# Evidence for Treatment-by-Biomarker interaction for FDA-approved Oncology Drugs with Required Pharmacogenomic Biomarker Testing

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## Supplementary Information

**Table S1.** List of indications excluded based on a high (>90%) biomarker prevalence (n= 14)

**Table S2.** Characteristics of the 80 clinical studies supporting approval of oncology drugs with required pharmacogenomic biomarker testing

**Table S3.** Characteristics of the 40 pivotal trials supporting approval of oncology drugs with required pharmacogenomic biomarker testing

**Supplementary Methods.** Data extraction Form.

**Table S1. List of indications excluded based on a high (>90%) biomarker prevalence (n= 14).**

| Drug | Biomarker Gene | Indication |
|---|---|---|
| Arsenic Trioxide | PML/RARA | APL |
| Bosutinib | BCR/ABL1 | Ph+ CML |
| Dasatinib | BCR/ABL1 | Ph+ CML in chronic phase |
| Dasatinib | BCR/ABL1 | Chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML |
| Imatinib | KIT | Kit (CD117)-positive unresectable and/or metastatic malignant GIST |
| Imatinib | KIT | Adjuvant treatment of adult patients following resection of Kit (CD117)-positive GIST |
| Imatinib | BCR/ABL1 | Newly diagnosed adult and pediatric patients with Ph+ CML in chronic phase |
| Imatinib | BCR/ABL1 | Patients with Ph+ CML (blast crisis, acute phase or chronic phase) after failure of interferon-alpha therapy |
| Nilotinib | BCR/ABL1 | Ph+ CML in chronic phase |
| Nilotinib | BCR/ABL1 | Ph+ CML chronic phase and acute phase in adult patients resistant to or intolerant to prior therapy that included imatinib |
| Ponatinib | BCR/ABL1 | T315I-positive CML (chronic phase, accelerated phase, or blast phase) and T315I Ph+ ALL |
| Rituximab | MS4A1 | CD20-positive B-cell non-Hodgkin's lymphoma |
| Tositumomab | MS4A | CD20-positive, relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma with disease progression during or after rituximab |
| Tretinoin | PML/RARA | Induction of remission in patients with APL |

**Table S2. Characteristics of the 80 clinical studies supporting approval of oncology drugs with required pharmacogenomic biomarker testing. Data are n (%) .**

| Characteristic | Total | Restricted to BM+ | Non-restricted | Pivotal | Non-Pivotal |
|---|---|---|---|---|---|
| No. of studies | 80 | 54 | 25 | 40 | 40 |
| Phase | | | | | |
| I | 11 (14) | 7 (13) | 3 (12) | 2 (5) | 9 (22) |
| II | 30 (38) | 24 (44) | 6 (24) | 9 (22) | 21 (52) |
| III | 37 (46) | 23 (43) | 14 (56) | 29 (73) | 8 (20) |
| Case report | 2 (3) | 0 (0) | 2 (8) | 0 (0) | 2 (5) |
| Enrichment (one missing value) | | | | | |
| Clinical | 5 (6) | 0 (0) | 5 (20) | 3 (8) | 2 (5) |
| No | 20 (25) | 0 (0) | 20 (80) | 7 (18) | 13 (33) |
| Yes | 54 (68) | 54 (100) | 0 (0) | 30 (75) | 24 (62) |
| Design (one missing value) | | | | | |
| Single-arm with enrichment | 30 (38) | 29 (54) | 1 (4) | 6 (15) | 24 (62) |
| Single-arm without enrichment | 9 (11) | 0 (0) | 9 (36) | 4 (10) | 5 (13) |
| Randomized trial with enrichment | 25 (32) | 25 (46) | 0 (0) | 24 (60) | 1 (3) |
| Randomized trial without enrichment | 13 (17) | 0 (0) | 13 (52) | 6 (15) | 7 (18) |
| Case report | 2 (3) | 0 (0) | 2 (8) | 0 (0) | 2 (5) |
| Primary endpoint | | | | | |
| Multiple | 3 (4) | 3 (6) | 0 (0.0) | 3 (8) | 0 (0) |
| OS | 3 (4) | 1 (2) | 2 (8) | 1 (3) | 2 (5) |
| Other | 2 (3) | 2 (4) | 0 (0) | 0 (0) | 2 (5) |
| PFS/DFS | 24 (30) | 13 (24) | 11 (44) | 18 (45) | 6 (15) |
| Response | 45 (56) | 32 (59) | 12 (48) | 15 (38) | 30 (75) |
| Time to progression | 3 (4) | 3 (6) | 0 (0) | 3 (8) | 0 (0) |
| Median [IQR] no. of patients | 173 [62–572] | 163 [73–468] | 427 [49–865] | 457 [170–724] | 96 [40–185] |

**Table S3. Characteristics of the 40 pivotal trials supporting approval of oncology drugs with required pharmacogenomic biomarker testing.**

| Approval | Design | N | Endpoint |
|---|---|---|---|
| Ado-Trastuzumab Emtansine/ERBB2/HER2+ metastatic breast cancer | Phase 3 RCT | 991 | Multiple |
| Afatinib/EGFR/metastatic NSCLC | Phase 3 RCT | 345 | PFS/DFS |
| Anastrozole/ESR1, PGR/adjuvant treatment of postmenopausal women with HR + early breast cancer | Phase 3 RCT | 9366 | PFS/DFS |
| Anastrozole/ESR1, PGR/first-line treatment of postmenopausal women with HR + or HR unknown locally advanced or metastatic breast cancer | Phase 3 RCT | 668 | Multiple |
| Cetuximab/EGFR/EGFR-expressing colorectal cancer | Phase 2 RCT | 329 | Response |
| Cetuximab/KRAS/EGFR-expressing, KRAS-mutation negative colorectal cancer | Phase 3 RCT | 572 | PFS/DFS |
| Crizotinib/ALK/metastatic NSCLC | Phase 1 Single-arm trial | 154 | Response |
| | Phase 2 Single-arm trial | 148 | Response |
| Dabrafenib/BRAF/BRAF V600E mutation-positive unresectable or metastatic melanoma as a single agent | Phase 3 RCT | 250 | PFS/DFS |
| Dabrafenib/BRAF/BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma combined with trametinib | Phase 3 RCT | 162 | Response |
| Denileukin Diftitox/IL2RA/persistent or recurrent cutaneous T-cell lymphoma with malignant cells expressing the CD25 component of the IL-2 receptor | Phase 3 RCT | 71 | Response |
| Erlotinib/EGFR/first-line treatment of patients with metastatic NSCLC | Phase 3 RCT | 173 | PFS/DFS |
| Everolimus/ERBB2/HER2-negative breast cancer (advanced HR+ BC) combined with exemestane after failure of treatment with letrozole or anastrozole | Phase 3 RCT | 724 | PFS/DFS |
| | Phase 3 RCT | 724 | PFS/DFS |
| Exemestane/ESR1/adjuvant treatment of postmenopausal women with estrogen receptor-positive early breast cancer | Phase 3 RCT | 4724 | PFS/DFS |
| Fulvestrant/ESR1/hormone receptor-positive metastatic breast cancer | Phase 3 RCT | 473 | PFS/DFS |
| | Phase 3 RCT | 451 | PFS/DFS |
| Imatinib/KIT/aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown | Phase 2 Single-arm trial | 5 | Response |
| Imatinib/BCR/ABL1/adult patients with relapsed or refractory (Ph+ ALL) | Phase 2 Single-arm trial | 48 | Response |
| Imatinib/BCR/ABL1/pediatric patients with newly diagnosed (Ph+ ALL) combined with chemotherapy | Phase 3 Single-arm trial | 50 | PFS/DFS |

| | | | |
|---|---|---|---|
| Imatinib/PDGFRB/adult patients with MDS/MPD associated with PDGFR gene re-arrangements | Phase 2 Single-arm trial | 7 | Response |
| Lapatinib/ERBB2/combined with capecitabine for treating patients with advanced or metastatic breast cancer overexpressing HER2 and who have received prior therapy | Phase 3 RCT | 324 | TTP |
| Lapatinib/ERBB2/combined with letrozole for treating postmenopausal women with HR+ metastatic breast cancer expressing HER2 receptor for whom hormonal therapy is indicated | Phase 3 RCT | 1286 | PFS/DFS |
| Letrozole/ESR1, PGR/adjuvant treatment for early breast cancer | Phase 3 RCT | 5187 | PFS/DFS |
| Letrozole/ESR1, PGR/first- and second-line treatment for advanced breast cancer | Phase 3 RCT | 551 | Response |
| | Phase 3 RCT | 555 | Response |
| | Phase 3 RCT | 907 | TTP |
| Panitumumab/EGFR/EGFR-expressing metastatic colorectal carcinoma | Phase 3 RCT | 463 | PFS/DFS |
| Pertuzumab/ERBB2/metastatic breast cancer | Phase 3 RCT | 808 | PFS/DFS |
| Pertuzumab/ERBB2/neoadjuvant treatment for breast cancer | Phase 2 RCT | 417 | Response |
| Trametinib/BRAF/unresectable or metastatic melanoma with BRAF V600E or V600K mutation | Phase 3 RCT | 322 | PFS/DFS |
| Trastuzumab/ERBB2/metastatic breast cancer | Phase 3 RCT | 469 | TTP |
| | Phase 2 Single-arm trial | 222 | Response |
| Trastuzumab/ERBB2/adjuvant therapy for breast cancer | Phase 3 RCT | 1944 | PFS/DFS |
| | Phase 3 RCT | 2043 | PFS/DFS |
| Trastuzumab/ERBB2/metastatic gastric or gastroesophageal junction adenocarcinoma | Phase 3 RCT | 594 | OS |
| Vemurafenib/BRAF/unresectable or metastatic melanoma with BRAF V600E mutation | Phase 3 RCT | 675 | Multiple |
| Ceritinib/ALK/ALK-positive metastatic NSCLC with disease progression or intolerance to crizotinib | Phase 1 Single-arm trial | 246 | Response |
| Lenalidomide/del (5q)/transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality | Phase 2 Single-arm trial | 43 | Response |
| | Phase 2 Single-arm trial | 148 | Response |

# Level of evidence of studies in FDA submission

*Obligatoire

## Identification of drug, biomarker and study

**Pair.Num** *

ID of drug/biomarker combinaison

Veuillez saisir un nombre supérieur à 0.

Cette question est obligatoire.

**Indication**

Only if there are more than one indication for the drug

Cette question est obligatoire.

**Indication.Num**

ID of of indication/drug/biomarker combination

Veuillez saisir un nombre supérieur à 0.

Cette question est obligatoire.

**Name or ID of study**

In FDA review

Cette question est obligatoire.

**ClinicalTrials.gov Identifier**

Cette question est obligatoire.

**Status of Trial**

- Published
- Not published, but results available elsewhere
- Terminated but no results available
- Ongoing

Cette question est obligatoire.

**Type of study**

According to FDA statement; cf Downing Jama for definition

- Pivotal Study
- Supportive Study
- Only safety data included
- Other or NA

Cette question est obligatoire.

**Article Name**

Author Year Journal. State all articles if necessary.

Cette question est obligatoire.

**Biomarker-based Criteria for inclusion in the study**

Cette question est obligatoire.

# Other Methods

**Phase of trial**

Cette question est obligatoire.

**Comparator**

- ○ Actively controlled
- ○ Placebo controlled
- ○ Uncontrolled

Cette question est obligatoire.

**Primary Endpoint**

- ○ Overall Survival (OS)
- ○ Disease Free Survival (DFS)
- ○ Progression Free Survival (PFS)
- ○ Response Rate (RECIST Criteria)
- ○ Major Cytogenetic Response (MCyR)
- ○ Complete Cytogenetic Response (CCyR)
- ○ Overall Response Rate
- ○ Major Hematologic Response (MaHR)
- ○ Autre :

Cette question est obligatoire.

**Total number of patients randomized**

or treated if there is no randomization

Veuillez saisir un nombre supérieur à 0.
Cette question est obligatoire.

# Biomarker assesment

**Use of biomarker**

- ○ Prior to the initiation of study
- ○ Retrospectively assesed

Cette question est obligatoire.

**Technique to measure biomarker**

Cette question est obligatoire.

# Design and level of evidence

**Design** *

Adaptated from Tajik and Simon and Mandrekar and Sargent

- ○ 1a Single-arm with enrichment
- ○ 1b Single-arm without enrichment
- ○ 2 Comparative Study, with enrichment
- ○ 3 Comparative Study, without enrichment
- ○ 4a Biomarker-strategy with biomarker measurement in the control arm
- ○ 4b Biomarker-strategy without biomarker measurement in the control arm
- ○ 4c Biomarker-strategy with treatment randomization measurement in the control arm
- ○ 5 Combination of patients flows
- ○ 6 Case report
- ○ NA

Cette question est obligatoire.

**Level of evidence determination** *

From Simon et al, JNCI 2009

- A. Prospective experimental
- B. Prospective using archived samples
- C. Prospective observational
- D. Retrospective observational
- NA

Cette question est obligatoire.

# Comments

**Any comments**

Cette question est obligatoire.

**Rationale for using enrichment design**

Cette question est obligatoire.

Envoyer