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# **PROJECT AIM**

The aim of COSMIC 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.

Clinical trials rarely identify variants at the DNA level, so all variants in Actionability are identified at the protein level. Trials are included in actionability if:

 Confirmation of a variant, expression, or predictive marker is a condition of patient recruitment

Or,

2. The trial details state the intention to correlate variant/expression with patient outcome. Once included in actionability, all trial records are checked for updated details and results at every release until 10 years after the primary completion date.

### **HOW TO OPEN AND NAVIGATE THE DOWNLOAD FILE**

- 1. The Actionability Download file is in TSV format. It's likely that the file will open automatically in your default spreadsheet software, if not, launch the spreadsheet application and navigate to the downloaded file. The delimiters in the file are tabs, not spaces or commas.
- 2. Once the file is opened, navigate through the data by searching the tabular content, e.g. by National Clinical Trial ID (NCTID) or gene name (approved HUGO Gene Nomenclature Committee (HGNC) symbol).
- 3. Using a combination of filters may be useful if the result of your query is likely to be a list or involves searching data in more than one column:
  - A. In Excel, select the 'Data' tab followed by the 'Filter' button.
  - B. There will now be a button with a downward pointing arrow on the header row of every column. Click on any of these buttons to open a panel that displays a list of all the values present in the column, with a check box (tick mark) on the left side. By default, all values are selected (ticked).
  - C. To display individual values of interest, click the 'select all' check-box to unselect all values and re-select individual values of interest



#### **SOURCES OF DATA**

Actionability content is manually curated from public clinical trial records, articles, conferences, labelling for marketed drugs, and company websites. Trial results are frequently published more than once, typically as interim results and later as a full record, with details of outcome measures that previously could not be calculated. Trial results available in a repository such as ClinicalTrials.gov often differ from published results or the corresponding clinical studies section of FDA drug labels. COSMIC aims to represent the most recent and/or complete results. The source of trial data is always indicated.

For trials with no results, the source identifies where the details of the trial were found. For trials with results, the source identifies where the results were obtained. Frequently, the source identifying the existence of the trial and the trial results are not the same; manual literature curation consistently identifies results for 40-50% more trials than are recorded in clinical trial repositories. There are 9 source types:

- 1. Pubmed
- 2. DOI
- 3. Unindexed journals, Conference abstracts
- 4. ClinicalTrials.gov
- 5. Corporate website
- 6. Submitted to clinicaltrials.gov
- 7. FDA drug label
- 8. EU clinical trials register
- 9. ANZCTR

For source types 1, 4, 6, Source will show the appropriate identifier. For source type 2, Source will show the DOI name. For source types 3, 5, 7, 8 and 9, Source shows the full URL



#### **DATA STRUCTURE SUMMARY**

Actionability data is stored in a relational database with appropriate referencing to the core COSMIC database. The download file is the result of a selective export from the relational database.

Actionability has three principal units: drug, mutation, and disease. 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,, 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.

### **FULLY CURATED GENES**

Content in actionability is curated by gene. A gene is considered fully curated when every relevant trial systematically identified in clinical trial repositories and scientific literature has been added (for the latest list please see the Release Notes). For fully curated genes, searches are carried out at each release to identify new trials.

When a trial is added, all cohorts selecting or intending to correlate variants/expression with outcome measures are recorded, including those for genes that are not part of the fully curated set. Additional trials may exist for genes that are not fully curated.



### LINKING ACTIONABILITY RECORDS TO CORE COSMIC RECORDS

The download file contains genomic\_mutation\_IDs for single amino acid substitutions and some colocated variants. Similarly, fusion IDs can be linked to COSMIC fusion records. The disease nomenclature used in actionability is a simplified version of the COSMIC classification system. The column Classification ID shows a COSO Identifier that allows linking to COSMIC core records at the level of disease classification.

#### **ACTIONABILITY RANK**

Actionability rank is based on the availability of treatments for the combination of the variant, defined in Mutation Remark, and the Disease. It is not associated with individual trial records (rows in the download file), rather it is an indication of the most advanced development stage reached by any of the drugs that have been tested for the specified mutation-disease combination. Values range from approved, marketed drugs through clinical trial phases to case studies. There may be multiple drugs at each of the stages of drug development. Individual drugs are not assigned an actionability rank, there is no intention to suggest a 'best' treatment.

# There are 4 main ranked categories:

- **1/1†** Approved marketed drug with demonstrated efficacy at the mutation. 1 indicates that the treatment is approved by the FDA. 1† indicates that the treatment is approved by a regulatory authority other than the FDA
- 2 Phase 2/3 clinical results meet primary outcome measures\*
- **3** Drug in ongoing clinical trials
- **4** Case studies only

\*Primary outcome measure is met if the primary outcome (or any of the primary outcomes if there was more than one) has a p-value <=0.05, or the trial has been described as meeting objectives in publications, or for phase 1 trials, described as having no serious adverse event/toxicology issues.

## There are two more categories:

- 6 Use of the treatment depends on testing for another variant
- **7** All trial results identified to date have not met their primary objectives



### **PATIENT PRE-SCREENING**

This value indicates whether the patients included in the trial were confirmed to have the variant/express the protein represented in the Mutation Remark column. Trials are included in actionability either when confirmation of the variant/expression is a condition of recruitment, or when the trial details state the intention to correlate variant/expression with patient outcome.

# There are 5 categories:

- 1. Yes confirmation is part of the patient selection process
- 2. Expression confirmation of protein expression
- 3. Overexpression confirmed over expression
- 4. Comparison with wt the aim of the trial is to compare outcomes in patients that do/do not have a variant
- 5. No confirmation of the variant is not required for patient entry into but the trial details suggest the intention to correlate variant/expression status with outcome.

Note that when Patient pre-screening is No, trial results represent patients that have not undergone variant/expression screening. If at a later date results are published that correlate variant/expression with outcome, unselected patient results are replaced and the Patient pre-screening value changed.

#### **GENE**

Genes are represented using the **HGNC** gene symbol

#### **MUTATION REMARK**

Identifies the gene, variant and specificity of patient selection/correlation with treatment efficacy. See Nomenclature of Variants for a full explanation. Filter this column to select specific variants.



## **NOMENCLATURE OF VARIANTS (MUTATION SELECTIVITY)**

Clinical Trials use variable levels of precision to describe and select patients with variants. This granularity is reflected in Actionability by variant selection categories. In order of decreasing precision the categories are:

- Single amino acid substitution
- Co-located mutations i.e. substitution of a protein residue by more than one alternative residues
- Cluster i.e. mutations at more than one location grouped by common functional consequence
- Exon i.e. any variant within a defined exon
- Gene where the location of the mutation is unspecified

# There are 5 further categories:

- Fusion: for gene fusions
- Multigene: to indicate that patients have mutations identified in more than one gene
- Set: where patients are grouped by the presence of variants in any of a list of genes
- Region: any variant that affects a chromosomal region
- Methylation: selection by level of DNA methylation

## HOW TO IDENTIFY THESE CATEGORIES IN THE DOWNLOAD FILE

The variant category can be identified by the nomenclature used for the Mutation Remark:

**Single amino acid substitutions:** Shown as the gene symbol followed by underscore followed by the unmutated residue in single letter code followed by the coordinate followed by the resulting residue in single letter code, e.g. AKT1\_E17K represents a variant of the gene AKT1 where the glutamate (E) at position 17 is substituted by lysine (K).

**Co-located substitutions:** Shown using the same nomenclature as single amino acid substitutions except that the letter representing the resulting residue is omitted. For example, ALK\_F1174 represents variants of ALK that result in the substitution of the phenylalanine residue at position 1174 with any of the substitutions that are possible.

## **Clustered mutations:** Shown in two different ways.

1. A list of substitutions that are considered to be functionally equivalent, e.g. EGFR\_G719,L861Q,S768I (there are no spaces between the list items)



represents variants in EGFR that lead to any substitution at G719 or the substitutions L816Q or S768I.

2. Used for insertions/deletions, shows the exon number followed by ins or del, e.g. EGFR\_Exon\_20ins represents EGFR exon 20 insertions.

**Exon level specificity:** Shown as the gene symbol followed by underscore followed by the word Exon followed by the exon number.

**Gene level specificity:** Where the variant can be anywhere in the protein coding sequence, is shown as the gene symbol followed by underscore followed by the word unspecified.

**Fusions:** Represented by the gene symbols connected by a hyphen, followed either by underscore followed by the word fusion, e.g. FGFR3-TACC3\_fusion. For fusions with defined subtypes, the subtype shown in parentheses, e.g. BCR-ABL e14a2 (b3a2). Sets of fusions, where only one partner is defined, are shown by the gene symbol of the defined partner followed by underscore followed by the plural word fusions, e.g. NTRK1\_fusions.

**Multi-gene patient selection:** Where the patient is required to have variants in two or more genes, are shown following the nomenclature described above connected by the word 'and'. Set selection: Where patients can have variants in any of a set of genes, are shown using the nomenclature described above connected by the word or.

**Chromosomal abnormalities:** Named using the chromosome number, arm and region, followed by, in parentheses, the symbols for genes that are suggested to be primarily connected with the functional consequence of the abnormality, if indicated in the trial description or literature.

**Methylation:** Represented by the gene symbol followed by underscore followed by the word methylation.

#### **DISEASE NAMES**

The nomenclature used for Disease is a simplified version of the COSMIC classification system. COSO IDs, shown as Classification ID, allow linking actionability records by specific disease to COSMIC core records.



#### **DRUG NAMES**

Drug names used in Actionability give preference to the generic name, rather than commercial names. Early-stage compounds use a development name or code until a generic name becomes available, with preference given to the name used in the NCI Drug Dictionary, if available. Conceptually, Drug includes any therapy or treatment including those that are not traditionally considered as drugs, e.g. immunotherapies, cellular therapies and transplantation, radiotherapies. Surgical procedures are not included unless required to differentiate experimental and control arms of a trial.

#### **DRUG COMBINATIONS**

The therapies used in clinical trials are very often combinations of drugs. When this is the case, the set of all drugs given to the patient is annotated and associated with the trial record. If the treatment is a single drug, the name is shown. If the treatment is a combination of more than one drug, a list of the names with intervening, is shown. For full details of the nomenclature used see Drug Names. The order of names does not imply the order that the treatments were given.

#### **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 or complete set of results and the source of the data is indicated.

For most trials (exceptions explained below) the values of Number of Patients, Treated Number and Control Number indicate the total number of patients, the number receiving experimental treatment, and when relevant, the number receiving the control treatment, respectively. For single arm trials, the values of Number of Patients and Treated Number will be the same. For comparative

trials, Number of Patients is the sum of treated + control. Sometimes only the total number can be identified. For trials without results, any patient numbers are recruitment targets. Trials with results will show the number of patients included for calculation of the primary outcome.

Patient numbers are represented in a slightly different way for trials that compare patients with a variant to unmutated patients, and trials that compare patients by expression level or expression/absence of a marker.

Trials that compare patients with a variant to those that do not have the variant (mutant v wt) show Patient Pre-screening as 'Comparison with wt'. The value of Treated Number is the number of patients with the variant, the Control Number is the number of unmutated patients.

Trials that compare patients expressing a protein with those that don't, or compare patients with expression above/below a defined threshold, show Patient Pre-screening as 'Expressed/not'. The value of Treated Number is the number of patients with expression/expression above the threshold, Control Number is the number of patients not expressing/expressing below the threshold. When relevant the threshold value is shown in the Trial name field.

#### **TRIALS AND COHORTS**

Clinical trials may have one or many subsets or cohorts. When results are released they may represent one, all, or some cohorts from a trial. Post-hoc segregation of patients into previously undescribed subgroups is common. Each row in the download file represents a trial cohort or subgroup. If a cohort has been assigned a name, it may be appended to/used in the absence of the Trial name. Trial cohorts that do not include patients with variants/expression, unless representing a control treatment, are not included in actionability.

#### TRIAL PRIMARY COMPLETION DATE

Primary Completion Date (PCD) is the date when all patient data required for calculation of primary outcome measures is expected to be/has been obtained. Completion Status is shown as Expected Completion Date (ECD) when the date is an estimate, PCD is shown when the date shown is the confirmed date of primary completion. Note that the trial is likely to continue beyond this date if there are multiple objectives.

#### PRIMARY OUTCOME MEASURE

Clinical trials use a wide range of observational and statistical measures to represent patient outcome. Most trials specify a particular measure or measures 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 (see Primary Outcome Abbreviations).

#### **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. Not all trials specify status and many trials do not report at every stage. Possible values are: Not yet recruiting, Recruiting, Active, Complete, Terminated, Suspended, Withdrawn, Unknown. Definitions of these stages can be found at <a href="ClinicalTrials.gov">ClinicalTrials.gov</a>

#### **RESULTS AVAILABILITY**

Indicates whether the trial/cohort has results or not. Note that if the value in Patient pre-screening is No, results do not reflect variant/expression status.



#### **RESULTS MEASURES**

As they become available, the results of trials are recorded. Clinical trials use a wide range of outcome measures. All time measurements are represented in months and as mean values with 95% Confidence Intervals. The most used measures are recorded in the following columns:

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 haematological disorders are captured:

Blood response – Defines the measure using one of the following controlled vocabulary terms: Complete cytogenetic; Complete hematologic; Complete molecular; Major cytogenetic; Major hematologic; Major molecular; Partial cytogenetic; Complete morphologic Response value – percentage of patients Timepoint – time after treatment that measurement was taken

Other results measures are recorded in the column Progression Remark.

Note that results from studies comparing the effect of treatment in patients with/without a variant (with a Patient pre-screening value of 'Comparison with wt') or with high/low expression (with a Patient pre-screening value of 'Expressed/not') record results for mutated/expressing patients in results columns used for treatment values and results for unmutated/non-expressing patients in results columns used for control treatment values.

#### **PROGRESSION REMARK**

Controlled vocabulary remarks with five subtypes. More than one subtype may be shown, multiple comments are separated by commas.

- Results for less common primary outcomes that are not recorded in a defined result column. The primary outcome measure type is indicated by an abbreviation. The abbreviations used are shown in the table Primary Outcome Abbreviations
- 2. Indication that a publication suggests the trial has/has not met its primary objective. If described to have met the primary objective, the remark is 'Primary outcome met'. If described to have not met the primary objective, the remark is 'Primary outcome not met'.
- 3. For trials that have a Trial Status of Terminated or Withdrawn, describes why the trial ended, if identified, e.g. Slow accrual, Toxicity issues, Lack of efficacy.
- 4. Publication comments on treatment efficacy or correlation of variant/expression with efficacy, e.g. No benefit of treatment, Response correlated with mutation status, Response not correlated with expression status.
- 5. For Phase 1 studies, indicates the incidence of serious adverse events, if identified, with the abbreviation SAE followed by a percentage of patients.

## **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: Required, Not required, Expression, wt KRAS, EGFR expression and KRAS mutation, HER2 expression.

# TREATMENT HISTORY

Indicate whether the patients have/have not received prior treatment for the indicated disease. There are 3 categories: Untreated, Previously-treated, or blank meaning either a mixture, or not specified.



#### **PATIENT AGE**

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

## **LAST UPDATED**

Indicates when details of a trial record were last edited, allowing the identification of records that have new details. The date is updated when any of the following details of the trial are changed: Name, ID, Treatment history, Primary completion status, Primary completion date, Patient count, Control patient count, Primary outcome type, Progression remark, Development stage, Trial status, Disease type, Treatment, Results availability, Evidence source, or any of the results details.

#### PRIMARY OUTCOME ABBREVIATIONS

DESCRIPTION	ABBREVIATION
Progression free survival	PFS
Overall survival	OS
PFS, TTP, OS	PFS, TTP, OS
Not defined	ND
Overall Response Rate	ORR
Maximum tolerated dose/toxicity	MTD
Unknown	UN
Response rate	RR
Clinical activity	CA
Disease free survival, relapse free survival, regression free	RFS
survival, recurrence free survival	
Absorption rate	Cmax/AUC
Time to progression	TTP
MTD, ORR, Toxicity	MTD, ORR, Tox
Disease control rate, Clinical benefit rate	DCR
ORR, OS	ORR, OS
OS, PFS	OS, PFS
Locoregional control	LRC
Immune cell infiltration	ICI
Complete response, Pathological complete response	CR
Change in ocular side effect management	OSE
Marker phosphorylation	MP

Data Set Feb-2025



ORR, PFS, OS Best overall response BOR Resection rate RR Time to Second Objective Disease Progression CR, ORR Cell cycle arrest CCA Change in Ki-67 expression Metabolic endpoints (malonyl carnitine and tripalmitin levels) PFS, ORR PFS, ORR PFS, ORR PFS, ORR EES Tumour volume TV Functional airway response PFAR DCR, TTP Radiographic response rate Number of adverse events Prostate Specific Antigen (PSA) response rate RRA RRA RAB Treatment rate, Treatment completion, Compliance, Adherence to protocol Biomarker discovery BDCR, ORR CR, DFS, OS Complete remission CR, OS Reduced alrege expression level Quality of life QOL Vitamin C serum bioavailability Immune response IR Hematological response MR Reduced alresponse MR Reduced laresponse MR Reduced arget expression level Quality of life QOL Vitamin C serum bioavailability VCB Immune response MR Major cytogenetic response MR Major cytogenetic response MR Major cytogenetic response MCR Major cytogenetic response MCR MA Major cytogenetic response MCR Major cytogenetic response MCR Major cytogenetic response MCR Major cytogenetic response	DESCRIPTION	ABBREVIATION
Resection rate Time to Second Objective Disease Progression PD2 CR, ORR CR, ORR CCA CH cycle arrest CCA Change in Ki-67 expression Metabolic endpoints (malonyl carnitine and tripalmitin levels) PFS, ORR Event free survival FFS Tumour volume TV Functional airway response DCR, TTP Radiographic response rate Number of adverse events PFS, DOR Spleen volume reduction SyR Reduced allele burden Treatment rate, Treatment completion, Compliance, Adherence to protocol Biomarker discovery BCR, OS Composite complete remission CCR CR, OS Non-relapse mortality Cumulative incidence of relapse Reduced target expression level Immune response IR Hematological response IR Hematological response IR Remator ACA CRC CRC CRC CRC CRC CRC CRC CRC CRC	ORR, PFS, OS	ORR, PFS, OS
Time to Second Objective Disease Progression PD2  CR, ORR CR, ORR Cell cycle arrest CCA Change in Ki-67 expression Ki67  Metabolic endpoints (malonyl carnitine and tripalmitin levels) PFS, ORR PFS, ORR Event free survival EFS Tumour volume TV Functional airway response FAR DCR, TTP Radiographic response rate RRR Number of adverse events nAE Prostate Specific Antigen (PSA) response rate PSA Spleen volume RAB Treatment rate, Treatment completion, Compliance, Adherence to protocol Biomarker discovery BD CCR, ORR CR, DFS, OS Complete remission CRM OS, FFS Composite complete remission CRR CCR, OS Non-relapse mortality NRM Cumulative Incidence of relapse Reduced and response RR Hematological response RR Hematological response RR HR Hematological response RR TCA Molecular response MR RR Hematological response RR CCA MCR TCA Molecular response MR MR	Best overall response	BOR
CR, ORR Cell cycle arrest CCA Change in Ki-67 expression Metabolic endpoints (malonyl carnitine and tripalmitin levels) PFS, ORR PFS, ORR Event free survival FILIMORE FAR DCR, TTP Radiographic response rate Number of adverse events Prostate Specific Antigen (PSA) response rate Preatment rate, Treatment completion, Compliance, Adherence to protocol Biomarker discovery BD DCR, ORR CR, DFS, OS Complete remission CR, OS Non-relapse mortality Cumulative incidence of relapse Reduced target expression IR Hematological response IR Hematological response IR Hematological response IR Reduced Intel protocol IR Intel Carlot Intel Carlot IR Intel Carlot Intel Carlot IR Intel Carlot Inte	Resection rate	RR
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Metabolic endpoints (malonyl carnitine and tripalmitin levels)  PFS, ORR  Event free survival  EFS  Tumour volume  TV  Functional airway response  DCR, TTP  Radiographic response rate  RRR  Number of adverse events  Prostate Specific Antigen (PSA) response rate  ORR, PFS, DOR  Spleen volume reduction  SVR  Reduced allele burden  Treatment rate, Treatment completion, Compliance, Adherence to protocol  Biomarker discovery  BD  DCR, ORR  CR, DFS, OS  Complete remission  CRM  OS, EFS  Composite complete remission  CR, OS  Reduced larget expression level  Quality of life  VCB  Immune response  IR  Hematological response  MR  MR	Cell cycle arrest	CCA
levels)  PFS, ORR  PFS, ORR  Event free survival  EFS  Tumour volume  TV  Functional airway response  FAR  DCR, TTP  Radiographic response rate  Number of adverse events  Prostate Specific Antigen (PSA) response rate  ORR, PFS, DOR  Spleen volume reduction  Syr  Reduced allele burden  Treatment rate, Treatment completion, Compliance, Adherence to protocol  Biomarker discovery  BCR, ORR  CR, DFS, OS  Complete remission  CR, DFS, OS  Composite complete remission  CR, OS  Non-relapse mortality  Cumulative incidence of relapse  Reduced in a many and and a many and a man	Change in Ki-67 expression	Ki67
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Functional airway response  DCR, TTP  Radiographic response rate  Number of adverse events  Prostate Specific Antigen (PSA) response rate  Prostate Specific Antigen (PSA) response rate  ORR, PFS, DOR  Spleen volume reduction  SVR  Reduced allele burden  Treatment rate, Treatment completion, Compliance, Adherence to protocol  Biomarker discovery  BD  DCR, ORR  CR, DFS, OS  CR, DFS, OS  Complete remission  CRM  OS, EFS  OS, EFS  Composite complete remission  CR, OS  Non-relapse mortality  NRM  Cumulative incidence of relapse  Reduced target expression level  Uitamin C serum bioavailability  Immune response  HR  Target-specific T cell activity  Molecular response  MR	Event free survival	EFS
DCR, TTP Radiographic response rate RRR Number of adverse events Prostate Specific Antigen (PSA) response rate PSA ORR, PFS, DOR ORR, PFS, DOR RAB REduced allele burden RAB Treatment rate, Treatment completion, Compliance, Adherence to protocol Biomarker discovery BD DCR, ORR DCR, ORR CR, DFS, OS CR, DFS, OS CRM OS, EFS OS, EFS OS, EFS Composite remission CCR CR, OS CR, OS Non-relapse mortality NRM Cumulative incidence of relapse Reduced target expression level Utlamin C serum bioavailability VCB Immune response IR Hematological response HR Target-specific T cell activity MOlecular response MR	Tumour volume	TV
Radiographic response rate Number of adverse events Prostate Specific Antigen (PSA) response rate Prostate Specific Antigen (PSA) response rate PSA ORR, PFS, DOR ORR, PFS, DOR Spleen volume reduction Reduced allele burden RAB Treatment rate, Treatment completion, Compliance, Adherence to protocol Biomarker discovery BD DCR, ORR CR, DFS, OS CR, DFS, OS CRM OS, EFS OS, EFS Composite complete remission CRR CR, OS Non-relapse mortality NRM Cumulative incidence of relapse Reduced target expression level Quality of life Vitamin C serum bioavailability Immune response HR Target-specific T cell activity MR Molecular response MR	Functional airway response	FAR
Number of adverse events Prostate Specific Antigen (PSA) response rate Prostate Specific Antigen (PSA) response rate  ORR, PFS, DOR Spleen volume reduction SVR Reduced allele burden RAB Treatment rate, Treatment completion, Compliance, Adherence to protocol Biomarker discovery BD DCR, ORR CR, DFS, OS CR, DFS, OS Complete remission CRM OS, EFS OS, EFS Composite complete remission CR, OS Non-relapse mortality NRM Cumulative incidence of relapse Reduced target expression level Quality of life Vitamin C serum bioavailability Immune response HR Target-specific T cell activity MR More More ABB ORR, PFS, DOR ORR ORR ORR ORR ORR ORR ORR ORR ORR	DCR, TTP	DCR, TTP
Prostate Specific Antigen (PSA) response rate  ORR, PFS, DOR  Spleen volume reduction  Reduced allele burden  Treatment rate, Treatment completion, Compliance, Adherence to protocol  Biomarker discovery  BD  DCR, ORR  CR, DFS, OS  CR, DFS, OS  Complete remission  OS, EFS  Composite complete remission  CR, OS  Non-relapse mortality  Cumulative incidence of relapse  Reduced target expression level  Quality of life  Quality of life  VCB  Immune response  HR  Target-specific T cell activity  MCR  ORR, PFS, DOR  ORR, PFS, DOR  RAB  TTR  ABB  TTR  ABB  TTR  ABB  TTR  ABB  TR  TR  TR  TR  TR  TR  TR  TR  TR	Radiographic response rate	RRR
ORR, PFS, DOR  Spleen volume reduction  Reduced allele burden  Treatment rate, Treatment completion, Compliance, Adherence to protocol  Biomarker discovery  BD  DCR, ORR  CR, DFS, OS  Complete remission  CRM  OS, EFS  Composite complete remission  CR, OS  Non-relapse mortality  Cumulative incidence of relapse  Reduced target expression level  Quality of life  VCB  Immune response  HR  Target-specific T cell activity  MRR	Number of adverse events	nAE
Spleen volume reduction Reduced allele burden RAB  Treatment rate, Treatment completion, Compliance, Adherence to protocol  Biomarker discovery BD  DCR, ORR CR, DFS, OS CR, DFS, OS Complete remission CRM  OS, EFS Os, EFS Composite complete remission CR, OS  Non-relapse mortality NRM  Cumulative incidence of relapse Reduced target expression level Uquality of life Vitamin C serum bioavailability Immune response IR  Hematological response HR  Target-specific T cell activity MRA  Treatment rate, Treatment completion, Compliance, RAB Treatment rate, Treatment completion, Completion, CR Treatment rate, CR	Prostate Specific Antigen (PSA) response rate	PSA
Reduced allele burden Treatment rate, Treatment completion, Compliance, Adherence to protocol  Biomarker discovery BD DCR, ORR DCR, ORR CR, DFS, OS CR, DFS, OS Complete remission CRM OS, EFS Composite complete remission CR, OS Non-relapse mortality NRM Cumulative incidence of relapse Reduced target expression level Uquality of life VCB Immune response IR Hematological response HR Target-specific T cell activity MR TR ADB DCR CR, OR CR, OR CR, OR CR, OS CR, OS CR, OS NMM CURVED COL VICTURE COL TCA MOlecular response MR	ORR, PFS, DOR	ORR, PFS, DOR
Treatment rate, Treatment completion, Compliance, Adherence to protocol  Biomarker discovery  BD  DCR, ORR  DCR, ORR  CR, DFS, OS  CRM  OS, EFS  Complete remission  CR, OS  IR  Reduced target expression level  Quality of life  Quality of life  VCB  Immune response  IR  Hematological response  HR  Target-specific T cell activity  MRR	Spleen volume reduction	SVR
Adherence to protocol Biomarker discovery BD  DCR, ORR DCR, ORR CR, DFS, OS CR, DFS, OS Complete remission CRM OS, EFS OS, EFS Composite complete remission CR, OS  CR, OS  Non-relapse mortality NRM  Cumulative incidence of relapse Reduced target expression level Quality of life QOL  Vitamin C serum bioavailability Immune response IR  Hematological response HR  Target-specific T cell activity MR  DCR, OR  CR, OS  CR, OS  NRM  CIR  HR  TCA  Molecular response  MR	Reduced allele burden	RAB
Biomarker discovery  DCR, ORR  DCR, ORR  CR, DFS, OS  Complete remission  CRM  OS, EFS  Composite complete remission  CR, OS  INAM  Cumulative incidence of relapse  Reduced target expression level  Quality of life  Quality of life  VCB  Immune response  IR  Hematological response  HR  Target-specific T cell activity  MR	Treatment rate, Treatment completion, Compliance,	TR
DCR, ORR CR, DFS, OS CR, DFS, OS Complete remission CRM OS, EFS OS, EFS Composite complete remission CR, OS Non-relapse mortality NRM Cumulative incidence of relapse Reduced target expression level Uality of life Vitamin C serum bioavailability VCB Immune response IR Hematological response HR Target-specific T cell activity MR	Adherence to protocol	
CR, DFS, OS  Complete remission  CRM  OS, EFS  OS, EFS  Composite complete remission  CR, OS  CR, OS  CR, OS  CR, OS  Non-relapse mortality  NRM  Cumulative incidence of relapse  Reduced target expression level  Quality of life  VCB  Immune response  IR  Hematological response  HR  Target-specific T cell activity  Molecular response  CR, OS  NRM  CUR  HHC level  QOL  VCB  IR  Hematological response  HR  TCA  Molecular response  MR	Biomarker discovery	BD
Complete remission  OS, EFS  OS, EFS  Composite complete remission  CR, OS  Ron-relapse mortality  NRM  Cumulative incidence of relapse  Reduced target expression level  Quality of life  Quality of life  VCB  Immune response  IR  Hematological response  HR  Target-specific T cell activity  Molecular response  CR  ROS  NRM  CUR  REM  REM  REM  REM  REM  REM  REM  R	DCR, ORR	DCR, ORR
OS, EFS Composite complete remission CR, OS CR, OS Non-relapse mortality NRM Cumulative incidence of relapse Reduced target expression level Quality of life Vitamin C serum bioavailability VCB Immune response IR Hematological response HR Target-specific T cell activity Molecular response OS, EFS CCR CR, OS INR INR IHC level UHC level VCB IHC level VCB IMR IR INR INR INR INR INR INR INR INR INR	CR, DFS, OS	CR, DFS, OS
Composite complete remission  CR, OS  CR, OS  Non-relapse mortality  Cumulative incidence of relapse  Reduced target expression level  Quality of life  Quality of life  VCB  Immune response  HR  Hematological response  HR  Target-specific T cell activity  Molecular response  CIR  HC level  QOL  VCB  HR  HR  TCA	Complete remission	CRM
CR, OS  Non-relapse mortality  NRM  Cumulative incidence of relapse  Reduced target expression level  Quality of life  VCB  Immune response  IR  Hematological response  HR  Target-specific T cell activity  Molecular response  CR, OS  NRM  PRM  IHC level  QOL  VCB  IR  HR  Target-specific T cell activity  TCA  MR	OS, EFS	OS, EFS
Non-relapse mortalityNRMCumulative incidence of relapseCIRReduced target expression levelIHC levelQuality of lifeQOLVitamin C serum bioavailabilityVCBImmune responseIRHematological responseHRTarget-specific T cell activityTCAMolecular responseMR	Composite complete remission	cCR
Cumulative incidence of relapse  Reduced target expression level  Quality of life  Vitamin C serum bioavailability  Immune response  IR  Hematological response  HR  Target-specific T cell activity  Molecular response  CIR  IHC level  QOL  VCB  IR  HR  TCA	CR, OS	CR, OS
Reduced target expression level  Quality of life  QOL  Vitamin C serum bioavailability  VCB  Immune response  IR  Hematological response  HR  Target-specific T cell activity  Molecular response  IHC level  QOL  VCB  IR  HR  HR  TARRA  TARRA  MR	Non-relapse mortality	NRM
Quality of lifeQOLVitamin C serum bioavailabilityVCBImmune responseIRHematological responseHRTarget-specific T cell activityTCAMolecular responseMR	Cumulative incidence of relapse	CIR
Vitamin C serum bioavailability  Immune response  IR  Hematological response  HR  Target-specific T cell activity  Molecular response  MR	Reduced target expression level	IHC level
Immune responseIRHematological responseHRTarget-specific T cell activityTCAMolecular responseMR	Quality of life	QOL
Hematological response HR  Target-specific T cell activity TCA  Molecular response MR	Vitamin C serum bioavailability	VCB
Target-specific T cell activity TCA  Molecular response MR	Immune response	IR
Molecular response MR	Hematological response	HR
	Target-specific T cell activity	TCA
Major cytogenetic response MCyR	Molecular response	MR
	Major cytogenetic response	MCyR



DESCRIPTION	ABBREVIATION
Major hematologic response	MHR
Complete hematologic response	CHR
Major molecular response	MMR
Participants with <=1% BCR-ABL1 at 12m	MMR1PC
Complete cytogenetic response	CCyR
Complete molecular response	CMR
Minimal residual disease (MRD)	MRD
12 Month treatment free remission	TFR12
Cytogenetic response	CyR
Erythroid response	ER
Donor engraftment, GVHD rate	DE
Transplant-ready patient rate	TR
Pathologic Response	PaR
Major pathologic response	MpaR
Metabolic response	MetR
Altered genomic signature	GenS
Marker correlation with progression	MkP
ORR, DOR	ORR, DOR
Change in CD3+ lymphocytes	CD3+
Intracranial Response Rate	IRR
ORR, EFS	ORR, EFS
Malonyl carnitine and tripalmitin levels	MCT
Drug resistance	DR
DCR, ORR, DOR	DCR, ORR
Distant Brain Metastasis-free Survival	DBMFS
Complete morphologic response	CMR
Neutrophil recovery	NR
Lymph node clearance rate	LNCR
DFS, OS	DFS, OS
CNS ORR, Intracranial ORR	IORR
Clearance of ctDNA	CTDNA
Cost of therapy	СО
Hyperglycemia	HYG
Residual disease, Residual cancer burden	MRD
No CNS progression	CNSN
Adverse Events of Primary Interest	AEPI
Duration of response	DOR
Cardiac event	CE



DESCRIPTION	ABBREVIATION
CelTIL score	CS
Improved hearing	IH
CR, EFS	CR, EFS
Brain metastasis response rate	BMRR
Failure free survival, Time to treatment failure	FFS
PFS, DCR	PFS, DCR
EFS, pCR	EFS, pCR
Complete metabolic response	CMR
TTP, OS	TTP, OS
2-HG suppression	2HG
PSA, ORR	PSA, ORR
Distant metastasis free survival	DMFS
OS, ORR, DOR	OS,ORR,DOR
Pre-operative Endocrine Prognostic Index (PEPI score)	PEPI
Circulating tumour cells	СТС
Accrual rate	AR
Neutropenia	NP
Ovarian cyst incidence	ОС
Treatment discontinuation	TD
Estradiol blood concentration	EBC
Bone scan response rate	BSR
Intratumoural hormone level	IHL
Reduction of BCR-ABL1 stem cells	BASC
Recruitment	REC
CR, PFS	CR, PFS
TTP, ORR	TTP, ORR
ctDNA mutation detection	СТМ
Radiologic partial response	RPR
Intracranial progression free survival	IPFS
Total symptom score	TSS
PFS, TTP	PFS, TTP
FLT uptake	FLT
PAM50 proliferation signature	PAM50
Biomarker protein downregulation	BD
Time to response	TTR
Organ preservation	OP
IRR, IPFS	IRR, IPFS
Intracranial time to progression	ITTP



DESCRIPTION	ABBREVIATION
Globulin level	GL
ORR, TTP, PFS	ORR, TTP, PFS
IPFS, IORR	IPFS, IORR
PFS, RFS	PFS, RFS
Radiologic complete response	RCR
FFS, DOR, PFS	FFS, DOR, PFS
PFS, OS, DOR	PFS, OS, DOR
Vector copy number	VCN
CR, EFS, OS	CR, EFS, OS
CR, DFS	CR, DFS
Intracranial duration of response	IDOR
Intracranial disease control rate	IDCR
Globulin level	GL
ORR, TTP, PFS	ORR, TTP, PFS
IPFS, IORR	IPFS, IORR
PFS, RFS	PFS, RFS
Radiologic complete response	RCR
FFS, DOR, PFS	FFS, DOR, PFS
PFS, OS, DOR	PFS, OS, DOR
Vector copy number	VCN
CR, EFS, OS	CR, EFS, OS
CR, DFS	CR, DFS
Intracranial duration of response	IDOR
Intracranial disease control rate	IDCR
Laryngectomy-free survival	LFS
ctDNA clearance	ctDNA
PFS, DOR	PFS, DOR
IPFS, IORR, IDCR	IPFS, IORR, IDCR
Early tumour shrinkage	ETS
Immune effector cell associated neurotoxicity syndrome rate	ICANS
Cytokine release syndrome rate	CRS
ICANS, CRS	ICANS, CRS
Residual Cancer Burden I	RCB1
Residual Cancer Burden II	RCB2
Grade 1-2 Cytokine Release Syndrome	Grade I-II CRS
Grade 4 Cytokine Release Syndrome	Grade IIII CRS
Excellent and Indeterminate Response - defined by ATA 2015	E&IR
MTD, OS	MTD, OS
Invasive Breast Cancer-Free Survival	IBCFS
Acute leukemia response-complete rate	ALRC

DESCRIPTION	ABBREVIATION
PFS, MTD	PFS, MTD
EFS, OS, ORR	EFS, OS, ORR
Tumour microenvironment changes	TMC
Tumour Burden	ТВ
Leukemia free survival	LFS

### **FURTHER INFORMATION**

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