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NCCN Guidelines Panel: NCCN Melanoma Panel

To the NCCN panel members:

On behalf of Foundation Medicine, Inc., I respectfully request that the NCCN Melanoma Panel review the following information and thereafter recommend validated comprehensive genomic profiling (CGP) assays to support clinical trial selection and enrollment for patients with melanoma.

We define validated CGP as hybrid capture, next-generation sequencing based testing with high unique coverage (>250x) of hundreds of cancer-related genes known to be somatically altered in human cancer that is capable of detecting all four classes of genomic alterations (base pair substitutions, insertion/deletions, copy number alterations, and rearrangements) and has been analytically validated in one or more manuscripts published in peer reviewed journals. We feel it is critical that patients, who are being assessed for enrollment in a clinical trial of a molecularly targeted therapy, be tested with validated CGP given the studies that have shown that patients on molecularly matched clinical trials have been demonstrated to have superior RR, PFS¹ and OS vs. those on unmatched trials^{1,2}.

Specific Changes:

1. In footnotes “o” for Stage III evaluation and treatment (ME-4, ME-5), change:

Current language:

“Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but not recommended for patients who are otherwise NED.”

To Requested language:

“Mutational analysis, including use of validated comprehensive genomic profiling (CGP) is recommended if patients are being considered for either routine treatment or clinical trials, but not recommended for patients who are otherwise NED.”

2. In the Stage IV workup (ME-6), change

Current language:

“Biopsy preferred over FNA if archival tissue is not available for genetic analysis”

To Requested language:

“Biopsy preferred over FNA if archival tissue is not available for genetic analysis, including use of validated comprehensive genomic profiling (CGP)”

3. In footnotes “w” for Stage IV evaluation and treatment (ME-6), change:

Current language:

“Obtain tissue for genetic analysis from either the biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy or if the tissue is relevant to eligibility for participation in a clinical trial.”

To Requested language:

“Obtain tissue for genetic analysis, including validated comprehensive genomic profiling (CGP), from either the biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy or if the tissue is relevant to eligibility for participation in a clinical trial.”

4. In footnote “3” in Section ME-A, Principles of Biopsy and Pathology, change:

Current language:

“While there is interest in newer prognostic molecular techniques, such as gene expression profiling, to differentiate melanomas at low-versus high-risk for metastasis, routine (baseline) genetic testing of primary melanomas (before or following SLNB) is not recommended outside of a clinical trial. Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but not recommended for patients who are otherwise NED.”

To Requested Language:

“While there is interest in newer prognostic molecular techniques, such as gene expression profiling, to differentiate melanomas at low-versus high-risk for metastasis, routine (baseline) genetic testing of primary melanomas (before or following SLNB) is not recommended outside of a clinical trial. **Validated comprehensive genomic profiling (CGP)** is recommended if patients are being considered for either routine treatment or clinical trials, but not recommended for patients who are otherwise NED.”

Rationale:

It is well understood that patients on molecularly matched clinical trials have been demonstrated to have superior PFS¹ and OS vs. those on unmatched trials^{1,2}. Beyond the well-known BRAF V600E alteration, melanomas can harbor other clinically relevant alterations associated with both sensitivity and resistance to targeted therapies that can assist in optimizing clinical trial selection for eligible patients. See examples in the table below.

Emerging Targeted Agents for Patients with Genomic Alterations (as of May 15, 2015)

Genomic Alteration (i.e. Driver event) associated with sensitivity to targeted agent	Available targeted agents with activity against driver event in melanoma
<i>BRAF</i> V600E mutations	Dabrafenib or vemurafenib ^{3,4} , +/-trametinib (MEKi) ⁵
Non-V600E <i>BRAF</i> mutations	Trametinib ^{6,7} , and other experimental MEK-inhibitors
<i>BRAF</i> rearrangements	Sorafenib ^{8,9} ; trametinib ¹⁰ and other experimental MEK-inhibitors
<i>KIT</i> mutations	Imatinib ^{11,12} , nilotinib ¹³ , dasatinib ¹⁴
<i>NRAS</i> mutations	Trametinib ¹⁵ and other experimental MEK-inhibitors +/- CDK4/6 inhibitors ¹⁶
<i>MAP2K1</i> mutations	Trametinib ¹⁷ and other experimental MEK-inhibitors

Genomic Alteration (i.e. Driver event) associated with resistance to targeted agents	Available targeted agents with <u>lack of activity</u> against driver event in melanoma
<i>NRAS</i> mutations	Vemurafenib/dabrafenib ^{18,19}
<i>MAP2K1</i> mutations	Vemurafenib/dabrafenib ^{19,20}

Validated CGP has identified an expanded set of targetable genomic alterations that can be treated with drugs approved specifically for melanoma or currently under clinical investigation (Figure 1). Stage III and Stage IV patients who are candidates for systemic treatment will have more options available to them when their tumors are screened using validated CGP. The goal should not be to “sample” targetable driver alterations through narrow molecular testing, but to simultaneously evaluate *all* cancer-related genes to find alterations that might render sensitivity to a targeted therapy and thus have an impact on clinical trial eligibility and stratification. Results from validated CGP have the potential to identify known and novel oncogenic alterations in this disease that may guide precision trial selection.

In Foundation Medicine’s experience with patients with melanoma (see figure 1), validated CGP identifies FDA approved on-label therapies, therapies on NCCN Guidelines, or clinical trials for >95% of patients. Additionally, there are >90 active trials for targeted agents (see Table 1) that require a genomic alteration as inclusion criteria. Due to both the greater breadth and superior sensitivity and specificity of validated CGP, more patients will be identified for targeted therapy.

Validation of CGP assays should demonstrate high sensitivity and specificity (95-99% sensitivity, PPV >99%) across all classes of alterations determined through testing of clinical samples ($\geq 20\%$ tumor content) and cell line models²¹. Additionally, sequencing should cover the entire coding regions of cancer-related genes to a median unique sequencing depth of >250x to ensure that all classes of clinically relevant alterations will be detected, thus maximizing the number of therapeutic targets and increasing treatment options for patients including clinical trials. Conservation of tissue using this approach helps ensure that genomic alterations are not missed due to limitations in tissue availability or purity, and reduces the risk of repeat biopsy procedures.

We appreciate the panel’s consideration of this request and are optimistic the panel will arrive at a recommendation that encourages approved targeted treatment options, as well as clinical trial enrollment, for melanoma patients with stage III or stage IV cancer. Should you have any questions about the information in our submission, please do not hesitate to contact me.

Sincerely,


Vincent Miller, M.D., Chief Medical Officer
Foundation Medicine, Inc.

References

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