eFigure 1 Evidence of Overall Survival Benefit in Applications for Targeted Cancer Drug Indications, 2015-2021.

FDA-pivotal trials were obtained from FDA approved-labels. FDA-pivotal trials were obtained from FDA approved-labels. FDA-approved labels of All-trans Retinoic Acid (EML decision year 2015) and Filgrastim (EML decision year 2015) could not be found. Tislelizumab (EML decision year 2021) is not approved by FDA, and the label is not available. Those corresponding cancer drug indications were categorized as not having documented evidence of OS benefit based on FDA-pivotal trials.


Note: WHO EML selection criteria for 2015 and 2017 EMLs included “meaningful clinical benefit”; for 2019 and 2021 EMLs, selection criteria included overall survival benefit >4-6 months. eFigure1 presents the most recent overall survival benefit criteria for all 54 indication applications for the 2017-2021 EMLs.
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- **Recommended + OS**: Unknown or unavailable
- **Recommended + OS=4 months**: Yes
- **Recommended + OS=4 months**: Not recommended + OS=4 months: Yes

2015 FDA-Approved Label | 2017 FDA-Approved Label | 2019 FDA-Approved Label | 2021 FDA-Approved Label

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Zhou Y, et al. BMJ Glob Health 2023; 8:e012899. doi: 10.1136/bmjgh-2023-012899
eFigure 2 EML Recommendation Decisions and Documented Evidence of OS Benefit for 54 Targeted Cancer Drug Indications, 2015-2021.

FDA-pivotal trials were obtained from FDA approved-labels. FDA-pivotal trials were obtained from FDA approved-labels. FDA-approved labels of All-trans Retinoic Acid (EML decision year 2015) and Filgrastim (EML decision year 2015) could not be found. Tislelizumab (EML decision year 2021) is not approved by FDA, and the label is not available. Those corresponding cancer drug indications were categorized as not having documented evidence of OS benefit based on FDA-pivotal trials.

OS, Overall survival; ALK, anaplastic lymphoma kinase; ALL, Acute lymphoblastic leukaemia; CLL, Chronic lymphocytic leukaemia; CML, Chronic myeloid leukemia; EGFR, Epidermal growth factor receptor; Chemotherapy Facilitation, (1) Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy, (2) Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy, (3) To facilitate administration of dose dense chemotherapy regimens; HR, Hormone receptor; HER2, Human epidermal growth factor receptor 2; NSCLC, Non-small-cell lung carcinoma; WHO-TRS, WHO Technical Report Series, FDA-Approved Label, the U.S. Food and Drug Administration-approved labels.
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<td>Not available</td>
<td>Rejected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Imatinib-CML</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Imatinib-Gastrointestinal stromal tumour</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Nilotinib-Imatinib-resistant CML</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Rejected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Rituximab-CLL</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Rituximab-Diffuse large B-cell lymphoma</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Rituximab-Follicular lymphoma</td>
<td>Not found; Not available</td>
<td>Not found; Not available</td>
<td>Not found; Not available</td>
<td>Recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Trastuzumab-Early stage HER2 positive breast cancer</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>Recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Trastuzumab-Metastatic HER2 positive breast cancer</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Recommended</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

† Not found: The drug cannot be found on the ESMO-MCBS website; Not available: no trials were cited in WHO Technical Report Series; Letter score, e.g., “A”, means score in the curative setting while number, e.g., “4”, means score in non-curative setting.

ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale.

ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukemia; EGFR, epidermal growth factor receptor; Chemotherapy facilitation, (1) primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy, (2) secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy, (3) to facilitate administration of dose dense chemotherapy regimens; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; NSCLC, Non-small-cell lung cancer.
### Table 2 Discrepancies in Documented Evidence of OS Benefit in World Health Organization Technical Report Series and Pivotal Trials Obtained from US Food and Drug Administration-Approved Labels

<table>
<thead>
<tr>
<th>EML Year</th>
<th>Drug_Indication</th>
<th>Recommended for inclusion in WHO EML</th>
<th>Documented OS benefit†</th>
<th>FDA-approve d label</th>
<th>Discrepancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>WHO-TRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Trastuzumab_Early stage HER2 positive breast cancer</td>
<td>Yes</td>
<td>N/A</td>
<td>Yes</td>
<td>WHO-TRS: no OS data mentioned [no reference cited]</td>
</tr>
<tr>
<td></td>
<td>Afatinib_EGFR mutation-positive advanced NSCLC</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>WHO-TRS: documented lack of OS benefit [clinical trials: afatinib vs chemotherapy]</td>
</tr>
<tr>
<td>2015</td>
<td>Imatinib_Gastrointestinal stromal tumour²</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>FDA-approved label: documented lack of OS benefit [clinical trials: different dosing comparison]</td>
</tr>
<tr>
<td>2015</td>
<td>Rituximab_CLL</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>WHO-TRS: documented OS benefit [a systematic review of RCTs]</td>
</tr>
<tr>
<td></td>
<td>Rituximab_Diffuse large B-cell lymphoma³</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>FDA-approved label: no OS data mentioned</td>
</tr>
<tr>
<td>2015</td>
<td>Rituximab_Follicular lymphoma</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>WHO-TRS: documented OS benefit [clinical trials: rituximab + cyclophosphamide, vincristine, and prednisone (CVP) vs CVP]</td>
</tr>
<tr>
<td>2015</td>
<td>Trastuzumab_Metastatic HER2 positive breast cancer</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>WHO-TRS: documented OS benefit [systematic review of RCTs]</td>
</tr>
<tr>
<td></td>
<td>Crizotinib_ALK-positive metastatic NSCLC</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>WHO-TRS: documented OS benefit [retrospective analysis: crizotinib vs chemotherapy]</td>
</tr>
<tr>
<td>2019</td>
<td>Erlotinib_EGFR mutation-positive advanced NSCLC⁴</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>WHO-TRS: documented OS benefit [retrospective analysis, TKI →chemo vs chemo→TKI, OS benefit]</td>
</tr>
<tr>
<td></td>
<td>Gefitinib_EGFR mutation-positive advanced NSCLC⁴</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>FDA-approved label: documented lack of OS benefit [clinical trials: gefitinib vs standard chemotherapy]</td>
</tr>
<tr>
<td>2019</td>
<td>Thalidomide_Multiple myeloma</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>WHO-TRS: documented OS benefit [a rapid Cochrane network meta-analysis of RCTs]</td>
</tr>
<tr>
<td>2015</td>
<td>All-Trans Retinoic Acid_Acute promyelocytic leukaemia</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>FDA-approved label: documented lack of OS benefit [clinical trials: Thalidomide/Dexamethasone vs placebo/Dexamethasone]</td>
</tr>
<tr>
<td>2021</td>
<td>Imatinib_Philadelphia chromosome positive ALL</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>WHO-TRS: documented OS benefit [systematic review of eight comparative cohort studies]</td>
</tr>
</tbody>
</table>

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Zhou Y, et al. BMJ Glob Health 2023; 8:e012899. doi: 10.1136/bmjgh-2023-012899
†: No documented OS benefit includes three scenarios: (a) lack of OS benefit, i.e., WHO-TRS/FDA-approved label mentioned OS but there was no statistically significant OS benefit; (b) no OS data mentioned, i.e., WHO-TRS/FDA-approved label did not report any information on OS; (c) the label was unavailable or the drug was not approved by FDA, e.g., a label for all-Trans Retinoic Acid could not be found, and Tislelizumab (EML decision year 2021) is not approved by FDA.

#: Targeted cancer drug indications with conflicting evidence: WHO-TRS documented OS benefit while at the time of WHO EML decision, the trial results documented in FDA-approved labels were not statistically significant.