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NCCN Guidelines Panel: Breast Cancer

Dear Panel Members,

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

Requested Updates:

1. **Amend "Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease" section on page BINV-R 1 of 3 include TMB testing by validated and/or FDA approved targeted next generation sequencing panel to inform the use of pembrolizumab. (refence Merino 2020 for validation standards)**
2. **Add pembrolizumab as a treatment option for patients with unresectable or metastatic tumors with tissue tumor mutational burden-high (tTMB-H) ≥10 mutations/megabase, as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options. (footnote f page BINB-R 1 of 3)**

Rationale for Requested Updates:

KEYNOTE-158 (NCT02628067) was a multicohort, single-arm, open-label phase 2 study evaluating pembrolizumab monotherapy in 1066 patients with selected previously treated advanced solid tumors, who were administered pembrolizumab 200 mg once every 3 weeks by intravenous infusion[1]. 790/1073 patients had an evaluable tissue TMB (tTMB) score (efficacy population), and 102 (13%) were tTMB-high, defined as ≥10 mutations/megabase. TMB-high status was associated with a clinically meaningful improvement as demonstrated by an objective response rate (ORR) of 29% (95% CI, 21-39), compared to 6% (95% CI, 5-8) in the non-tTMB-high group (primary endpoint). At a median follow-up of approximately 3 years, the median duration of response was not reached in the tTMB-high group and was 33.1 months in the non–tTMB-high group. Additional secondary outcomes at landmark timepoints include the 2-year PFS rate of 22% in the tTMB-high group vs. 7% in the non–tTMB-high group, and the 3-year OS rate of 32% in the tTMB-high group versus 22% in the non–tTMB-high group. The predictive value of tTMB was independent of other biomarkers, including microsatellite instability (MSI)-high and PD-L1 expression. Additionally, the predictive value of tTMB did not appear to be driven by a particular tumor type, with an increased response rate for TMB-high patients observed across most tumor types. Based on the results of KEYNOTE-158, pembrolizumab is now FDA-approved for patients with unresectable or metastatic solid tumors with tTMB-high (≥10 mutations/megabase), as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options[2,3].

TMB is a complex continuous biomarker and TMB estimation provided by next generation sequencing (NGS) targeted panels can vary across laboratories due to factors such as differences in panel size, gene coverage, and bioinformatics pipelines. Because of the important role TMB now plays in clinical decision-making and the potential for variation across laboratories, the Friends of Cancer Research convened a consortium of key stakeholders to recommend best practices and approaches for TMB measurement, validation, alignment and reporting[4]. Stakeholders, including the FDA, the National Cancer Institute, diagnostic manufacturers, academics, and pharmaceutical companies published detailed recommendations around TMB reporting consistency, standardization of analytical validation studies for TMB estimation, and alignment of panel TMB values to a whole exome sequencing (WES)-derived universal reference standard[4]. All tests that report a TMB value should comply with the recommendations as published and/or be FDA-approved for TMB measurement and reporting purposes[3,5].

Thank you for your review of this submission.

Sincerely,



Brian Alexander, M.D.
Chief Medical Officer
Foundation Medicine

References

1. Marabelle, Fakih, Lopez et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab in the multicohort, open-label, phase 2 KEYNOTE-158 study, *Lancet Oncology*, in submission. (ESMO 2019 presentation attached)
2. KEYTRUDA (pembrolizumab) FDA approved label found at https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf
3. FDA Label: Foundation Medicine Inc. FoundationOne® CDx Technical Information. attached
4. Merino DM, McShane LM, Fabrizio D, et al. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. *J Immunother Cancer* 2020;8:e000147.
5. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med*. 2017;9(1):34. Published 2017 Apr 19. doi:10.1186/s13073-017-0424-2