TMLA

TUMOUR MUTATION LOAD FOR IMMUNOTHERAPY
The Oncofocus Tumor Mutation Load Test is a next-generation sequencing (NGS) assay that targets 409 genes spanning 1.7Mb of the genome to accurately provide an assessment of Mutation Load (mutations/Mb). The test is designed to select patients most likely to respond to immunotherapies.

**Clinically Significant Biomarkers**

<table>
<thead>
<tr>
<th>Genomic Alteration</th>
<th>Relevant Therapies (In this cancer type)</th>
<th>Relevant Therapies (In other cancer type)</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Mutational Burden</td>
<td>Clinical trials and/or off-label</td>
<td>ipilimumab + nivolumab, nivolumab</td>
<td>10</td>
</tr>
<tr>
<td>22.68 Mut/Mb measured</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources included in relevant therapies: EMA¹, FDA², ESMO, NCCN
QC acceptance criteria: Average coverage >300, SNPs consistent with deamination 80%

**Relevant Therapy Summary**

- In this cancer type
- In other cancer type
- In this cancer type and other cancer types
- Contraindicated
- Both for use and contraindicated
- No evidence

**Tumor Mutational Burden**

<table>
<thead>
<tr>
<th>Relevant Therapy</th>
<th>EMA</th>
<th>FDA</th>
<th>ESMO</th>
<th>NCCN</th>
<th>Clinical Trials*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ipilimumab + nivolumab</td>
<td>x</td>
<td>x</td>
<td>o</td>
<td>o</td>
<td>(II)</td>
</tr>
<tr>
<td>nivolumab</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>o</td>
<td>(II)</td>
</tr>
<tr>
<td>atezolizumab</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>(II)</td>
</tr>
<tr>
<td>BAT 1306 + aspirin, BAT 1306 + celecoxib</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>(II)</td>
</tr>
<tr>
<td>durvalumab + tremelimumab</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>(II)</td>
</tr>
<tr>
<td>ipilimumab + nivolumab, nivolumab</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>(II)</td>
</tr>
<tr>
<td>ipilimumab + nivolumab, pembrolizumab</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>(II)</td>
</tr>
<tr>
<td>sintilimab</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>(I/II)</td>
</tr>
<tr>
<td>BI 754091 + BI 754111</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>(I)</td>
</tr>
</tbody>
</table>

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

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Relevant Therapy Details

Current ESMO Information

**ipilimumab + nivolumab**

- **Cancer type:** Non-Small Cell Lung Cancer
- **Variant class:** Tumor Mutational Burden

**ESMO Level of Evidence/Grade of Recommendation:** I / A

- **Population segment (Line of therapy):**
  - Stage IV Squamous and Non-squamous Cell Carcinoma (First-line) (Not EMA-approved)


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Current NCCN Information

- ipilimumab + nivolumab
  - Cancer type: Non-Small Cell Lung Cancer
  - Variant class: Tumor Mutational Burden
  - NCCN Recommendation category: 2A
  - Population segment (Line of therapy):
    - Non-Small Cell Lung Cancer; Emerging targeted agents

- nivolumab
  - Cancer type: Non-Small Cell Lung Cancer
  - Variant class: Tumor Mutational Burden
  - NCCN Recommendation category: 2A
  - Population segment (Line of therapy):
    - Non-Small Cell Lung Cancer; Emerging targeted agents
Current Clinical Trials Information

Clinical Trials information is current as of 2018-12-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers'.

Tumor Mutational Burden

No NCT ID - see other identifier(s)
A Multicenter Phase II Study Of Nivolumab Monotherapy In Recurrent And/or Metastatic Gastrointestinal Cancer Patients With High Tumor Mutation Burden (TMB-H)
Cancer type: Colon Cancer
Variant class: Tumor Mutational Burden
Other identifiers: TMB-H basket, UMIN000033182
Population segments: First line, Second line, Stage III, Stage IV
Phase: II
Therapy: nivolumab
Location: Japan

No NCT ID - see other identifier(s)
TR Accompanied with the Study Titled A Multicenter Phase II Study of Nivolumab Monotherapy in Recurrent and/or Metastatic Gastrointestinal Cancer Patients with High Tumor Mutation Burden (TMB-H).
Cancer type: Colon Cancer
Variant class: Tumor Mutational Burden
Other identifiers: TMB-H basket TR, UMIN000033560
Population segments: Line of therapy N/A, Stage III, Stage IV
Phase: II
Therapy: nivolumab
Location: Japan

NCT02091141
My Pathway: An Open-Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib/Cobimetinib, Vismodegib, Alectinib, and Atezolizumab in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents
Cancer type: Unspecified Solid Tumor
Variant class: Tumor Mutational Burden
Other identifiers: 1403013519, 2014-0459, AAAN9701, J1480, ML28897, ML28897/PRO 02, ML28897PRO/02, My Pathway, MyPathway, NCI-2014-01811, PRO 02
Population segments: BRCA, EGFR, Fourth line or greater, HER2 positive, Second line, Stage III, Stage IV, Third line
Phase: II
Therapy: atezolizumab
Location: United States
US States: AR, AZ, CA, CO, FL, GA, IL, MD, MN, MO, NC, ND, NY, OH, OK, OR, PA, SD, TN, TX, VA, WA, WI
Contact: Reference Study ID Number: ML28897 [888-662-6728; global-roche-genentech trials@gene.com]

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| NCT03638297 | Other identifier: Glishysu13  
Cancer type: Colorectal Cancer  
Variant class: Tumor Mutational Burden  
Population segments: First line, Second line, Stage IV  
Phase: II  
Therapies: BAT 1306 + aspirin, BAT 1306 + celecoxib  
Location: China |
|---|---|
| NCT02029001 | Other identifiers: ET12-081, EudraCT number: 2012-004510-34, MOST, ProfiLER  
Cancer type: Unspecified Solid Tumor  
Variant class: Tumor Mutational Burden  
Population segments: Maintenance/Consolidation, Second line, Stage III, Stage IV, Third line  
Phase: II  
Therapy: Durvalumab + Tremelimumab  
Location: France |
| NCT03297606 | Other identifiers: CA209-9DL, CAPTUR, ESR-17-12831, ML39800, PM1, WI233446  
Cancer type: Unspecified Solid Tumor  
Variant class: Tumor Mutational Burden  
Population segments: Aggressive, Diffuse large B-cell lymphoma (DLBCL), Extranodal marginal zone B-cell lymphoma (MALT), First line, Follicular lymphoma (FL), Indolent, Lymphoblastic lymphoma (LBL), Mantle cell lymphoma (MCL), Other subtype, Second line, Stage III, Stage IV, Waldenström’s macroglobulinemia (WM)  
Phase: II  
Therapy: Ipilimumab + Nivolumab  
Location: Canada |
| NCT03668119 | Other identifiers: 16-71, BMS CA209-848, BMS Checkmate 848, CA209-848, CheckMate 848, CTRIAL-I616-71, EudraCT Number: 2016-002898-35, U1111-1185-1326  
Cancer type: Unspecified Solid Tumor  
Variants class: Tumor Mutational Burden  
Population segments: Second line, Stage III, Stage IV  
Phase: II  
Therapies: Ipilimumab + Nivolumab, Nivolumab  
Locations: Australia, Italy, Romania |
### Tumor Mutational Burden (continued)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Title</th>
<th>Other identifiers</th>
<th>Population segments</th>
<th>Phase</th>
<th>Therapies</th>
<th>Location</th>
<th>US States</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02693535</td>
<td>Targeted Agent and Profiling Utilization Registry (TAPUR) Study</td>
<td></td>
<td>(N/A), Aggressive, Diffuse large B-cell lymphoma (DLBCL), Extramarginal zone B-cell lymphoma (MALT), Follicular lymphoma (FL), Indolent, Lymphoblastic lymphoma (LBL), Mantle cell lymphoma (MCL), Other subtype, Second line, Small lymphocytic lymphoma (SLL), Stage III, Stage IV, Waldenstrom’s macroglobulinemia (WM)</td>
<td>II</td>
<td>ipilimumab + nivolumab, pembrolizumab</td>
<td>United States</td>
<td>AL, AZ, CA, FL, GA, IL, MI, NC, ND, NE, OK, OR, PA, SD, TX, UT, VA, WA</td>
<td>Pam Mangat [<a href="mailto:pam.mangat@asco.org">pam.mangat@asco.org</a>]</td>
</tr>
<tr>
<td>NCT03568539</td>
<td>An Open-label, Phase Ib Multicenter Study of IBI308 in Subjects With Advanced/Metastatic Solid Malignancies</td>
<td></td>
<td>ALK, EGFR, Second line, Stage III, Stage IV</td>
<td>I/II</td>
<td>sintilimab</td>
<td>United States</td>
<td>CA, GA, IN, MI, NV, NY, OK, SC, TX</td>
<td>Xiaolei Sun [213-182-0291; <a href="mailto:xiaolei.sun@innoventbio.com">xiaolei.sun@innoventbio.com</a>]</td>
</tr>
<tr>
<td>NCT03156114</td>
<td>An Open Label, Phase I Dose-finding Study of BI 754111 in Combination With BI 754091 in Patients With Advanced Solid Cancers Followed by Expansion Cohorts at the Selected Dose of the Combination in Patients With Non-small Cell Lung Cancer and Other Solid Tumors</td>
<td></td>
<td>Second line, Stage III, Stage IV, Third line</td>
<td>I</td>
<td>BI 754091 + BI 754111</td>
<td>Canada, United States</td>
<td>FL, OK, TN, WI</td>
<td>Boehringer Ingelheim [800-243-0127; <a href="mailto:clintria.ge.rdg@boehringer-ingelheim.com">clintria.ge.rdg@boehringer-ingelheim.com</a>]</td>
</tr>
</tbody>
</table>

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### Tumor Mutational Burden (continued)

**NCT03156114**
An Open Label, Phase I Dose-finding Study of BI 754111 in Combination With BI 754091 in Patients With Advanced Solid Cancers Followed by Expansion Cohorts at the Selected Dose of the Combination in Patients With Non-small Cell Lung Cancer and Other Solid Tumors

**Cancer type:** Unspecified Solid Tumor  
**Variant class:** Tumor Mutational Burden

**Other identifiers:** 1381-0002, EudraCT Number: 2017-005042-29

**Population segments:** Second line, Stage III, Stage IV, Third line

**Phase:** I

**Therapy:** BI 754091 + BI 754111

**Locations:** Canada, United States

**US States:** FL, OK, TN, WI

**Contact:** Boehringer Ingelheim [800-243-0127; clintriage.rdg@boehringer-ingelheim.com]

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Evidence Summary by Variant Class

A variant class hierarchy was created to summarize gene variants with associated clinical evidence. Evidence items refers to citations across the different global data sources.

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Evidence Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Mutational Burden</td>
<td>14</td>
</tr>
</tbody>
</table>

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Report Authorised by

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BMS (Senior)

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