Evolving Treatment Paradigm for Patients With Advanced Prostate Cancer: The Emerging Role of Androgen Receptor Pathway Inhibitors

The Treatment Plan for Patients With Advanced Prostate Cancer: Where Do Androgen Receptor Pathway Inhibitors Belong?

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An Evidentiary Review of Emerging Androgen Receptor Pathway Inhibitors

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In this activity, experts in the management of prostate cancer discuss sequencing strategies with current and emerging androgen receptor pathway inhibitors (ARPIs) in order to maximise patients' survival and quality of life.

Upon completion of this activity, participants should be better able to:

- Identify patient- and disease-related factors that may affect treatment decisions and response to therapy with androgen receptor pathway inhibitors (ARPIs)
- Describe how current treatment plans may change for patients with advanced prostate cancer, given the recent and emerging clinical trial data
- Explain the similarities and differences between current and emerging ARPIs

Target Audience

This activity has been designed to meet the educational needs of medical oncologists, urologists, and other clinicians involved in prostate cancer management.

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The Treatment Plan for Patients With Advanced Prostate Cancer: Where Do Androgen Receptor Pathway Inhibitors Belong?

Conceptual Framework for the Management of Advanced Prostate Cancer (St Gallen APCCC)

Castration-Naïve PC

| M0 | ADT | Management of patients with non-metastatic (M0) CRPC |
| M1 | ADT |

CRPC

| M1 | 1st Line |
| M1 | 2nd Line |
| M1 | 3rd Line |

Abbreviation(s): ADT: androgen-deprivation therapy; APCCC: Advanced Prostate Cancer Consensus Conference; CRPC: castration-resistant prostate cancer (PC); M0: no evidence of metastases on imaging; M1: metastases documented on imaging.


Karim Fizazi, MD, PhD: Hello, this is Karim Fizazi from Institut Gustave Roussy in Villejuif, France. Welcome to this educational activity on treatment of advanced prostate cancer. We’re going to review what is the current role of androgen receptor pathway inhibitors in the treatment sequence; and also, we’ll look at how this role may evolve in the near future.

So, this slide is derived from the St Gallen Consensus Meeting in 2015, and it’s really showing you the framework for advanced prostate cancer. So some patients have non-metastatic disease, but we already know that they have advanced disease because the disease has become resistant to castration, which is M0 CRPC; while some other patients are entering the disease upfront with evidence of metastasis—what we call M1 castration-naïve prostate cancer.

Whatever the pathway, the disease evolves to metastatic castration-resistant disease (mCRPC), and we are talking about first-line, second-line, third-line, etc, CRPC treatments.

Abiraterone and enzalutamide are the two approved androgen receptor pathway inhibitors that showed efficacy in large phase 3 trials. This is, for example, the COU-301 and AFFIRM randomised phase 3 trials, respectively, showing that approximately a 30% reduction in the risk of death can be achieved when using these agents in the post-docetaxel setting.

Abbreviation(s): ABI: abiraterone acetate; ARPI: androgen receptor pathway inhibitor; ENZA: enzalutamide; mCRPC: metastatic CRPC; OS: overall survival; PBO: placebo; Pred: prednisone.


Efficacy Associated With Approved ARPIs Abiraterone and Enzalutamide for mCRPC (Post-Docetaxel)

Data are from multiple trials and cannot be directly compared.

COU-AA-301: Abiraterone/Pred<sup>1,1</sup>

HR, 0.74 (95% CI, 0.64-0.86)

P < .0001

PBO + Pred

ABI + Pred

100

80

60

40

20

0

0 6 12 18 30 36 42

Time, mo

OS, %

AFFIRM: Enzalutamide<sup>2,2</sup>

HR, 0.63 (95% CI, 0.53-0.75)

P < .001

PBO

ENZA

100

80

60

40

20

0

0 6 12 18 24

Time, mo

OS, %

Abbreviation(s): ARPI: androgen receptor pathway inhibitor; COU-AA-301: Abiraterone/Pred; AFFIRM: Enzalutamide/PBO; mCRPC: metastatic CRPC; OS: overall survival; PBO: placebo; Pred: prednisone.


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Let’s briefly review what is the safety pattern of these agents. Hypertension and a slight excess of cardiac disorders were seen in patients treated with abiraterone.

Now, fatigue and cognitive impairment emerge as side effects that are linked to enzalutamide use. This might be related to the fact that enzalutamide penetrates the blood-brain barrier. This agent is associated with a risk of seizure, and this is, of course, something, again, to pay attention to. We need to question the patient about seizures. Finally, again, we need to pay attention to hypertension and generally speaking, cardiac events. When considering treating your patients with these agents, you really need to ask the patient whether he has a previous history of cardiac disorders and perhaps you need to refer him to the cardiologist before starting treatment.

Also, because these treatments are generally well tolerated, they are now used [as approved] more and more in patients who are chemotherapy-naïve.
The Evolving Role of ARPI Therapy for Advanced Prostate Cancer

Evolving role of ARPIs for advanced prostate cancer

Abbreviation(s):
- CSPC: castration-sensitive prostate cancer.

Now let’s talk about where the use of these ARPI agents is heading. One obviously is to use them upfront, so earlier in the course of the disease. For example, in patients with castration-sensitive or castration-naïve metastatic disease—so patients who are just entering this disease with evidence of metastasis.

A second potential indication in the near future might be non-metastatic CRPC (M0 CRPC)—so patients with nondetectable lesions that are progressing while on castration therapy.

Finally, the third strategy might be to combine these drugs, either together, or with other agents.

Metastatic CSPC: Clinical Studies Assessing Docetaxel Treatment

Abbreviation(s):
- NA: not available; SOC: standard of care; ZA: zoledronic acid.

Reference(s):

In the meantime, after these trials were designed and conducted, docetaxel emerged as a standard of care for fit patients [good performance status] with castration-sensitive disease—at least those patients with multiple bony metastasis or visceral disease.

This is, for example, the meta-analysis of large phase 3 trials. The overall analysis resulted in a 23% reduction in the risk of death when docetaxel is, indeed, used upfront in these gentlemen. So this is for most of us, I guess, now a current standard.
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For example, many experts see a role for early use of docetaxel in patients with:
- Multiple bony metastases
- Visceral metastases

Q: Do you recommend ADT + docetaxel in patients with castration-naïve “high-volume” disease?

Findings from the second St Gallen APCCC Expert Panel will be published soon

Majority, 50%
Minority, 39%
No, 11%


There is debate as whether this is true for all-comers, or whether we should restrict docetaxel use for patients with very advanced disease—namely those with multiple bony metastases or those with visceral metastases. The experts just had the second St Gallen consensus meeting; most of us are now using docetaxel early in advanced prostate cancer.

### Metastatic CSPC: St Gallen APCCC Expert Use of Docetaxel

For example, many experts see a role for early use of docetaxel in patients with:
- Multiple bony metastases
- Visceral metastases


Now, a very different clinical situation, again, is that of patients with non-mCRPC [M0 CRPC]. So again, we do have the ARAMIS phase 3 trial testing ODM-201 (darolutamide), also the SPARTAN phase 3 trial looking at ARN-509 (apalutamide), and the PROSPER phase 3 trial looking at enzalutamide. With ARN-509 (apalutamide), honestly, we don’t necessarily see much different as compared with enzalutamide. In the phase 1/2 development, you also don’t see much difference.
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Metastatic CRPC: Phase 3 Combination Strategies With Approved and Emerging ARPIs

<table>
<thead>
<tr>
<th>Experimental Arm</th>
<th>Control Arm</th>
<th>Clinical Trial Identifier</th>
<th>Clinical State</th>
<th>Prior Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apalutamide* + Abiraterone + PBO</td>
<td>Abiraterone + PBO</td>
<td>NCT02257736</td>
<td>mCRPC</td>
<td>No</td>
</tr>
<tr>
<td>Enzalutamide + Enzalutamide</td>
<td>Enzalutamide</td>
<td>NCT01949337</td>
<td>mCRPC</td>
<td>No</td>
</tr>
</tbody>
</table>

* Emerging agent, currently unapproved for CRPC.


Now, another strategy, obviously, when you have a drug that is active is to try to combine it with another drug that is also active with perhaps a different mechanism of action. So there is a rationale to combine, for example, abiraterone together with enzalutamide. This is now being tested randomly versus enzalutamide.

A very similar trial is also testing abiraterone plus placebo versus abiraterone plus ARN-509 (apalutamide). This trial is currently enrolling patients. So hopefully we’ll have data in one or two years from now.

Summary: ARPI Therapy for Advanced Prostate Cancer

So, as a conclusion, I would say that really the evolution of treatment for patients with advanced prostate cancer has really evolved tremendously in the last five years or so. We are mostly using androgen receptor pathway inhibitors quite early in the course of mCRPC, in patients who are usually naive of chemotherapy. The role of androgen receptor pathway inhibitors in two very important situations—namely, M1 castration-sensitive prostate cancer and non–metastatic M0 CRPC—will be clarified very soon because we’re expecting several major phase 3 trials to readout probably this year or next year.

We’re now using many agents sequentially; the ideal sequence is something that we don’t really know for sure. Now having said that, the cross-resistance between these agents—enzalutamide and abiraterone, for example—is quite high. So, before using them sequentially, you really need to think twice whether it’s the best thing to do for your patients instead of using another agent such as chemotherapy. Thank you very much for your kind attention.
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An Evidentiary Review of Emerging Androgen Receptor Pathway Inhibitors

Currently Approved Therapies for mCRPC: Moving From Palliation to Survival Benefit

Abbreviation(s): ARPI: androgen receptor (AR) pathway inhibitor; BP: bisphosphonate; CT: chemotherapy; IO: immunotherapy; mCRPC: metastatic castration-resistant prostate cancer; RP: radiopharmaceutical.

Reference(s): Adapted by: Matthew Smith, MD, PhD; March 2017.

Matthew Smith, MD, PhD: Hello, I’m Dr. Matthew Smith, Professor of Medicine at Harvard Medical School, and Director of the Genitourinary Malignancies Program at Massachusetts General Hospital Cancer Center. Currently, there are six FDA-approved therapies for metastatic castration-resistant prostate cancer (mCRPC).

These approved agents include two androgen receptor pathway inhibitors, abiraterone acetate and enzalutamide. Abiraterone acetate and enzalutamide are important parts of our toolbox for the management of advanced disease. Both drugs are approved for the treatment of mCRPC before and after docetaxel chemotherapy, based on Level 1 evidence for improved progression-free (PFS) and overall survival (OS).

Abbreviation(s): ARPI: androgen receptor (AR) pathway inhibitor; BP: bisphosphonate; CT: chemotherapy; IO: immunotherapy; mCRPC: metastatic castration-resistant prostate cancer; RP: radiopharmaceutical.

Reference(s): Adapted by: Matthew Smith, MD, PhD; March 2017.

Matthew Smith, MD, PhD: While abiraterone acetate and enzalutamide are well tolerated, there are some patients who, in fact, have unacceptable side effects with one or both of those agents, so there is an unmet need for drugs that are better tolerated. There’s also a need to look at this class of agents in other clinical settings, including some settings where tolerability will be particularly important. For example, in the setting of non–metastatic CRPC, there would be an expected long period of treatment, and in order for that to be acceptable, we would prefer to have agents that have an extremely favourable safety profile.

Abbreviation(s): PSA: prostate-specific antigen.

This activity will review the role of novel androgen receptor pathway inhibitors in phase 3 clinical development, and how the ongoing clinical trials may shape the future use of this class of drugs in other important settings in prostate cancer, including non--metastatic CRPC (non–mCRPC) and hormone-sensitive (or castration-sensitive) prostate cancer.

In a phase 2 clinical trial, apalutamide demonstrated activity in mCRPC. Among 25 patients who were abiraterone acetate–naive, PSA response rate at 12 weeks was 88%. Among patients who had progression despite prior abiraterone acetate, response rates dropped to 22%, consistent with overlapping cross-resistance between the androgen pathway inhibitors.

There are two novel androgen pathway inhibitors in phase 3 clinical development, apalutamide and darolutamide.

Apalutamide, formerly known as ARN-509, is an anti-androgen that is structurally very similar to enzalutamide. Like enzalutamide, it also has a high affinity for the androgen receptor and crosses the blood–brain barrier.

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Abbreviation(s): BBB: blood–brain barrier.


Abbreviation(s): TEAE: treatment-emergent adverse event (AE).


The most common adverse events associated with apalutamide were fatigue, nausea, abdominal pain, and diarrhoea. Notably, most of the adverse events were grade 1 or 2.

Abbreviation(s): Pred: prednisone.

Abbreviation(s): ABI: abiraterone; ADT: androgen deprivation therapy; GnRH: gonadotropin-releasing hormone; LA: locally advanced; mCSPC: metastatic castration-resistant prostate cancer; PBO: placebo; RT: radiation therapy.

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There are currently four phase 3 clinical trials of apalutamide. The ATLAS study will evaluate the addition of apalutamide to androgen deprivation therapy (ADT) and radiation therapy for men with high-risk localised prostate cancer. The SPARTAN study will evaluate apalutamide in men with high-risk non–mCRPC. The TITAN study will evaluate apalutamide in men with low-volume metastatic hormone-sensitive prostate cancer. Another study will evaluate the addition of apalutamide to abiraterone in men with mCRPC.

Limited penetration of the blood-brain barrier also distinguishes darolutamide from other anti-androgens. In this non-clinical model, for example, the blood-brain-barrier penetration for darolutamide was only 3% compared with 19% and 29% for enzalutamide and apalutamide, respectively. The predicted lower blood-brain penetration and lower brain exposure with darolutamide may confer a safety advantage for darolutamide relative to other anti-androgens. This will be assessed in multiple ongoing large clinical trials.

Darolutamide, formerly known as ODM-201, is also a potent anti-androgen; it is structurally distinct from other known anti-androgens. It also has a greater affinity for the androgen receptor.

Darolutamide (ODM-201)

- Anti-androgen
- Structurally distinct from any known anti-androgens
- Great affinity for AR

Abbreviation(s): QWBA: quantitative whole-body autoradiography.


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Darolutamide (ODM-201)

- Anti-androgen
- Structurally distinct from any known anti-androgens
- Great affinity for AR

Abbreviation(s): QWBA: quantitative whole-body autoradiography.

The most commonly reported adverse events associated with darolutamide were nausea, fatigue, bone pain, and abdominal pain. Notably though, the rate of these adverse events was very low, between 3% and 13%, and the majority of adverse events were grade 1.

While we always have to be careful about comparing between different phase 2 clinical trials—these were not head-to-head trials—the reported safety profile of darolutamide looked particularly favourable.

Abbreviation(s): DOC: docetaxel.

There are two ongoing phase 3 clinical trials of darolutamide in prostate cancer. The ARAMIS trial will evaluate darolutamide in men with high-risk non–mCRPC. The ARASENS trial evaluates ADT plus docetaxel, with or without darolutamide, in men with hormone-sensitive metastatic disease.

In summary, the androgen receptor is a validated target in prostate cancer. There are two novel anti-androgens in phase 3 clinical development. Apalutamide, or ARN-509, is structurally similar to enzalutamide, and is undergoing evaluation in four phase 3 clinical trials. Darolutamide is structurally distinct and is currently in phase 3 clinical development in two clinical trials.
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