomized trial of radiation with or without androgen deprivation therapy for localized prostate cancer. *JAMA.* 2015;314(12):1291-3.
 29. Nabid A et al. Duration of androgen deprivation therapy in high-risk prostate cancer: a randomized phase III trial. *Eur Urol.* 2018;74(4):432-41.
 30. Hussain M et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med.* 2013;368(14):1314-25.
 31. Crook JM et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med.* 2012;367(10):895-903.
 32. Prostate Cancer UK. Hormone therapy. 2024. Available at: <https://prostatecanceruk.org/prostate-information-and-support/treat-ment/malests/hormone-therapy>. Last accessed: 27 March 2024.
 33. Sturgeon KM et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J.* 2019;40(48):3889-97.
 34. Bosco C et al. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. *Eur Urol.* 2015;68(3):386-96.
 35. Nguyen PL et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. *JAMA.* 2011;306(21):2359-66.
 36. Albertsen PC et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *Eur Urol.* 2014;65(3):565-73.
 37. Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. *J Urol.* 2009;181(5):1998-2008.
 38. Levine GN et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk. *Circulation.* 2010;121(6):833-40.
 39. Lyon AR et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J.* 2022;43(41):4229-361.
 40. Shahinian VB et al. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med.* 2005;352(2):154-64.
 41. Smith MR et al. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. *J Urol.* 2006;175(1):136-9.
 42. Alibhai SMH et al. Fracture types and risk factors in men with prostate cancer on androgen deprivation therapy: a matched cohort study of 19,079 men. *J Urol.* 2010;184(3):918-23.
 43. Smith MR et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med.* 2018;378(15):1408-18.
 44. Sternberg CN et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2020;382(23):2197-206.
 45. Graff JN et al. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naive metastatic castration-resistant prostate cancer: results from PREVAIL. *Ann Oncol.* 2016;27(2):286-94.
 46. Sedhom R, Antonarakis ES. Radium-223 plus abiraterone in metastatic castration-resistant prostate cancer: a cautionary tale. *Transl Androl Urol.* 2019;8(Suppl 3):S341-5.
 47. Smith MR et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med.* 2009;361(8):745-55.
 48. Israeli RS et al. The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy. *Clin Genitourin Cancer.* 2007;5(4):271-7.
 49. National Institute for Health and Care Excellence. Osteoporosis: assessing the risk of fragility fracture. Clinical guideline [CG146]. 2017. Available at: <https://www.nice.org.uk/guidance/cg146>. Last accessed: 27 March 2024.
 50. Michaëlsson K et al. Leisure physical activity and the risk of fracture in males. *PLoS Med.* 2007;4(6):e199.
 51. Watts NB et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2012;97(6):1802-22.
 52. Richman EL et al. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. *Cancer Res.* 2011;71(11):3889-95.
 53. Kenfield SA et al. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol.* 2011;29(6):726-32.
 54. Payne H et al. 'Prehabilitation' checklist for men with prostate cancer starting androgen deprivation therapy. *Trends in Urology & Men's Health.* 2024;15(3):2-8.