Submitted by: Vincent A. Miller, MD Company: Foundation Medicine, Inc. Address: 150 Second Street, Cambridge, MA 02141 Phone: 617-418-2259 Email: <u>vmiller@foundationmedicine.com</u> Date of request: August 23, 2018 NCCN Guidelines Panel: Bladder

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN<sup>®</sup> Bladder Cancer Guideline Panel to consider the requested updates and enclosed references, pertaining to the evaluation and management of patients with bladder cancer.

## **Specific Changes and Rationale**

We respectfully request that the Panel clarify the footnote "Consider molecular testing in a CLIA-laboratory. See Discussion" (BL-8, Footnote Z) and expand the discussion to indicate that molecular testing is optimally completed as part of a validated comprehensive genomic profiling (CGP) assay<sup>1</sup>, such as FoundationOne CDx, via a single assay (as opposed to sequential testing of single biomarkers or use of limited molecular diagnostic panels) in order to conserve tissue and to obtain as much information as possible to inform the use of currently available biomarker driven therapies and define/refine clinical trial options.

CGP can identify genomic alterations in *FGFR3, ERBB2, ERBB3, TSC1, NF2, MTOR, BRCA2* and other DNA damage response genes, as well high tumor mutational burden (TMB) or high microsatellite instability status (MSI-High) that may inform the patient's treatment, including the option to enroll in genomically matched clinical trials. The following data supports the rationale for our request:

- FGFR3 mutation, fusion or amplification are observed in 17% of bladder cancer cases<sup>2</sup>. In a Phase 2 trial of the FGFR inhibitor erdafitinib for patients with FGFR-altered inoperable or metastatic urothelial carcinoma, the overall response rate (ORR) was 42% (3% complete response) and the disease control rate (DCR) was 80%<sup>3</sup>. In a trial of the FGFR inhibitor BGJ398 for patients with advanced or metastatic urothelial harboring an FGFR3 alteration, the overall response rate (ORR) was 25.4% and the disease control rate (DCR) was 64.2%<sup>4</sup>.
- ERBB2 (HER2) mutation or amplification is observed in 9% of bladder cancer cases and ERBB3 (HER3) mutation is observed in 6% of cases<sup>2</sup>. In a Phase 2 trial of a pan-ERBB kinase inhibitor for patients with metastatic platinum-refractory urothelial carcinoma, 5 of 6 (83%) patients with an ERBB2 or ERBB3 alteration achieved progression-free survival at 3 months (PFS3); in contrast 0 of 15 without an ERBB2 or ERBB3 alteration were progression free at this landmark<sup>5</sup>. In the Phase 2 basket study (MyPathway trial), of 9 patients with HER2-positive (amplification or overexpression) bladder cancer treated with the HER2 targeted antibodies pertuzumab plus trastuzumab the overall response rate was 33% (including 2 partial responses and 1 complete response) and 2/9 additional patients had prolonged stable disease (>120 days)<sup>6</sup>.
- *TSC1* mutations are observed in 8% of bladder cancer cases<sup>2</sup>. In a Phase 2 trial of the mTOR inhibitor everolimus for patients with metastatic urothelial carcinoma, retrospective genomic profiling identified a subset of patients harboring *TSC1* mutation who remained on treatment longer compared to patients without *TSC1* mutation (7.7 months versus 2.0 months)<sup>7</sup>.
- DNA damage response and repair (DDR) genomic alterations are observed in 25% of patients with urothelial carcinoma<sup>8</sup>. In a study of patients with metastatic urothelial carcinoma treated with either anti-PD-1 or PD-L1 antibodies, the response rate was higher for patients harboring a deleterious DDR genomic alteration compared to patients without a DDR alteration (67.9%

versus 18.8%)<sup>8</sup>; DDR alterations in 34 genes were identified using a next-generation sequencingbased assay.

- Responses to matched targeted therapy have also been reported for patients with urothelial carcinoma harboring genomic alterations in *BRCA2<sup>9</sup>*, *MTOR*<sup>10</sup> or *NF2*<sup>11</sup>.
- In the Phase 3 IMvigor211 trial of atezolizumab versus chemotherapy for patients with
  platinum-treated locally advanced or metastatic urothelial carcinoma, in the high TMB subset
  overall survival was improved for patients treated with atezolizumab compared to
  chemotherapy (11.3 months vs 8.3 months), whereas overall survival was similar between
  treatment groups for cases with low TMB<sup>12</sup>. Similarly, in the Phase 2 IMvigor 210 study of
  atezolizumab for patients with locally advanced or metastatic urothelial carcinoma, for patients
  with platinum-treated urothelial carcinoma TMB was significantly increased in responders
  versus non-responders<sup>13</sup>; for patients with cisplatin-ineligible disease treated with first-line
  atezolizumab, TMB was significantly increased in responders versus non-responders and
  patients with high TMB had significantly longer overall survival compared to patients with low
  TMB<sup>14</sup>.
- MSI-High status is observed in 3% of urothelial carcinomas<sup>15</sup>. In one study 5 of 5 patients with MSI-High urothelial carcinoma treated with immune checkpoint blockade, had a response including 3/5 who experienced a complete response<sup>15</sup>. Given the low frequency of MSI-High urothelial carcinoma, routine testing of MSI using CGP, which also identifies other clinically relevant genomic alterations, allows more efficient use of tissue than standalone MSI-testing.

Taken together these data suggest that routine broad-based CGP of patients with bladder cancer via a single assay is the most efficient and thorough approach to identify both common genomic alterations and genomic signatures such as TMB and MSI which identify patients for treatment with approved agents (such as pembrolizumab) and enrollment into genomics-matched clinical trials.

Thank you for your review of this submission.

Sincerely,

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