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NCCN Guidelines Panel: Prostate Cancer

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Prostate Cancer Guidelines Panel consider the requested updates pertaining to the evaluation and management of patients with prostate cancer.

- 1. Requested Update: Amend “Genetic and Molecular Biomarker Analysis for Advanced Prostate Cancer” (PROS-8) and “Principles of Genetics” (PROS-B) to indicate that comprehensive genomic profiling via a validated and/or FDA-approved assay (versus “tumor testing”) is recommended for all patients diagnosed with metastatic prostate cancer**

Rationale: Comprehensive genomic profiling (CGP) using a validated NGS-based assay will simultaneously detect pathogenic alterations that lead to FDA-approved targeted therapies, immunotherapies, and eligibility for biomarker-driven clinical trials.^{1,2} CGP can efficiently detect both somatic and germline gene alterations (e.g. HRRm, *NTRK* fusions, MMR gene alterations), tumor mutational burden (TMB), genome-wide loss of heterozygosity (g-LOH), and MSI status using a single sample.³⁵ This allows conservation of tissue while obtaining as much information as possible to inform the use of currently available biomarker driven therapies, immunotherapy, define/refine clinical trial options, as well as potentially inform the need for confirmatory germline testing for the patient and their family members when appropriate.

- Current FDA-approved targeted therapies with a CGP companion diagnostic in prostate cancer include: Olaparib^{1-3,5} and Rucaparib.^{1,2,4,6}
- Current FDA-approved targeted therapies with a CGP companion diagnostic across all solid tumors include: TMB-pembrolizumab^{1,7,8}; *NTRK* 1/2/3 fusions-larotrectinib.^{1,9,11}
- MSI-H status leading to FDA-approved immunotherapy (pembrolizumab, no current CDx) and *NTRK* 1/2/3 fusions leading to FDA-approved targeted therapy (entrectinib, no current CDx) can also be determined by CGP.^{1,2,7,10,12}

Rationale: CGP testing has the ability to simultaneously detect emerging biomarkers and complex signatures enabling access to clinical trials.

CDK12-CDK12 pathogenic alterations occur in 5-7% of mCRPC,¹³⁻¹⁵ representing an aggressive prostate cancer subgroup that responds poorly to standard systemic therapies, including ADT, novel hormonal therapies, and taxanes.^{16,17} A proportion of this subgroup may respond favorably to PD-1 inhibitors, suggesting that anti-PD-1 agents potentially should be utilized earlier in the disease course in *CDK12*-altered mCRPC. Clinical trials are ongoing (IMPACT NCT03570619)³¹ and under development, making identification of *CDK12*-altered mCRPC of high importance.

Tumor mutational burden (TMB) – In addition to current FDA-approved immunotherapy selection,^{1,7} TMB as measured by a validated and/or FDA-approved assay may inform response to combination immunotherapy,¹⁸ as well as determine eligibility for clinical trial enrollment in patients with metastatic prostate cancer (NCT04019964, NCT02693535).^{32,34} In recently presented data, patients with advanced solid tumors (including prostate cancer) and a TMB above 16 mutations per megabase (mut/Mb) who were treated with atezolizumab (Tecentriq) as part of the multi-basket MyPathway (NCT02091141) trial, demonstrated durable clinical activity regardless of microsatellite instability (MSI) status.^{36,37}

Clinical Trials

Studies have shown that a CGP testing strategy, as compared to a smaller hotspot panel test strategy, increases clinical trial enrollment. In a prospective trial of patients with a wide variety of refractory tumors at an academic institution, a CGP test strategy with a large (409) gene NGS panel increased clinical trial enrollment from 11% to 19 % compared to a smaller (46 or 50) gene NGS hotspot panel.¹⁹ A retrospective analysis of medical records at a community oncology practice over a three year period for patients with advanced cancers concluded that clinical trial enrollment was facilitated by CGP use in the community setting.²⁰

Numerous promising therapeutic approaches are based upon genomic characterization of tumors and therefore many clinical trials require specified genomic alterations for patient enrollment, including trials offered by the NCI (MATCH NCT02465060)³³ and ASCO (TAPUR NCT02693535).³⁴ Consistent with the NCCN® recommendation to provide patients with opportunities to participate in therapeutic clinical trials, comprehensive genomic profiling assays like FoundationOne® CDx, can potentially match more patients to targeted therapies in clinical trials based on detected alterations. Foundation Medicine is an approved

testing platform for both NCI-MATCH and ASCO TAPUR and is accelerating accrual to these transformative trials using the combination of CGP and clinical trial matching capabilities.

- 2. Requested update: Add footnote (PROS-16) and indication statement for somatic tumor testing (PROS-B 2 of 2) stating that AR amplifications as determined by a validated NGS-based assay can aid treatment decisions where novel hormonal therapy and taxane chemotherapy are being considered.**

Rationale: Anticipation of the degree of benefit of novel hormonal therapy (NHT) is useful for considering treatment planning, and could potentially aid the decision to escalate chemotherapy use or enrollment in clinical trials.²¹ AR amplifications are assessed as part of routine comprehensive genomic profiling and have relatively high prevalence of detection on NGS-based assays.²²

A recent meta-analysis has highlighted the association with pre-therapy detection of AR amplifications with subsequent reduced benefit of NHT, without observed reduced magnitude of reduced benefit of taxane chemotherapy.²³ This analysis was remarkable in a few ways: the number of patients (> 1500), number of studies (16), number of countries (9) and continents (3) of origin of patients, observing highly homogenous results: $I^2 = 0\%$ for both PFS and OS from time of NHT initiation dependent upon AR amplification detection at that time. Of the 1224 treated with abiraterone or enzalutamide, compared to patients testing negative, those testing positive for AR amplification had worse PFS (HR: 2.33, 95% CI: 2.00 – 2.72, $p < 0.001$) and OS (HR: 3.83, 95% CI: 3.11 – 4.70, $p < 0.001$). Conversely, among the 421 patients treated with taxane chemotherapy, the poor prognostic association was weaker for PFS (HR: 1.41, 95%CI: 0.88 – 2.27) and OS (HR: 1.76, 95%CI: 1.13 – 2.72), suggesting that taxane chemotherapy might be preferable to abiraterone or enzalutamide for maximizing progression free survival or overall survival for patients with AR amplifications. While many of the studies included in the meta-analysis were single cohort retrospective studies, at least one was a prospective randomized controlled trial explicitly designed to evaluate efficacy and durability of benefit of abiraterone and enzalutamide²² and two studies explicitly evaluated both NHT and taxane outcomes in tandem with use of formal test for predictive treatment interactions.^{24,25} Notably, the PFS and OS associations of AR amplification status prior to NHT initiation are consistent whether it was the initiation of 1st line NHT or later line NHT ($I^2 = 0\%$). Tolmeijer²³ and colleagues noted that the proportion of patients testing positive across studies evaluating 1st line mCRPC patients was 21.4% vs. 37.3% for 2nd or higher lines of therapy. This establishes clinical validity for AR amplification at both of these treatment decision points, and indirectly supports the notion that repeat testing might have value for optimized treatment decisions where the use of NHT is considered

- 3. Requested update: Indicate that plasma ctDNA testing may be the preferred option for molecular profiling when the metastatic site is bone on page PROS-B 2 of 2.**

Rationale: Obtaining sufficient tumor from metastatic bony lesions is a known challenge in prostate cancer where 85-90% of men with mCRPC have bone metastasis, and 42.9% have bone-only disease.²⁶⁻²⁸ In the PROfound trial, data presented on 204 men with bone metastatic biopsy specimens showed that only 42.6% had successful CGP testing, making the option of ctDNA testing at diagnosis particularly important in bone-only disease.²⁹

A recent analysis from a large (N=3334) cohort of patients with prostate cancer undergoing plasma-based CGP testing (including 1674 screening samples from TRITON2/3) showed high concordance at the variant level for BRCA1/2 to matched tissue-based CGP testing. These results support a high level of confidence in the ability of plasma-based CGP to detect BRCA1/2 alterations in prostate cancer, with reflex to tissue-based CGP if no actionable alterations are identified.³⁰

- 4. Requested update: Indicate that the panel strongly recommends molecular evaluation (preferably with comprehensive genomic profiling) at the time of biochemical recurrence or radiographic progression on pages PROS-10,11,12.**

Rationale: Early and broad molecular profiling is becoming increasingly important as novel targeted therapies and immunotherapies are being tested and approved in earlier lines of treatment. Early detection of AR alterations including ARamp (above) aids in anticipating degree of NHT benefit (and potential for NHT resistance), potential role of Docetaxel, and potential eligibility for clinical trials targeting the AR pathway.^{21-25,30}

- 5. Requested update: Indicate that comprehensive genomic profiling via a validated and/or FDA-approved assay is indicated for the 'very high risk' group on page PROS-2.**

Rationale: Very high risk patients urgently need novel therapies and access to clinical trials. Broad molecular profiling of the very high risk patient will optimally identify potential targets for therapeutic intervention and opportunities for clinical trials.^{19,20,31-34}

- 6. Requested Update: Add TMB-H to pembrolizumab indication in immunotherapy section and add NTRK gene fusions with larotrectinib and entrectinib therapeutic options on PROS-H 2 of 3.**

Rationale: The above indications are FDA-approved across all solid tumors, including prostate cancer.^{1,7,9,10}

Thank you for your review of this submission.

Sincerely,



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