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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.

Requested Update and Rationale: Amend the sections "Genetic and Molecular Biomarker Analysis for Advanced Prostate Cancer"(PROS-8) and "Principles of Genetics" (PROS-B) to indicate that testing for homologous recombination repair mutations (HRRm), NTRK gene fusions, mismatch repair deficiency (dMMR), microsatellite instability (MSI) status, and tumor mutational burden (TMB) can be achieved via a single validated NGS-based comprehensive genomic profiling (CGP) assay (as opposed to sequential testing of single biomarkers or use of limited molecular diagnostic panels).

CGP can efficiently detect both somatic and germline individual gene alterations (eg. HRRm, *NTRK* fusions, MMR gene alterations), TMB, and MSI status using a single sample. This would allow conservation of tissue while obtaining as much information as possible to inform the use of currently available biomarker driven therapies, immunotherapy, and define/refine clinical trial options, as well as to potentially inform the need for confirmatory germline testing for the patient and their family members when appropriate.

- **HRR genes**
  - CGP can identify pathogenic alterations in all NCCN recommended HRR genes (*BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CDK12, CHEK2*) simultaneously[21].
  - Homologous recombination deficiency is associated with poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitor responses in prostate cancer. Up to 27% of metastatic castration resistant prostate cancer (mCRPC) harbor somatic or germline deleterious alterations in DNA damage repair genes (DDR), including HRR genes[1,2,4]. HRR gene alterations may predict sensitivity to PARP inhibition; of which *BRCA1, BRCA2* and *ATM* are the most well characterized[3,5-8].
  - Several clinical trials have demonstrated that PARP inhibitors have antitumor activity against mCRPC.
    - PROfound (NCT02987543) is a phase III study evaluating the PARP inhibitor, olaparib, in men with mCRPC and highlights the importance of genomic testing through CGP in this population. In patients with mCRPC with disease progression on prior NHA, olaparib provided a statistically significant and meaningful improvement in the primary endpoint of imaging-based PFS compared with physician's choice of enzalutamide or abiratone + prednisone. Cohort A included patients with germline or somatic alterations in *BRCA1, BRCA2* and/or *ATM* as identified by CGP testing through Foundation Medicine. The median imaging-based PFS was significantly longer in the olaparib group than in the control group (7.4 months vs. 3.6 months; HR for progression or death, 0.34; 95% CI, 0.25 to 0.47; P<0.001). The confirmed ORR among patients who could be evaluated was 33% in the olaparib group and 2% in the control group (odds ratio for objective response, 20.86; 95% CI, 4.18 to 379.18; P<0.001). Olaparib improved multiple clinical and patient-reported endpoints (rPFS, ORR, time to pain progression) and was well tolerated with a safety profile generally consistent with that seen in other cancers. Despite >80% cross-over, at interim analysis olaparib had a favorable trend in OS vs physician's choice for patients with *BRCA1*, *BRCA2* and/or *ATM* alteration (HR = 0.64)[10]. Based on this data, the FDA has granted priority review of olaparib for the treatment of men with mCRPC and deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene mutations, who have progressed following prior treatment with a new hormonal agent[13].
    - The phase 2 TRITON2 (NCT02952534) and phase 3 TRITON3 (NCT02975934) studies are investigating the PARP inhibitor, rucaparib, in patients with mCRPC harboring an alteration in an HRR gene. Both tumor tissue and plasma CGP assays through Foundation Medicine were used to detect HRR gene alterations among study participants. Among evaluable patients with a *BRCA1/2* alteration, 43.9% (25/57) had a confirmed investigator-assessed radiographic response; 52.0%(51/98) had a confirmed PSA response. Among patients who demonstrated a confirmed radiographic response, the majority (60%) had a response lasting longer than 24 weeks. Out of the 57 evaluable patients with BRCA1/2 alterations, 61% (35/57) were somatic in origin, 37% (21/57) were germline in origin, and 1 patient had undetermined germline/somatic status. Patients with a germline BRCA1/2 alteration had a similar ORR by investigator assessment to those with a somatic BRCA1/2 alteration, with ORRs of 38.1% (8/21; 95% CI, 18.1%–61.6%) and 48.6% (17/35; 95% CI, 31.4%–66.0%). Confirmed radiographic or PSA responses were also observed in patients with alterations in other DDR genes, including *PALB2, BRIP1, FANCA, and RAD51B*[3,5]. Based on initial efficacy and safety data from TRITON2, the FDA

granted Clovis Oncology priority review for rucaparib as a monotherapy treatment of adult patients with *BRCA1/2*-mutated mCRPC who have received at least 1 prior AR-directed therapy and taxane-based chemotherapy[12].

- **NTRK gene fusions**
  - Vitrakvi®(larotrectinib) is FDA-approved for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment[19]. In a pooled analysis of three phase 1-2 trials (NCT02122913;NCT02637687;NCT02576431), the proportion of patients with NTRK-fusion positives solid tumors with investigator-assessed objective response was 121 (79%,95% CI 72-85) of 153 evaluable patients, with 24 (16%) having complete response[17].
  - Rozyltrek®(entrectinib) is FDA-approved for the treatment of adults and pediatric patients 12 years and older with *NTRK* gene fusion positive solid tumors[20]. In an integrated analysis of three phase 1-2 trials of entrectinib (ALKA-372-001 (EudraCT, 2012-000148-88); STARTRK-1 (NCT02097810); STARTRK-2 (NCT02568267)), the efficacy evaluable population was comprised of 54 adults with advanced or metastatic NTRK fusion-positive solid tumours. Over a median follow-up of 12.9 months, 57% (31/54) of patients had an objective response and the median duration of response was 10 months[18].

- **Clinical Trials**
  - 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) and ASCO (TAPUR NCT02693535). 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.

Requested Update and Rationale: Amend the sections "Genetic and Molecular Biomarker Analysis for Advanced Prostate Cancer"(PROS-8) and "Principles of Genetics" (PROS-B) to indicate that CGP testing via a validated, NGS-based liquid biopsy test is an acceptable testing method.

Given that tumor profiling in metastatic tissue samples from prostate cancer patients is challenging, particularly bone and lung, these patients should have the option of NGS-based CGP via a liquid biopsy sample.

- Obtaining sufficient tumor from metastatic bony lesions is a known challenge in prostate cancer where 85% of mCRPC patients have bone-only disease[9,11].
- In a study of n=59 patients with metastatic prostate cancer that were biopsied for testing with a tissue-based broad panel molecular test, adequate tissue for testing form a bone biopsy (n=31) was obtained in 71% of patients. Additionally, lymph node samples (n=18) resulted in 78% having adequate tumor tissue for testing[15].
- In another analysis of patients enrolled in the phase 2 TRITON2 and phase 3 TRITON3 studies investigating rucaparib in patients with mCRPC harboring an alteration in an HRR gene, a total of 1311 tumor samples (from 1516 patients) were collected to determine eligibility for these studies; the test failure rate was 32%, mainly (18%) due to insufficient tumor content or DNA yield[14].

Studies have shown high concordance between actionable alterations identified by tissue CGP and liquid CGP testing methodologies in prostate cancer patients, making liquid biopsy an acceptable sample type.

- In the analysis of patients enrolled in the phase2 TRITON2 and phase 3 TRITON3 referenced above, the concordance between BRCA1/2 mutations in tissue and liquid samples (using FoundationOne Liquid) was evaluated in 161 patients, 34 of whom had a BRCA1/2 mutation; 74% (25/34) of patients with a BRCA1/2 mutation were identified by both tissue and liquid samples[14].

Thank you for your review of this submission.

Sincerely,

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