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NCCN Guidelines Panel: Prostate Cancer

On behalf of Epic Sciences, I respectfully request the NCCN Prostate Cancer panel review the enclosed data which updates the evidence supporting AR-V7 testing and its implications for metastatic castration resistant prostate cancer (mCRPC). We are specifically providing updated data with respect to the nuclear-localized AR-V7 protein test performed utilizing the Epic Sciences technology.

Specific Changes:

1. Request the panel review all new AR-V7 literature and consider updating the discussion section to reflect such literature supporting utility of nuclear-localized AR-V7 testing (Oncotype DX Nucleus Detect).

2. Request the panel consider strengthening the 'ss' footnote language around utilization of nuclear-localized AR-V7 testing given the literature and consider algorithm placement and table insertion of AR-V7 testing.

FDA Clearance: Not applicable. CAP/CLIA certification for AR-V7 testing.

Rationale:

Requesting updated discussion section: New studies, not available at the time of the current NCCN guidelines, provide stronger clinical validation and utility which support inclusion of the nuclear-localized AR-V7 test into the next revision of the NCCN Guidelines. Two recent blinded, multi-center studies, combined with existing literature, have resulted in a positive local coverage determination (LCD) through Medicare's Molecular Diagnostics program (MolDX). The results of these studies are consistent with previous studies of nuclear-localized AR-V7 in CTCs, and demonstrate incorporation of the test extends patient survival through therapeutic decisions based on AR-V7 status. Below are the key rationale for the clinical necessity of the test.

Current reasons, per NCCN discussion, for not recommending the AR-V7 biomarker (NCCN guidelines pg MS-44 "Progression after Enzalutamide or Abiraterone") followed by the new data supporting coverage are listed below:

- "*These single-center clinical experiences suggest that AR-V7 assays are promising predictors of abiraterone and enzalutamide resistance, but they have not yet been validated prospectively and externally.*"
    - Armstrong AJ *et al*. The PROPHECY trial: Multicenter independent prospective trial of circulating tumor cell AR-V7 detection in men with mCRPC receiving abiraterone or enzalutamide; Oral Abstract #5004 ASCO 2018

        - Trial overview: Blinded, multi-center prospective validation of AR-V7 CTCs to portend poor outcomes of mCRPC patients on ARSi. Primary endpoint- rPFS; Secondary endpoints- OS, PSA response, RECIST response.
        - Results Summary: nuclear-localized AR-V7+ patients were validated to have no clincial benefit to Abiraterone or Enzalutamide, with 0% of nuclear-localized AR-V7+ having PSA or RECIST responses, a median 3.1 vs. 6.1 mo rPFS, and median 8.4 mo vs. 20.3 mo OS.
    - Scher HI *et al.* Assessment of the Validity of Nuclear-Localized Androgen Receptor Splice Variant 7 in Circulating Tumor Cells as a Predictive Biomarker for Castration-Resistant Prostate Cancer. *JAMA Oncology* 2018 (in Press)
        - Trial overview: Blinded, multi-center prospective-retrospective validation of clinical utility of nuclear-localized AR-V7 in the standard of care clinical decision between ARSi & taxane for patients who are already receiving a systemic therapy in the metastatic setting. Powered statistical analysis plan with OS as primary endpoint.
        - Result summary: nuclear-localized AR-V7 biomarker is associated with the following unadjusted therapy outcomes. AR-V7+ patients live longer on taxanes than ARSis (14.3 mo vs. 7.3 mo), whereas AR-V7- patients lived longer on ARSis than taxanes (19.8 mo vs. 12.8 mo). Independent application of risk scores to adjust for physician therapy selection bias demonstrate the test provides advantage across the risk profiles and support the predictive nature of the biomarker in the context of use.

- "*…but data have shown already that abiraterone/enzalutamide crossover therapy is effective rarely and taxanes are more effective in this setting. Therefore, the panel does not recommend use of these tests to determine treatment selection at this time.*"
    - The statement above makes reference to small cohorts using surrogate outcomes for OS such as PSA response. There still remains no randomized controlled trial comparing ARSi to taxane use post-ARSi. Despite the recommendation against consecutive ARSi, current real-world data suggests >60% of physicians in the US prescribe such a therapy regimen.
    - Oh W *et al.* Real-world Characteristics and Outcomes of Patients with mCRPC Receiving Chemotherapy Versus Androgen Receptor-targeted Therapy After Failure of First-line Androgen Receptor-targeted Therapy in the Community Setting. *Clinical Genitourinary Cancer*, February 2018
        - Study overview: Analysis of therapy selection in patients who had already received an ARSi to receiving another ARSi or taxanes in the community setting. Analysis of OS based upon therapy selection and patient risk by established prognostic factors.
        - Results: 340 (62%) received consecutive ARSis and 206 (38%) received a taxane after ARSi. A wide range of survival were observed in both groups, however no difference between group survival was observed (Hazard ratio of OS, 0.90; P= 0.511) in models adjusting for observed differences in underlying patient risk.
        - Implications: Consecutive ARSi utilization occurs more often than not in the U.S., no evidence points to one therapy choice being more favorable for overall

survival in unselected populations post-ARSi. Understanding who should go on chemotherapy vs. ARSi is a relevant unmet medical need.

- Armstrong AJ *et al*. The PROPHECY trial: Multicenter prospective trial of circulating tumor cell AR-V7 detection in men with mCRPC receiving abiraterone or enzalutamide; accepted Oral Abstract ASCO 2018
  - In the context of a high-risk patient who is considering an ARSi, the median patient with Nuclear-localized AR-V7(-) patients had a median rPFS of 6.1 months, which demonstrates and supports clinical benefit for the median patient.
- Scher HI *et al.* Assessment of the Validity of Nuclear-Localized Androgen Receptor Splice Variant 7 in Circulating Tumor Cells as a Predictive Biomarker for Castration-Resistant Prostate Cancer. *JAMA Oncology* 2018 (in Press)
  - In the context of a patient who has already received 1 systemic therapy and considering an ARSi or a taxane, the nuclear-localized AR-V7(-) patients had a median OS of 22.6 mo which was greater than taxanes and shown to be an independent predictor of OS in a multivariate model adjusting for patient risk factors.

2. Requesting update to ss footnote and algorithm placement of nuclear-localized AR-V7 testing:

Proposed ss footnote language for panel's consideration

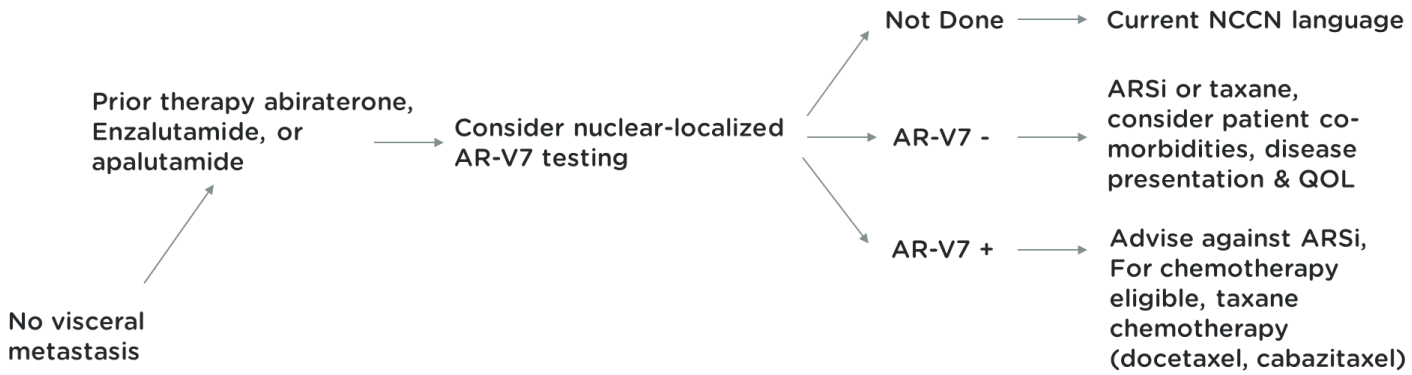
A. ss: Consider obtaining status of nuclear-localized AR-V7 (or AR-V7 Nucleus Detect) to determine selection of therapy. Panel recommends considering taxane therapy for nuclear-localized AR-V7 (or AR-V7 Nucleus Detect) positive patients due to clinical non-response to ARSi (Armstrong et al 2018.; Scher et al. 2016) and improvement in overall survival noted in Scher et al. 2018

B. Proposed algorithm placement for Nuclear AR-V7 testing

The new aforementioned data highlights the critical nature of the unmet medical need and the additional validation of the Oncotype DX AR-V7 Nucleus Detect test for this purpose through two independent, blinded, prospective studies. In the 2017 NCCN guidelines, it notes the need for prospective validation which Armstrong et al and Scher et al now provide.

As such below are proposed recommendations based upon the clinical studies:

- nuclear-localized AR-V7(+) patients should not receive an ARSi, given the lack of observed clinical responses, short rPFS & OS in multi-center blinded cohorts. Nuclear-localized AR-V7+ patients who are chemotherapy eligible patients should consider a taxane chemotherapy as these patients will statistically have longer OS on taxane chemotherapy.
- nuclear-localized AR-V7(-) patients may have clinical benefit to a consecutive ARSi and are demonstrated to have equivalent or better OS if receiving an ARSi over a taxane chemotherapy. However, since not all resistant disease is AR-V7 positive, the decision on therapy recommendation should be based upon co-morbidities, presentation of disease, and optimizing quality of life.



The Recurrence Score algorithm (see BINV-6 of Breast Cancer guidelines) in the NCCN guidelines provides a good predicate example of a treatment algorithm that could be adapted to AR-V7. As such, above is proposed algorithm for utilization of AR-V7.

Test	Platform	Population Studied in Validation Studies	Outcome Reported (Test independently predicts)	Clinical Validation Claims	References	Molecular Diagnostic Services Program (MolDX) Recommendations
Oncotype Dx AR-V7 Nucleus Detect	Epic Sciences: Nuclear-localized AR-V7 protein in CTCs	mCRPC patients prior to receiving an ARSi or taxane chemotherapy	• PSA, RECIST, rPFS, & OS for non-response to an ARSi. • OS in relationship to use of an ARSi vs. taxane chemotherapy.	AR-V7+: • Resistance to ARSi • Improved outcomes on taxane AR-V7-: • May respond and have improved OS to ARSi		Covered for mCRPC patients who have failed 1 ARSi and are considering another
AR-V7 Prostate Cancer	Johns Hopkins: RT-PCR detection of AR-V7 mRNA following CTC selection	mCRPC patients prior to receiving an ARSi	• PSA, RECIST, rPFS, & OS for non-response to an ARSi.	AR-V7+: • Resistance to ARSi		Not recommended

Since not all AR-V7 tests are the same, both in the methodology of detection in test analytics, and clinical applicability of the tests, the above chart provides an overview of AR-V7 testing modalities which have undergone clinical validation.

The data support that the utilization of the test can improve clinical outcomes should treatment decisions be informed based on AR-V7 status. This testing has the potential to benefit patients directly by maximizing life extension and quality of life through a more personalized application of current FDA-approved therapies. We ask the NCCN panel to consider updating the NCCN discussion guide, ss footnote and treatment algorithm based on the strength of the latest evidence on nuclear AR-V7 testing.

Sincerely,

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