Mutation Actionability in Precision Oncology (Actionability)

Help documentation readme file

Project aim

The aim of COSMIC Mutation Actionability in Precision Oncology (Actionability) is to indicate the availability of drugs that target mutations in cancer and track the progress of clinical studies towards making new drugs available. Drugs that target somatic mutations are represented at all stages of drug development, through safety and clinical phases to market and repurposing, with additional case studies.

Sources of data

Content is manually curated from public clinical trial records, journal articles and company websites. The principal sources of the clinical trial data represented in Actionability are ClinicalTrials.gov and scientific literature. A relatively small number of trials have been sourced from other clinical trial databases, conference proceedings, corporate reports and FDA drug labels.

Many trials detailed at ClinicalTrials.gov have no have no record of the study results when they are available in publications. Actionability data is manually curated by experienced PhD level experts. This approach identifies trial outcomes that are not available in clinical trials databases, adding almost 3x more data. Trial results available in ClinicalTrials.gov records may differ from published results or the corresponding clinical studies section of FDA drug labels. COSMIC aims to represent the most recent and therefore complete results. The source of trial data is always indicated.

Data structure summary

Actionability data is stored in a relational database with 23 tables, where appropriate referencing the core COSMIC database. The download file and web table are the result of a selective export from the relational database.

The principal units of actionability are mutation, disease and drug. Mutations are cross-referenced to COSMIC core mutation records and thereby to a gene. These mutation instances are associated with one or more diseases, using COSMIC's internal cancer classification scheme. Mutation-disease instances are associated with one or more drugs. The triple of drug-mutation-disease (DMD) indicates that a mutation has been associated with the effect of a drug in a specified cancer type. DMD instances are annotated with relevant data from clinical trials and case studies. Study details include

the source of the data (typically ClinicalTrials.gov or a publication), trial name, stage/phase of clinical development, primary completion date, number of patients, their treatment history, primary outcome measure and where relevant identity of the control. When the results of a trial are available they are recorded. If published results comment on whether the trial was successful or not, or the likelihood of progression, this is annotated as a Progression Remark.

Mutation and associated values

Mutations in the Actionability product are linked by the use of a common identifier (COSV or COSF) to the main COSMIC mutation database.

Actionability rank

Actionability rank is an annotation of a mutation-disease instance. It is an indication of the most advanced development stage reached by drugs that have been tested in patients with the specified mutation and disease. Values range from approved, marketed drugs (most advanced) through clinical trial phases to case studies. Note that there may be multiple drugs at the same stage of development; individual drugs are not ranked.

COSMIC actionability is based on clinical results, with 4 ranked categories:

1 - Approved marketed drug with demonstrated efficacy at the mutation
2 - Phase 2/3 clinical results meet primary outcome measures*
3 - Drug in ongoing clinical trials
4 - Case studies

*Promising is defined as a trial that has met its primary outcome measure with a p-value statistic <= 0.05, or has been described as meeting trial objectives in associated publications, or for phase 1 trials, with no adverse event/toxicology issues.

There are three more categories, outside of the ranking:
1† - Drug approved for use outside US
6 - Use dependent on test for another mutation
7 - Trial results all negative

Patient screening

Clinical trials that might determine the effect of a mutation on drug efficacy may have this as a primary goal, or as a secondary one. When efficacy in mutated patients is primary, patients are typically enrolled only if they have the appropriate mutation. In other trials, patients are mutation profiled as the trial is underway and this information is used to segregate patients for statistical testing. Some drugs that are now known to have mutation-based selective efficacy reached the end of clinical progression and gained regulatory approval without consideration of patient mutation status. In some diseases, a mutation may occur at such high frequency that screening may not be considered necessary. Trials for rare diseases may not require confirmation of the mutation because doing so would reduce the number of patients to a level that would preclude statistically significant results. Actionability represents all trials that indicate patient screening for the indicated mutation as an outcome. The Patient screening annotation is used to indicate the patient selection strategy (possible values are patients screened, patients not screened, expression level based selection, mutation compared with wildtype, comparison of mutations). Trial records are periodically revisited as results become available to see if post-hoc mutation analysis reveals an association between mutation and efficacy. Additionally, all trial data examined by the FDA as part of the data set that led to drug approval are included in Actionability.

Mutation selectivity

Clinical studies typically group patients with similar or related mutations, e.g. synonymous mutations, mutations in an exon, or any mutation in the target gene. To reflect the different levels of precision used in clinical selection and reporting, Actionability uses a selectivity annotation that indicates the level of precision that was used to specify the mutation. Selectivity values indicate, in order of decreasing precision: point mutation, i.e. a single amino acid substitution; colocated, i.e. mutation of a single residue to more than one alternative residue; cluster, i.e. mutations at more than one location but functionally grouped; exon, i.e. within an exon but residue unspecified; gene, where the location of the mutation is unspecified. These categories and any coordinates used refer to the peptide. Selectivity has 3 further categories: Fusion, for gene fusions, Multigene, to indicate that patients have mutations identified in more than one gene, and Undefined, indicating that presence of a mutation has been inferred from the disease.

Disease names

Disease names are derived from those used elsewhere in COSMIC, using an internal cancer classification system based on site and histology. This classification is indexed against the NCI cancer thesaurus and is available from the COSMIC Downloads page.

Drug names

Drug names used in Actionability preferentially use the generic name. For early stage compounds with no generic name, development codes are used. When available, preference is given to the code name used in the NCI Drug Dictionary. Names used for drugs marketed in the US, names used in other markets and alternative drug names and codes are recorded in the Actionability database.

Drug combinations

The therapies used in clinical trials are very often combinations of drugs. Actionability assigns a drug combination identifier to individual drugs and drug combinations.

Drug-mutation-disease

Mutation-disease instances are associated with one or more drugs/drug combinations. Each drug-mutation-disease (DMD) instance has a unique identifier. DMDs are associated with one or more relevant clinical studies. A single DMD instance may be associated with clinical evidence from trials at different phases of development, case studies or clinical results obtained outside of an identifiable registered study.

Trial details

Clinical studies are annotated with information as available, including the source database identifier, the trial name, the development phase, the status of the trial, the primary (PCD) or estimated (ECD) completion date, patient treatment history, number of patients and the stated primary outcome measure. For comparative trials (those with a control), additional annotations include the number of control patients and their treatment. If results of the trial are available, they are recorded. As trial results may be

available in more than one form, e.g. in ClinicalTrials.gov and as a publication, preference is given to the most recent set of results and the source of the data is indicated, typically as an NCT ID or PubMed ID. If the results contain a comment on the success or otherwise of the trial this is recorded as a Progression remark.

Primary completion date

This annotation indicates the Primary completion date (PCD) or Expected primary completion date (ECD) in month/year format. This indicates when the study is expected to have results for the primary objective measure. The trial may continue beyond this date if there are multiple objectives.

Primary outcome measure

Clinical trials use a wide range of observational and statistical measures that are used to represent patient outcome. Most trials specify a particular measure that will be the key indicator of trial success or failure. This is usually referred to as the Primary Outcome Measure (PO). Trials may have more than one PO. Actionability uses a dictionary of primary outcome terms to record the primary outcome measure.

Development status

Drug development proceeds via a series of widely-recognised phases. Actionability uses an extended version of the FDA's phase definitions. Possible values are: Approved FDA, Approved other, Phase 3, Phase 2, Phase 1, Experimental, Orphan/Fast track, Case study, Out of trials human study, Retrospective/Meta-analysis, Phase 4, Unknown.

Trial status

Trial status indicates the progress of the trial. Note that not all trials specify status and many trials do not report at every stage. Possible values are Not yet recruiting, Recruiting, Active, Active, Not recruiting, Complete, Terminated, Suspended, Withdrawn, Unknown. Definitions of these stages can be found at ClinicalTrials.gov.

Results availability

This annotation indicates whether a study has results or not. Note that trial results are often reported more than once, as the trial progresses.

Results measures

As they become available, results of trials are recorded. Note that results may be interim results, released before the trial is considered to be completed. Clinical trials use a wide range of outcome measures. Commonly used measures are captured into the following categories: Objective response rate - treatment, Objective response rate - control, Objective response rate - 95% confidence interval, Objective response rate - p-value, Overall survival - treatment, Overall survival - control, Overall survival - hazard ratio, Overall survival - 95% confidence interval, Overall survival - p-value, Progression free survival - treatment, Progression free survival - control, Progression free survival - hazard ratio, Progression free survival - 95% confidence interval, Progression free survival - p-value, Time to progression - treatment, Time to progression - control, Time to progression - hazard ratio, Time to progression - 95% confidence interval, Time to progression - p-value, Disease control rate - treatment, Disease control rate - control, Disease control rate - p-value, Duration of response - treatment, Duration of response - control, Duration of response - 95% confidence interval, Duration of response - p-value, Number of patients with complete response, number of patients with partial response, number of patients with stable disease, Regression free survival - treatment, Regression free survival - control, Regression free survival - hazard ratio, Regression free survival - 95% confidence interval, Regression free survival - p-value.

Three additional measures specific to hematological disorders are captured:
Blood response, Response value and Timepoint.

Other results measures are recorded as Progression Remarks.

Note that studies that compare the effect of treatment in patients with/without the indicated mutation (annotated with a mutation_selected value of 'Comparison with wt') record results for the unmutated patients as control values.

All time measurements are represented as months.

Progression remarks

These controlled vocabulary remarks record uncategorised results or comments that indicate whether the trial is likely to progress to the next phase of development.
If the reason for termination of a trial can be identified it is recorded here, e.g. slow accrual, funding withdrawn. Comments on drug efficacy or mutation selectivity are recorded here, e.g. No benefit of treatment, Response not correlated with mutation status, Primary outcome not met. For phase 1 safety studies, the progression remark may be used to record comments suggesting serious/severe adverse events.

Source of results (evidence source)

This trial annotation indicates the source of the results associated with a study.
This is necessary because a single study can have multiple results representations, most commonly in a clinical trials database and a publication. Actionability will represent the most complete, typically the most recent, version of results.

Trial outcome measure (data available in website table only)

Clinical trials have a wide range of observational and statistical values that are used to determine patient outcome. Most trials set out to capture a particular measure that will likely be the key indicator of trial success or failure. This is usually referred to as the Primary Outcome Measure (PO). Trials may have more than one PO. Actionability examines trial results to determine whether the trial has met the objective indicated by the PO. The result of this test is given as a Trial outcome. If the PO has an associated p-value less than or equal to 0.05, the primary objective is considered to be met. If the PO is expressed as a controlled vocabulary term (in the Progression remark field), the test identifies whether the appropriate text string exists. If it does, the primary outcome has been met. If the lookup table indicates that there are multiple primary outcome measures, if any of them meets the cut-off, the primary outcome has been met.

Testing required

This annotation indicates whether patients must be tested to confirm the presence of the indicated mutation before they can receive the indicated treatment. It is applied only for drugs that have regulatory approval. Possible values are Testing required,

Testing not required, Test for expression, Test for wt KRAS, Test for EGFR expression and KRAS mutation, Test for HER2 overexpression.

Treatment history

This trial annotation records whether the patients have received prior treatment, or not, for the indicated disease.

Patient age

Indicates trials that select pediatric or geriatric patients. Note this does not represent a specific age range.

Abbreviations

CI	Confidence Interval	**OS**	Overall Survival
CR	Complete Response	**PCD**	Primary Completion Date
DCR	Disease Control Rate	**PFS**	Progression Free Survival
DMD	Drug-Mutation-Disease	**PR**	Partial Response
DOR	Duration Of Response	**RFS**	Regression Free Survival
ECD	Estimated Primary Completion Date	**SD**	Stable Disease
HR	Hazard Ratio	**TTF**	Time to Treatment Failure
OR	Overall Response	**TTP**	Time to Progression
ORR	Objective Response Rate	**wt**	Wildtype

Further information

Further information about COSMIC Actionability can be found on the website.

If you are still unable to find the answer to your query, please contact us via the COSMIC helpdesk using cosmic@sanger.ac.uk for academic users and bioinformaticssales@qiagen.com for commercial users.