**Purpose:** To establish guideline for MTB recommendations of off-label use of molecular-targeted therapies for advanced cancer. Off-label therapy will not be recommended outside of this guidance document.

**Elastic document:** This document can be amended to add/remove conditions for off label therapy MTB co-chairs based on new evidence. Amendments will occur by the following process: (a) MTB collaborator or co-chair will nominate adding or removing a biomarker-off label therapy pair and submit a minimum of two primary research articles supporting its use, including at least one human clinical investigation. Additionally a high-quality review article can be supplied. (b) At MTB journal club meeting the nominator or sponsoring co-chair will present evidence. Co-chairs will be responsible for identifying counter-evidence. (c) Decision will be made by agreement of co-chairs or, failing that, majority vote of co-chairs present.

**Provisional approval:** Provisional approval is granted for drug-biomarker pairs when exceptionally strong preclinical data is available with FDA approved drugs, but clinical data on drug-biomarker pair beyond case reports or abstracts is unavailable. Literature review is required for each subsequent MTB recommendation made under a provisional criterion.

**Global condition for off-label therapy recommendation:**
The patient is not eligible for a clinical trial specific for this molecular target locally or regionally, or an available basket trial (e.g. NCI-MATCH).

**Conditions for off-label therapy:**
1. **Direct pharmacologic inhibition of an activating oncogene mutation.** This is adopted because of the broad evidence supporting the idea of oncogene addiction with concordant data from multiple models (cell lines, animal models) and human clinical evidence across multiple disease types.
   Criteria for recommendation (all must apply):
   a. Sequencing or genetic testing of tumor reveals an oncogenic mutation\(^1\)
   b. An FDA-approved drug that inactivates oncogene function is available\(^2\)
   c. Single-agent targeted therapy is preferred, but on rare occasions combinations (including combinations of two off-label targeted agents that meet criteria) are allowed if appropriate rationale is provided under patient-specific regimen and safety is known.
   d. The targeted agent is not known to be ineffective for this disease (e.g. BRAF inhibitors in colorectal cancer).

   e.g. Allowed under this condition: Erlotinib or afatinib for activating EGFR mutations; Lapatinib or afatinib for activating HER2 mutations; Trastuzumab as a single agent for

\(^1\) Any genetic sequencing testing is allowed, such as point mutation, indel, or translocation. Amplification or overexpression is excluded. The alternation must be known to activate an established oncogene.

\(^2\) Antibodies used for oncogene overexpression are excluded (e.g. trastuzumab, cetuximab).
HER2 amplifications; Crizotinib for activating ALK mutations/translocations; Vemurafenib or dabrafenib for activating BRAF mutations (except colorectal cancer), Imatinib for activating CKIT mutations, Everolimus or rapamycin for activating TORC1 mutations. Disallowed: Trastuzumab for activating HER2 mutations; Lapatinib for amplification of HER2 in carcinoid.

2. mTOR inhibitor such as everolimus or temsirolimus for tumors with activating PIK3CA mutation (adopted 11/5/2015)\textsuperscript{1,2,3,4}

3. Dabrafenib in combination with Trametinib for activating BRAF mutations in all cancer types (adopted 4/7/16)\textsuperscript{10,11,12}

4. Olaparib for all BRCA1/2 mutant cancers (adopted 5/10/16)\textsuperscript{13,14,15}

5. Pembrolizumab for cancers with mismatch repair deficiency confirmed by IHC or MSI testing (adopted 7/7/2016)\textsuperscript{16,17,18}

6. Combination of trastuzumab and pertuzumab or trastuzumab and lapatinib for all HER2 amplified cancers if the amplification is confirmed by IHC or FISH analysis (adopted 8/4/2016)\textsuperscript{19,20,21}

Provisional approval:

1. Vandetanib for cancers with Fumarate Hydratase loss of function (adopted 1/7/2016)\textsuperscript{5,6}

2. Crizotinib or Cabozantinib for all c-Met amplified cancers if the amplification is confirmed by FISH analysis (adopted 3/3/2016)\textsuperscript{7,8,9}
References:


