

ゲノムバイオマーカーに基づいたがん治療選択


フィルジエン株式会社 バイオインフォマティクス部
(biosupport@filgen.jp)

- 遺伝子パネル検査によるがんゲノム医療では、検出された遺伝子変異などのゲノムバイオマーカーについて、推奨される治療薬などの臨床的意義を確認する必要がある

バイオマーカー例

- HER2+: High levels of HER2 receptor protein
- MSI-H: Microsatellite instability-high
- BRAF^{V600E}: Activating mutation V600E
- ERBB2^{Amp}: Amplification of ERBB2
- BCR-ABL1: Activation of ABL1 with BCR fusion
- TP53^{WT}: No significant alterations of critical TSG

- Golden Helix社VarSeq®の有償アドオンであるVSClinical AMPでは、体細胞バリエーションの腫瘍原性の評価に加え、バイオマーカーとしてのエビデンスレベルや治療薬、臨床試験情報の確認を行い、レポートにまとめて出力することが可能



Patient Name
NA12877

Report Date
06/18/2019

Tumor Type
Melanoma

Patient Information		Reference Information		Sample Information	
Patient Name	NA12877	Ordering Physician	Dr. Smith	Specimen Site	Skin
DOB	03/09/1993	Order Date	05/29/2019	Collection Date	06/09/2019
Sex	Female	Contact/Recipient		Received Date	06/10/2019
MRN	3513584			Accession #	3518451

ABOUT THE TEST
 Golden Labs utilizes a Next Generation Sequencing (NGS) based assay of 50 cancer related genes to detect relevant genomic alterations that provide therapeutic guidance, disease diagnostic evidence or prognostic indication. See Method & Limitations.

RESULTS SUMMARY

Multiple genomic alterations detected, including biomarkers for FDA approved drugs for the patient's tumor type.

SOMATIC ALTERATIONS DETECTED				
GENE	TYPE	DESCRIPTION	LOCATION	EVIDENCE
<i>BRAF</i>	Mutation	V600E	Exon 15 Missense	Tier I - Level A

BIOMARKER DETAILED RESULTS

BRAF

V600E

Tier I - Level A

Drug Sensitivity

Drug Resistance

Prognosis Evidence

Sensitivity to Drugs:

Dabrafenib + Trametinib

Vemurafenib + Cobimetinib

Encorafenib + Binimetinib

***BRAF* Clinical Significance:** *BRAF* (B-RAF proto-oncogene) is a serine/threonine specific protein kinase that regulates the MAP Kinase/ERK signaling pathways regulating many of the hallmarks of cancer including proliferation, differentiation, migration and apoptosis (PMID: 15520807, 15488754). *BRAF* that is commonly activated by somatic point mutation in many cancer types including melanomas, cancers of the colon and rectum, ovary, and thyroid gland (PMID: 17208430). Typically, *BRAF* mutations are mutually exclusive from other known oncogenic driver mutations *BRAF* mutation status can provide clinical utility as a diagnostic and prognostic marker as well as indicate sensitivity to *BRAF* and MEK inhibitors (PMID: 23594689).

***BRAF* Outcomes & Frequencies:** *BRAF*-mutant melanomas represent around 50% of all melanomas (PMID: 26091043). *BRAF* mutation status is crucial to determining whether a patient will benefit from *BRAF* inhibitor therapy (PMID: 25399551). The most prevalent *BRAF* mutations detected in melanoma are missense mutations that introduce an amino acid substitution at valine 600. Although the most common mutation is p.V600E (PMID: 12068308), a mutation resulting in substitution of valine (V) with a lysine (K) is seen in approximately 5-12% of melanomas (COSMIC, PMID: 20630094, 22536370). This mutation deregulates the protein's kinase activity leading to constitutive *BRAF* activation (PMID: 26150740).

V600E Biomarker Summary: The hotspot for mutations in *BRAF* is at codon p.V600. Mutations at p.V600 occur within the activation segment of the kinase domain resulting in increased kinase activity. The most common activating mutation is the p.V600E mutation which results in an amino acid substitution at position 600 in *BRAF*, from a valine (V) to a glutamic acid (E). Approximately 80-90% of p.V600 *BRAF* mutations are p.V600E (COSMIC).

Drug Sensitivity: *BRAF* p.V600E mutations are associated with increased sensitivity to *BRAF*

Signed Electronically by Darby Kammeraad | Medical Director: Leonard McCoy, M.D. | CLIA Number: 1234ABCD | Tue, Jun 18, 2019 page 1 of 6

Annotation

Variant Filtering

The screenshot displays the VarSeq software interface. At the top, there's a 'GenomeBrowse' window showing a genomic track for chromosome 16, with coordinates 16: 2,495,470 to 16: 2,495,530. Below this, there are tracks for 'Reference Sequence GRCH37 g1k, 1000Genomes', 'RefSeq Genes 105, NCBI' (showing the CCNF gene), and 'OMIM Genes 2010-10-27, UCSC' (showing gene 600227). A 'Variants - NA12878' track shows several variants, including T/G and C/A. On the left, a 'Trio Analysis' panel shows various metrics like 'Compound Het', 'Proband Genotype Quality', and 'Essential Gene'. At the bottom, a table lists variant sites with columns for 'Chr_Pos', 'Ref/Alt', 'Identifier', 'Genotypes', 'Classification', and 'Compound Het Variants'.

Chr_Pos	Ref/Alt	Identifier	Proband (NA12878)	Mother (NA12891)	Father (NA12892)	Sequence Ontology	Is CH? Inherited From
11:108183167	A/G	rs659243	G,G	G,G	G,G	missense_variant	False NA
13:49033835	G/A	rs20211...	A,G	A,G	A,G	missense_variant	False NA
14:24567498	A/C	rs30211...	C,C	C,C	C,C	missense_variant	False NA
14:73664751	T/G	rs19972...	G,T	G,T	G,T	missense_variant	False NA
14:106208082	G/T	rs11621...	G,T	T,T	?	missense_variant	False NA
16:2495482	T/G	rs20154...	G,T	T,T	G,T	missense_variant	True Father

Data Analysis

Genome Browser

■ 様々なデータソースを用いて、変異データ（VCFファイル）へアノテーション付けを実行

- RefSeq Genes
- dbSNP
- ClinVar
- OMIM
- COSMIC
- CIVic
- ICGC / TCGA
- Orphanet
- BRCA Exchange
- MSK Impact
- PMKB
- dbNSFP
- REVEL
- CADD
- 1000 Genomes
- NHLBI 6500 Exomes
- ExAC Variant
- gnomAD Exomes/Genomes
- GenomeAsia 100K
- 各種遺伝子パネルのターゲットデータ ...など

■ アノテーション付けされた変異データより、任意の検索条件でデータのフィルタリングを行うワークフローを作成

■ カバレッジ計算やトリオ解析、表現型情報に基づく遺伝子ランキングなどの解析アルゴリズムを搭載

■ ゲノムブラウザを搭載し、BAMファイルデータや各種アノテーションデータをグラフ表示

■ 有償アドオンによる機能拡張で、CNVコールやレポート作成、パイプライン機能などが利用可能

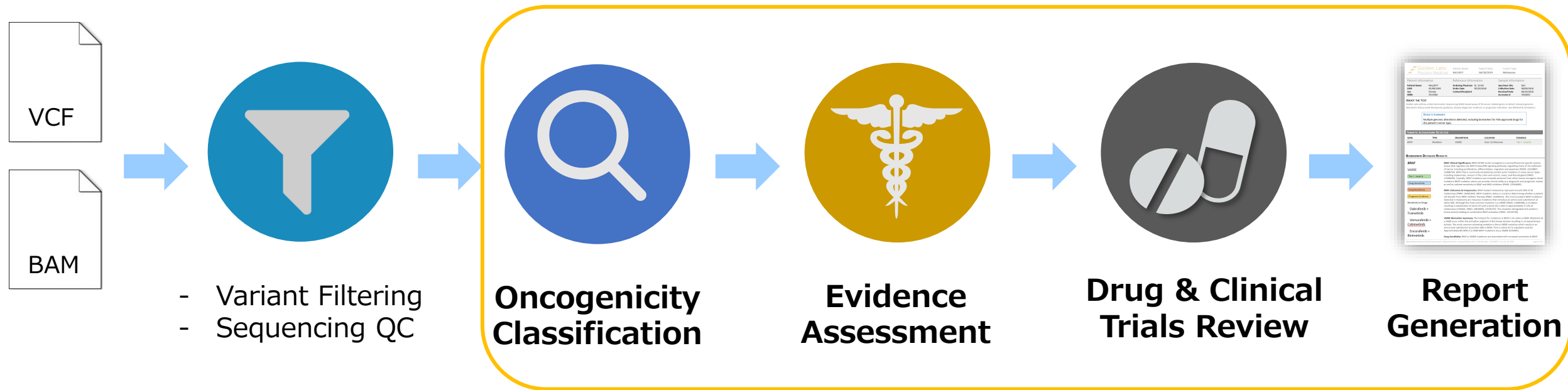


VS Clinical (ACMG)

- メンデル遺伝病における生殖細胞系列バリエントを、ACMGガイドラインの33種類の評価基準に基づいて分類し、病源性 (Pathogenic) や良性 (Benign) の判定を行う
- ガイドラインのうち18種類の評価基準については、バリエントのアレル頻度、機能予測、臨床情報データベースなどを用いて、自動分類を実行
- 専用の分類用ツールを実行することで、VCFファイルに含まれる全バリエントに対して一括で評価を行い、評価結果に基づきバリエントのフィルタリングが可能

VS Clinical (AMP)

- がんにおける体細胞バリエントの臨床的意義の評価に使用
- 体細胞バリエントの腫瘍原性 (Oncogenicity) をスコアで評価
- 各種バイオマーカー (Small Variant, CNV, 融合遺伝子など) に対して、AMPガイドラインのEvidence tierレベルで分類し、治療薬や臨床試験情報を含めたレポートを作成
- 主要ながんにおけるバイオマーカー情報などを収録した、専用のデータベースGolden Helix CancerKBが利用可能



Oncogenicity Classification

Oncogenicity Scoring Recommendations

Recommended to Score Oncogenic:

- SC+3** → The p.V600E variant occurs in 28376 samples in COSMIC.
- CE+3** → The p.V600E variant has been previously classified as pathogenic in ClinVar The p.V600E variant has been previously classified as oncogenic in CIVIC
- IP+1** → The p.V600E missense variant is predicted to be damaging by both SIFT and PolyPhen2 The valine residue at codon 600 of BRAF is conserved in all mammalian species The nucleotide c.1799 in BRAF is predicted conserved by GERP++ and PhyloP across 100 vertebrates.
- AR+1** → The p.V600E variant occurs in an active binding site.
- HR+1** → The p.V600E variant occurs in a cancer hotspot
- NP+1** → 16 variants within 6 amino acid positions of the variant p.V600E have been shown to be pathogenic, while none have been shown to be benign.

Recommended to Score Benign:
No Benign Criteria Recommended

Oncogenicity Classification given Scored Criteria:
Oncogenic (+10)

Scored Criteria:
SC+3 CE+3 IP+1 AR+1 HR+1 NP+1

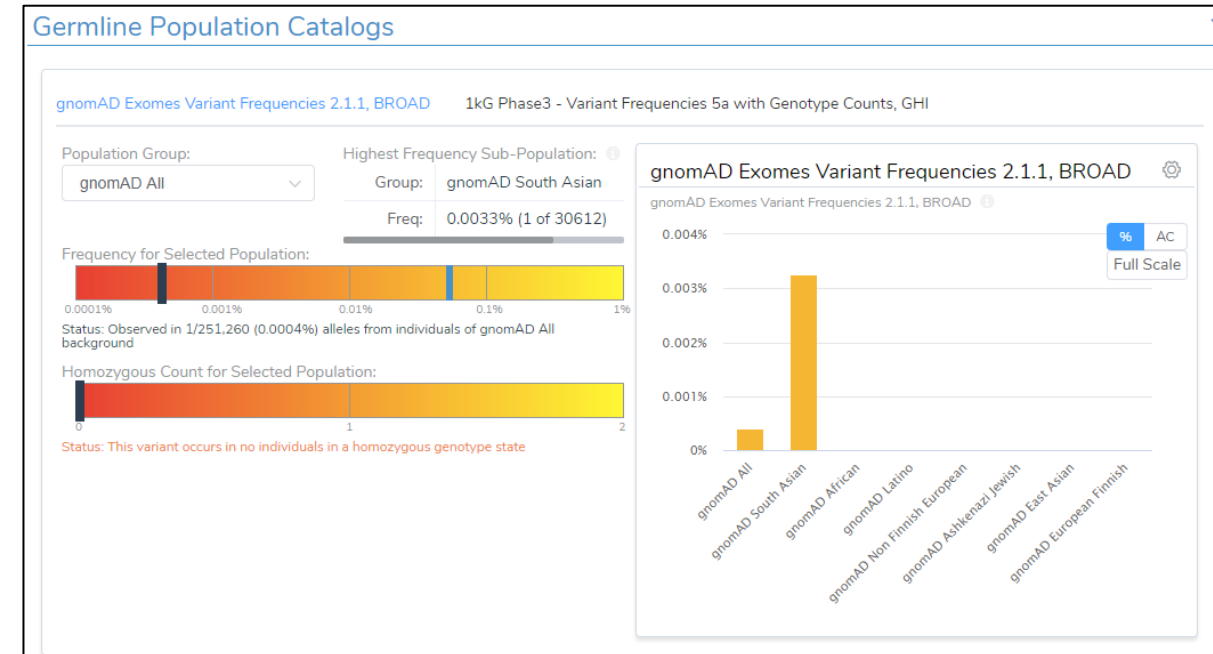
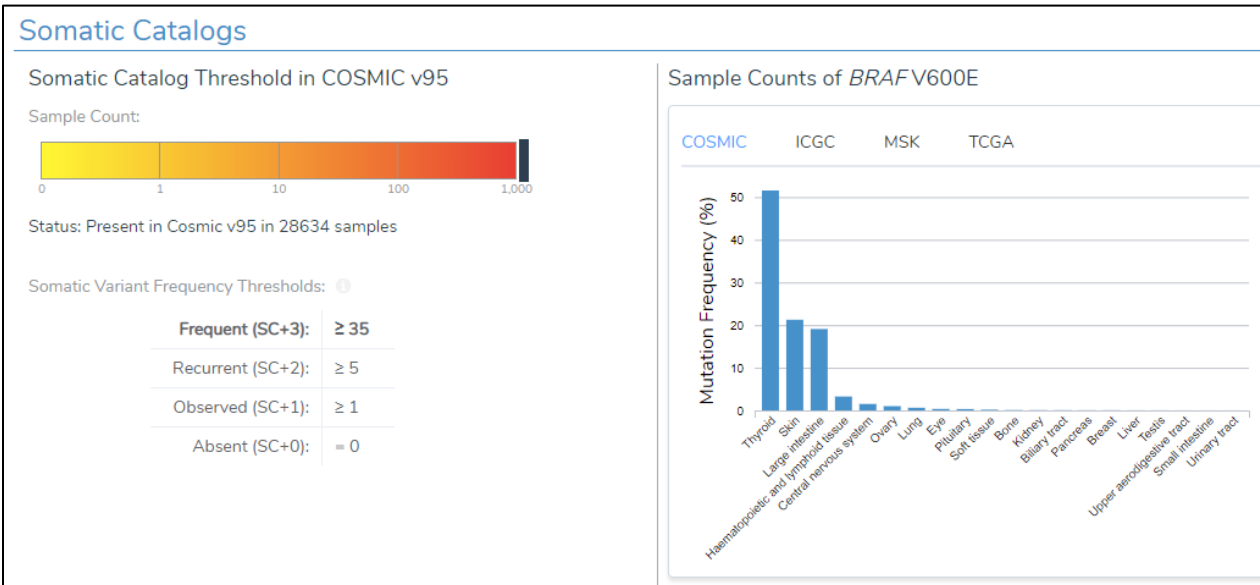
Oncogenicity Scale and Source:

The Golden Helix Oncogenicity score was developed to provide a criteria-based scoring system similar to the ACMG Guidelines but with the numeric pathogenicity scale introduced by Invitae's Sherlock scoring system. In consultation with the GA4GH Variant Interpretation in Cancer Consortium (VICC) system, the scoring rubric was designed to rank variants by their pathogenicity in the context of cancers. The most common somatic variants in COSMIC were used to tune and benchmark the scoring system along with variants with highly rated clinical evidence in CIVIC.

- Golden Helix社独自開発の、体細胞バリエーションの腫瘍原性評価アルゴリズム
- 評価結果のスコアに応じて、Oncogenic, Benign, VUSなどに自動で分類される

■ 評価項目例

- Germline Population Catalogs
- In-Silico Functional/Splicing
- Previous / Clinical Evaluations
- Somatic Catalogs
- Domain / Hotspot Analysis
- Gene Affinity to Variant Type



- ダッシュボードで評価項目ごとに関連データを確認
- 項目ごとに評価判定の根拠の確認や、評価スコアを手動で調整することも可能

Somatic Catalogs: Rate of recurrence of mutation in somatic catalogs

SC+0 Absent
 SC+1 Observed (≥ 1)
 SC+2 Recurrent (≥ 5)
 SC+3 Frequent (≥ 35)

Reasons for Oncogenic Comment:

- The p.V600E variant occurs in 28376 samples in COSMIC.

Report As: Biomarker

Variant Sets:

Classification: Oncogenic

Tumor Type: Melanoma

Interpretation:

The NM_004333.6(BRAF):c.1799T>A(p.V600E) variant is a missense mutation in exon 15 of BRAF. There is a moderate physicochemical difference between valine and glutamic acid. The p.V600E variant occurs in 29701 samples in COSMIC. The p.V600E variant has been previously classified as pathogenic in ClinVar. The p.V600E variant has been previously classified as oncogenic in CIViC. The p.V600E missense variant is predicted to be damaging by both SIFT and PolyPhen2. The valine residue at codon 600 of BRAF is conserved in all mammalian species. The nucleotide c.1799 in BRAF is predicted conserved by GERP++ and PhyloP across 100 vertebrates. The p.V600E variant occurs in an active binding site. The p.V600E variant occurs in a cancer hotspot. 23 variants within 6 amino acid positions of the variant p.V600E have been shown to be pathogenic, while none have been shown to be benign. For these reasons, this variant has been classified as oncogenic.

Inline References:
No inline references

Interpretation Notes:

Interpretation Actions: Interpretation History: ↻

Score Annotations Gene Literature Assessments

CIViC Assessment ◀ 1 of 7 ▶

Tumor Types: Colorectal Adenocarcinoma, Papillary Thyroid Cancer, Langerhans Cell Sarcoma, Biliary Tract, Melanoma, Larynx Squamous Cell Carcinoma, Ovary/Fallopian Tube, Non-Small Cell Lung Cancer, Cholangiocarcinoma, Intrahepatic Cholangiocarcinoma, Serous Ovarian Cancer, Astrocytoma, Cutaneous Melanoma, Plasma Cell Myeloma, Hairy Cell Leukemia, Gastrointestinal Neuroendocrine Tumors

Evidence Records: 92
Max Trust Rating: ★ ★ ★ ★ ★

BRAF V600E has been shown to be recurrent in many cancer types. It is one of the most widely studied variants in cancer. This variant is correlated with poor prognosis in certain cancer types, including colorectal cancer and papillary thyroid cancer. The targeted therapeutic dabrafenib has been shown to be effective in clinical trials with an array of BRAF mutations and cancer types. Dabrafenib has also shown to be effective when combined with the MEK inhibitor trametinib in colorectal cancer and melanoma. However, in patients with TP53, CDKN2A and KRAS mutations, dabrafenib resistance has been reported. Ipilimumab, regorafenib, vemurafenib, and a number of combination therapies have been successful in treating V600E mutations. However, cetuximab and panitumumab have been largely shown to be ineffective without supplementary treatment.

Source: CIViC (2022-05-01) [↗](#)

↑
自動生成されたテキスト

- 評価結果に基づき、臨床的解釈のテキストが自動生成される
- 参考文献やデータベースの情報なども、インラインで追加が可能

ACMG Criteria Recommendations

Scoring System:

ACMG Variant Classification (Richards et al. 2015) [↗](#)

To change the classification system close the evaluation and edit the Project Options...

Recommended to Score Pathogenic:

- PM2** [↗](#) The S257L variant is novel (not in any individuals) in gnomAD All. The S257L variant is novel (not in any individuals) in 1kG All.
- PM1** [↗](#) 25 variants within 6 amino acid positions of the variant S257L have been shown to be pathogenic, while none have been shown to be benign.
- PP2** [↗](#) The gene RAF1 has a low rate of benign missense variation as indicated by a high missense variants Z-Score of 2.46. The gene RAF1 contains 40 pathogenic missense variants, indicating that missense variants are a common mechanism of disease in this gene.
- PP3** [↗](#) The S257L missense variant is predicted to be damaging by both SIFT and PolyPhen2. The serine residue at codon 257 of RAF1 is conserved in all mammalian species. The nucleotide c.770 in RAF1 is predicted conserved by GERP++ and PhyloP across 100 vertebrates.
- PS1** [↗](#) The S257L variant is a missense mutation resulting in an amino acid change which is shared by the previously classified pathogenic variant p.S257L.
- PM5** [↗](#) The S257L variant is a missense mutation resulting in an amino acid change which occurs at the same amino acid position as 2 previously classified pathogenic variants.

Recommended to Score Benign:

No Benign Criteria Recommended

ACMG Classification given Scored Criteria:

Pathogenic

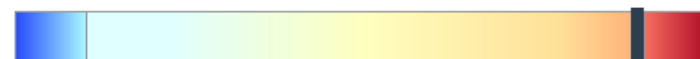
Rule Pathogenic (iii): 1 Strong AND ≥ 3 Moderate, OR 2 Moderate AND ≥ 2 Supporting, OR 1 Moderate AND ≥ 4 Supporting

Scored Criteria:

PM2 PM1 PP2 PP3 PS1 PM5

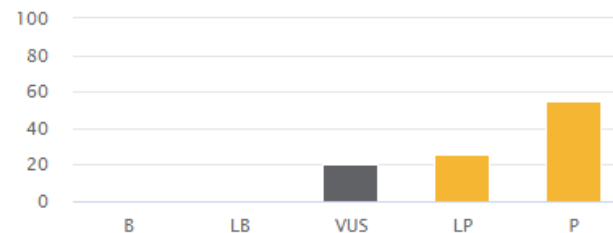
3 criteria currently unscored

Probability of Pathogenic given Scored Criteria:



Status: Probability of 88.7% predicting classification of **Pathogenic**

Probability for Each Classification:



- 生殖細胞系列バリエーションの評価には、ACMGガイドラインの評価項目を使用
- Secondary Germlineとしてレポートに追加も可能



Evidence Assessment

- バイオマーカーに対する、がんの治療方法のアクションナビリティに基づいた分類ガイドライン
- 治療薬の感受性や耐性、さらに予後／診断に関する臨床的な評価を、エビデンスレベルで分類を行う
- 同一バイオマーカーの場合でも、がん種ごとに分類結果は異なる
- VSclinical AMPでは、知識ベースから情報を引き出し、バイオマーカーごとのエビデンスレベルを、ソフトウェアが自動的に分類を行う

Tier I: Variants of Strong Clinical Significance

Therapeutic, prognostic & diagnostic

Level A Evidence

FDA-approved therapy included in professional guidelines

Level B Evidence

Well-powered studies with consensus from experts in the field

Tier II: Variants of Potential Clinical Significance

Therapeutic, prognostic & diagnostic

Level C Evidence

FDA-approved therapy for different tumor types or investigational therapies

Multiple small published studies with some consensus

Level D Evidence

Preclinical trials or a few case reports without consensus

Tier III: Variants of Unknown Clinical Significance

Not observed at a significant allele frequency in the general or specific subpopulation database, or pan-cancer or tumor-specific variant database

No convincing published evidence of cancer association

Tier IV: Benign or Likely Benign Variants

Observed at a significant allele frequency in the general or specific subpopulation databases

No existing published evidence of cancer association

(2017) Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer.

- Golden Helix社の臨床エキスパートがマニュアルキュレーションで作成した、がんゲノム医療向けの知識ベース
- 遺伝子またはバイオマーカーごとに、該当がん種のエビデンスレベル、臨床的解釈や候補治療薬の組み合わせ、参考論文などの情報が収録されている
- 臨床的解釈は7つのセクションに分類されており、目的に応じて使い分けが可能
 - Gene Summary
 - Outcomes & Frequency
 - Biomarker Summary
 - Clinical Evidence
 - Drug Sensitivity
 - Drug Resistance
 - Prognostic
 - Diagnostic
- 同一がん種における異なるバイオマーカーや、異なるがん種における同一バイオマーカーなどの情報も確認可能

▼ Related Interpretations for Melanoma (4)

V600R Melanoma < 2 of 4 >

Saved By: Golden Helix 3 months ago

Saved In: Golden Helix CancerKB 2022-03-08, GHI

Drug: Dabrafenib

Show More ▼

▼ Related Interpretations for other Tumor Types (11)

V600E Non-Small Cell Lung Cancer < 2 of 11 >

Saved By: Golden Helix 3 months ago

Saved In: Golden Helix CancerKB 2022-03-08, GHI

Drug: Vemurafenib

Show More ▼

Report *BRAF* V600E Drug Sensitivity:

Sensitivity to Drugs: Dabrafenib + Trametinib ✕

Vemurafenib + Cobimetinib ✕

Encorafenib + Binimetinib ✕

Add Drug or Drug Combination... ➕

Clinical Evidence Tier: Tier I - Level A ▼

Interpretation Saved for: Melanoma ▼

Interpretation Scope: BRAF V600E ▼

Interpretation:

BRAF p.V600E mutations are associated with increased sensitivity to BRAF inhibitors; vemurafenib (PMID: 21639808, 20818844, 22356324), dabrafenib (PMID: 22608338, 22735384), dabrafenib and trametinib (PMID: 23020132). The combination of a BRAF inhibitor along with a MEK inhibitor is shown not only to increase response rate but also to increase progression-free survival.

Patients whose tumors harbored p.V600E or p.V600K mutations showed better responses to the MEK inhibitor, trametinib, than to chemotherapy of dacarbazine or paclitaxel (PMID: 22663011). Patients with p.V600E or p.V600K-mutated tumors also showed better responses to trametinib than patients with *BRAF* wild type tumors (PMID: 22805292).

National Comprehensive Cancer Network (NCCN) guidelines advise that first-line systemic treatment options for patients with *BRAF*-mutant metastatic or unresectable melanoma include BRAF/MEK inhibitor combination therapy with dabrafenib/trametinib or vemurafenib/cobimetinib, or single-agent BRAF inhibitor therapy with vemurafenib or dabrafenib. The NCCN panel considers single-agent

Inline References:

21639808 [↗](#) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. Chapman PB et al., N Engl J Med. 2011 Jun 30

20818844 [↗](#) Inhibition of mutated, activated BRAF in metastatic melanoma. Flaherty KT et al., N Engl J Med. 2010 Aug 26

22356324 [↗](#) Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. Sosman JA et al., N Engl J Med. 2012 Feb 23

22608338 [↗](#) Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Falchook GS et al., Lancet. 20...

22735384 [↗](#) Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Hauschild A et al., Lancet. 2012 Jul 28

23020132 [↗](#) Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations.

- Golden Helix CancerKB以外に、公共データベースの知識ベースを活用することも可能
 - DrugBank
 - CIViC
 - PMKB (Precision Medicine Knowledgebase)
- Golden Helix CancerKBと同様に、バイオマーカーごとに該当がん種のエビデンスレベル、臨床的解釈や候補治療薬、参考論文などの情報が、研究レコードごとに納められている
- 感受性と耐性それぞれに関連する薬剤のリストも得ることが可能

CIViC Eld 1409 8 of 35

Drug: Vemurafenib

Evidence: Supports Sensitivity/Response

Disease: Skin Melanoma

Biomarker: BRAF V600E

Level: A - Validated Trust Rating: ★ ★ ★ ★ ★

Phase 3 randomized clinical trial comparing vemurafenib with dacarbazine in 675 patients with previously untreated, metastatic melanoma with the BRAF V600E mutation. At 6 months, overall survival was 84% (95% confidence interval [CI], 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine group. A relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression was observed with vemurafenib as compared with dacarbazine (P<0.001 for both comparisons).

References:

21639808 Improved survival with vemurafenib in melanoma with BRAF V600E mutation. Chapman PB et al. 364(26):2507-16.

NCT01006980 A Study of Vemurafenib (RO5185426) in Comparison With Dacarbazine in Previously Untreated Patients With Metastatic...

Source: CIViC Eld 1409 (2022-06-01)

Hide

Drug Sensitivity (35) Drug Resistance (4) Prognostic (3) Diagnostic (1)

Filter Evidence:

Disease / Tissue Specific: SKIN Skin All

Matching: Mutation Region Gene

Evidence Type: Drug Sensitivity All

Drugs	Biomarker	Disease / Tissue	Evidence	Level	Trust
Atezolizumab	BRAF Mutation	Cutaneous Melanoma / Skin	Drug Sensitivity. Atezolizumab is indicated to ...	1 - Drug Bank	FDA Approved
Cobimetinib, Vemurafenib, ...	BRAF V600E, BRAF	Melanoma / Skin	Drug Sensitivity. B-RAF is a member of the R...	1 - Tier I	PMKB
Cobimetinib, Vemurafenib, ...	BRAF V600D, BRAF	Melanoma / Skin	Drug Sensitivity. DrugVemurafenibDabrafenib...	1 - Tier I	PMKB
Fluorouracil, Binimetinib, C...	BRAF codon(s) 600 :	Melanoma, Langerhans Cell Hist	Drug Sensitivity. VemurafenibDabrafenibDabr...	1 - Tier I	PMKB
Dabrafenib + Trametinib	BRAF V600	Skin Melanoma / Skin	Supports Sensitivity/Response. The Combi-v (...	A - Validated	★ ★ ★ ★ ★

- バイオマーカーの評価を行う前に、サンプルのがん種を選択が必要
- 代表的ながん種を選択するか、対象となる臓器名より、手動で検索することも可能

Tumor Type - Melanoma

Tissue:	Tumor Type:
Nervous System	▼ Melanoma (MEL)
Peritoneum	Acral Melanoma (ACRM)
Pleura	Congenital Nevus (SKCN)
Prostate	Cutaneous Melanoma (SKCM)
Skin	Desmoplastic Melanoma (DESM)
Soft Tissue	Lentigo Maligna Melanoma (SKLMM)
Testis	Melanoma of Unknown Primary (MUP)
Thymus	Spitzoid Melanoma (SPZM)
Thyroid	Acral Lentiginous Melanoma (ALM)
Uterus	Merkel Cell Carcinoma (MCC)

Selected Tumor Type:
Melanoma (MEL)

Selected Main Type: NCI Concept ID:
Melanoma (MEL) **C3224**

Most Common:

- Non-Small Cell Lung Cancer (NSCLC)
- Invasive Breast Carcinoma (BRCA)
- Colorectal Adenocarcinoma (COADREAD)
- Prostate Adenocarcinoma (PRAD)
- Melanoma (MEL)
- Well-Differentiated Thyroid Cancer (WDTC)
- Ovarian Epithelial Tumor (OVT)
- Bladder Urothelial Carcinoma (BLCA)
- Glioblastoma (GB)
- Pancreatic Adenocarcinoma (PAAD)
- Sarcoma, NOS (SARC NOS)
- Renal Cell Carcinoma (RCC)
- Endometrial Carcinoma (UCEC)
- Lymphoid Neoplasm (LNM)
- Head and Neck Squamous Cell Carcinoma (HNSC)

Included Somatic Variants

Small Variants (2) CNVs (0) Fusions (0) Wild-Types (0)

Gene Variant Chr.Pos Origin State Classification Report Last Classified

Variants to Select:

Filter Variants (Variants)

<input checked="" type="checkbox"/>	Variant	VAF
<input type="checkbox"/>	PIK3CA p.G118D	
<input checked="" type="checkbox"/>	EGFR p.T790M	
<input checked="" type="checkbox"/>	EGFR p.L858R	
<input type="checkbox"/>	TP53 p.R273H	

Mutation Origin:
 Germline Suspected Somatic

Select All Clear All Select

✓ Small Variant

Enter CNV:

EGFR 19
e.x. BRCA2 3-5

Gene Matching Query:
Gene: EGFR
Genomic Region:
7: 55,242,415 - 55,242,513
Clinically Relevant Transcript:
NM_005228.5
Number of Exons:
28
Exons Selected:
Exon 19

Het Deletion Deletion Duplication
 Loss of Heterozygosity

Ratio Ratio Z-Score Z-Score

Select

✓ CNV

Enter Fusion:

EML4-ALK
e.x. BCR-ABL1

Genes Matching Query:

Primary Gene:
ALK
Genomic Region:
2:29,415,640 - 30,144,452
Clinically Relevant Transcript:
NM_004304.5

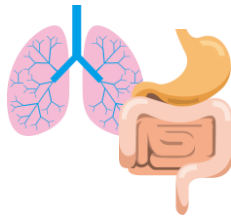
Secondary Gene:
EML4
Genomic Region:
2:42,396,493 - 42,559,688
Clinically Relevant Transcript:
NM_019063.5

Automatically Select Primary Gene

Select

✓ Fusion Gene

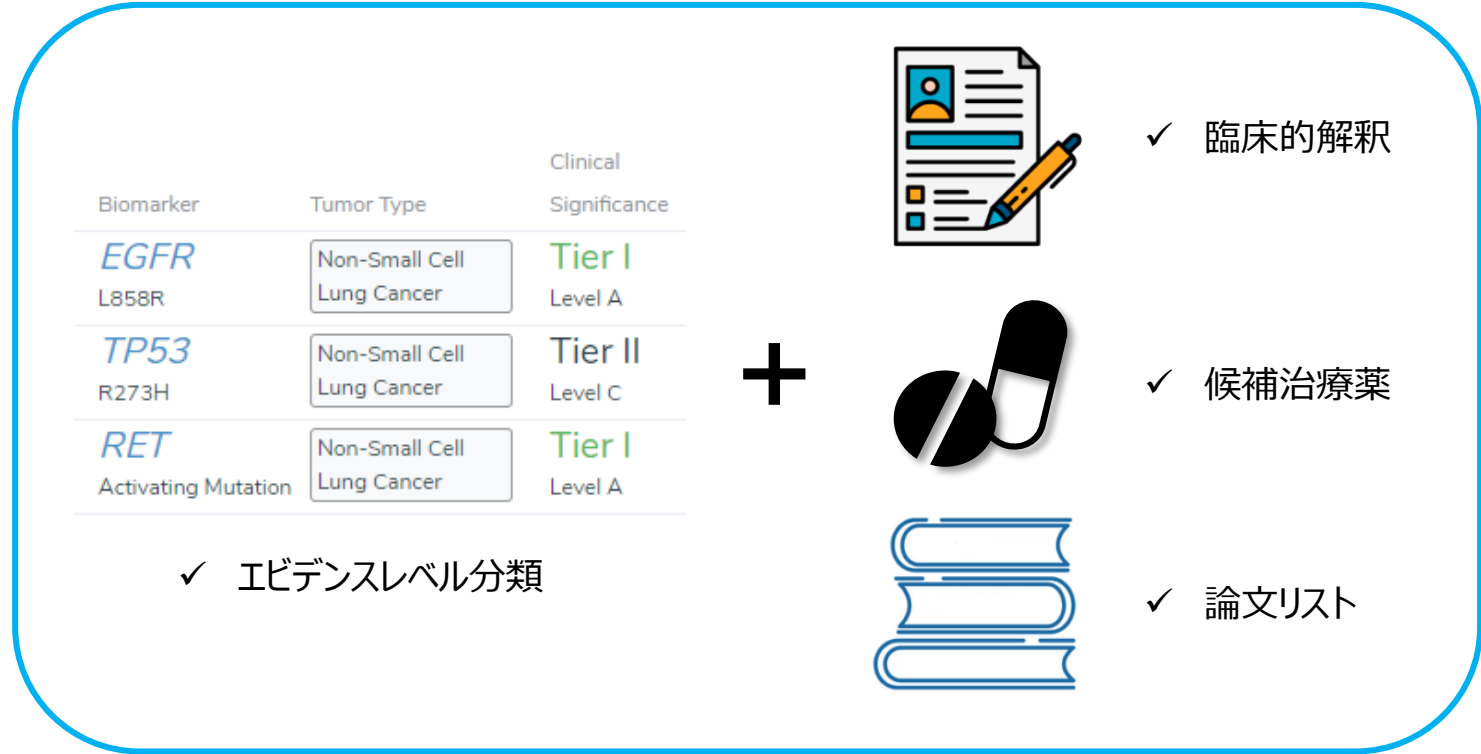
- 評価に用いるバイオマーカーは、VCFファイル内のバリエントを選択するか、またはバイオマーカー名を手動で入力
- バリエントでは体細胞／生殖細胞の選択や、CNVは重複／欠失の設定も行う



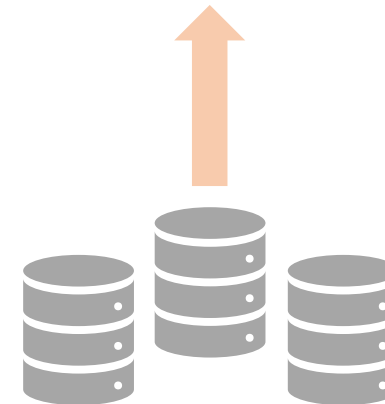
がん種情報



バイオマーカー



- がん種とバイオマーカーを入力すると、Golden Helix CancerKBに照合が行われ、自動的にエビデンスレベルや各種の臨床評価情報などが出力される
- Golden Helix CancerKBからの出力結果は、他の知識ベースの情報を参照しながら、編集が可能

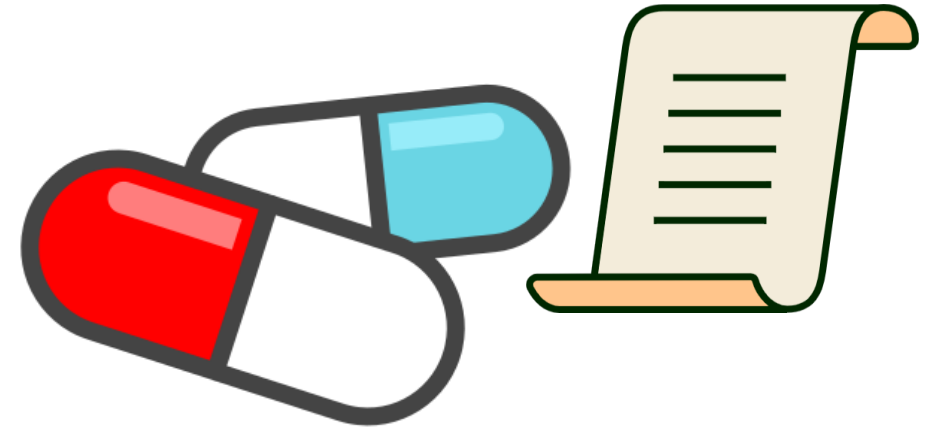


必要に応じて、他の知識ベースのデータを利用し、情報を編集



Drug & Clinical Trials Review

- 候補治療薬の詳細と、臨床試験情報の確認を行う
 - 薬剤情報 (DrugBank)
 - ✓ Drug Description
 - ✓ Indications and Use
 - ✓ Pharmacodynamics
 - ✓ Mechanism of Action
 - 臨床試験情報 (NCI Cancer Clinical Trials)
 - ✓ Phase/status
 - ✓ Study type and location
 - ✓ Contact information
 - ✓ Start and finish date
 - ✓ Min-max age/gender
- 臨床試験情報は、国名を指定しての検索が可能



Nearest Clinical Trial Sites:

Country: Japan ▼

Therapeutic Options

<input checked="" type="checkbox"/>	Drug	Biomarkers	Response	Clinical Trials
<input checked="" type="checkbox"/>	Osimertinib ↻	EGFR T790M	Sensitivity to FDA Approved Therapy Within Indication	0 Selected 🔍 Matching Trials (1)...
<input checked="" type="checkbox"/>	Capmatinib ↻	MET Activating Mutation	Sensitivity to FDA Approved Therapy Within Indication	0 Selected 🔍 Matching Trials (1)...
<input checked="" type="checkbox"/>	Tepotinib ↻	MET Activating Mutation	Sensitivity to FDA Approved Therapy Within Indication	0 Selected 🔍 Matching Trials (1)...
<input checked="" type="checkbox"/>	Crizotinib ↻	MET Activating Mutation, A...	Sensitivity to FDA Approved Therapy Within Indication	0 Selected 🔍 Matching Trials (0)...
<input checked="" type="checkbox"/>	Alectinib ↻	ALK Fusion	Sensitivity to FDA Approved Therapy Within Indication	0 Selected 🔍 Matching Trials (0)...

13 Records Total 13 Records < 1 2 3 > Records per page: 5 10 20 50

選択した国内で進行中の臨床試験あり

- 候補治療薬ごとに、FDA承認や臨床試験情報の一覧が表示される
- 国名を選択しておけば、選択国内で進行中の臨床試験の件数が表示される

- 候補治療薬ごとに、DrugBankに登録されている薬剤の詳細情報をダッシュボード画面で確認が可能
- バイオマーカーの候補治療薬リストとともに、レポートに掲載することも可能

Report Osimertinib
 ◀ 1 of 13 ▶

Biomarkers: EGFR T790M

Biomarker Association: Drug Sensitivity

Relevance to Patient:

Approved For:

Commercial Labels:

Clinical Trials: 0 Selected

Indication for Use:

Osimertinib is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA- approved test, who have progressed on or after EGFR-TKI therapy.

Description :

Osimertinib is an oral, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) drug developed by AstraZeneca Pharmaceuticals. Its use is indicated for the treatment of metastatic non-small cell lung cancer (NSCLC) in cases where tumour EGFR expression is positive for the T790M mutation as detected by FDA-approved testing and which has progressed following therapy with a first-generation EGFR tyrosine kinase inhibitor. Approximately 10% of patients with NSCLC have a rapid and clinically effective response to EGFR-TKIs due to the presence of specific activating EGFR mutations within the tumour cells. More specifically, deletions around the LREA motif in exon 19 and exon 21 L858R point mutations are correlated with response to therapy.

Development of third-generation EGFR-TKIs, such as osimertinib, has been in response to altered tumour resistance patterns following treatment and toxic side effects that impact patient quality of life. Treatment with first-generation

Inline References:

No inline references

▽ Osimertinib Details

Osimertinib DrugBank Details

Conditions: Metastatic Non-Small Cell Lung Cancer, Non-Small Cell Lung Carcinoma (NSCLC)

Status: FDA Approved [Label](#)

Product: Tagrisso

Synonyms: Mereletinib, N-(2-[[2-(dimethylamino)ethyl](methyl)amino]-4-methoxy-5-[[4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl]amino]phenyl)prop-2-enamide, Osimertinib, Osimertinibum

Drug Description:
Osimertinib is an oral, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) drug developed by [More...](#)

Indications and Use:
Osimertinib is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-posi [More...](#)

Pharmacodynamics:
A pharmacokinetic/pharmacodynamic analysis suggested a concentration-dependent QTc interval prolongation of 14 msec (upper bound o [More...](#)

Mechanism of Action:
Osimertinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that binds to certain mutant forms of EG [More...](#)

Source: DrugBank Drug DB09330 (2022-06-01) [↗](#)

Hide ^

✓ 試験IDとタイトル

NCT03940703 A Study of Tepotinib Plus Osimertinib in Osimertinib Relapsed MET Amplified NSCLC (INSIGHT 2)
Nearest Location: Hamamatsu-shi (Hamamatsu University School of Medicine, Universit...)

Summary/Diseases Inclusion Criteria Sites(11)

Status: Recruiting
Phase: Phase 2
Start/End: September 19, 2019 → March 30, 2023
Eligibility: Age 18 Years+, Male or Female
Drugs: Tepotinib
Osimertinib
Biomarkers: Gene Variant
Phosphotransferase Gene
Receptor Tyrosine Kinase Gene Mutation
Kinase Family Gene
Oncogene Deregulation
Gain of Function Gene Mutation
Growth Factor Receptor Gene
Receptor Gene
Gene Amplification Abnormality

✓ サマリー

Summary/Diseases Inclusion Criteria Sites(11)

Inclusion Criteria:

- Locally advanced or metastatic Non-small Cell Lung Cancer (NSCLC) histology (confirmed by either histology or cytology) with documented activating Epidermal Growth Factor Receptor (EGFR) mutation
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a minimum life expectancy of 12 weeks
- Acquired resistance on previous first-line osimertinib. Participants must meet both of the following 2 criteria:
- Radiological documentation of disease progression on first-line osimertinib
- Objective clinical benefit documented during previous osimertinib therapy, defined by either partial or complete radiological response, or durable stable disease (SD) (SD should last greater than (>) 6 months after initiation of osimertinib
- Have received only first-line osimertinib as a prior line of therapy in the non curative advanced or metastatic NSCLC setting

✓ 対象者の基準

Summary/Diseases Inclusion Criteria Sites(11)

Sites in Japan

- Hamamatsu-shi (Suspended)
Hamamatsu University School of Medicine, University Hospital - Dept of Respiratory Medicine
- Kitaadachi-gun (Recruiting)
Saitama Cancer Center
- Kurume-shi (Recruiting)
Kurume University Hospital
- Nagoya-shi (Recruiting)
Nagoya University Hospital - Dept of Respiratory Medicine
- Niigata-shi (Recruiting)
Niigata Cancer Center Hospital - Dept of Internal Medicine

✓ 実施サイト

- 臨床試験については、試験IDやタイトルに加え、各種詳細情報も確認可能
- 試験サイトについては、リクルート中かどうか表示される

- 臨床試験のレポート編集画面では、レポートに記載する実施サイトや対象基準の選択が可能

NCT03940703 [🔗](#) ◀ 2 of 2 ▶

A Study of Tepotinib Plus Osimertinib in Osimertinib Relapsed MET Amplified NSCLC (INSIGHT 2)

Relevant Therapies: Osimertinib Tepotinib

Relevant Biomarkers: MET Activating Mutation

Reported Attributes of Trial:

Status: Recruiting

Phase: Phase 2

Start/End: 2019-09-19 → 2023-03-30

Eligibility: Age 18 Years+, Male or Female

Selected Sites: 1 Selected

✖ Nagoya-shi (Recruiting)
Nagoya University Hospital - Dept of Respiratory Medicine

サイトの選択

Summary / Description:

This study will assess the antitumor activity, safety, tolerability, and pharmacokinetics (PK) of the Mesenchymal-epithelial Transition Factor (MET) inhibitor tepotinib combined with the 3rd generation EGFR inhibitor osimertinib in participants with advanced or metastatic non-small cell lung cancer (NSCLC).

Relevant Inclusion Criteria:

- Locally advanced or metastatic Non-small Cell Lung Cancer (NSCLC) histology (confirmed by either histology or cytology) with documented activating Epidermal Growth Factor Receptor (EGFR) mutation

Details and Sites

Summary/Diseases Inclusion Criteria Sites(11)

Sites in Japan

- Hamamatsu-shi (Suspended)
Hamamatsu University School of Medicine, University Hospital - Dept of Respiratory Medicine
- Kitaadachi-gun (Recruiting)
Saitama Cancer Center
- Kurume-shi (Recruiting)
Kurume University Hospital
- Nagoya-shi (Recruiting)
Nagoya University Hospital - Dept of Respiratory Medicine
- Niigata-shi (Recruiting)
Niigata Cancer Center Hospital - Dept of Internal Medicine
- Nishinomiya-shi (Recruiting)
Hyogo College of Medicine Hospital - Dept of Respiratory Medicine
- Okayama-shi (Recruiting)
Okayama University Hospital - Dept of Respiratory Medicine/Allergy
- Osaka-shi (Recruiting)
Osaka City General Hospital
- Osakasayama-shi (Recruiting)
Kindai University Hospital



Report Generation

- レポートを作成すると、以下のコンテンツが自動で収録され、項目の選択も可能
 - Patient information
 - Biomarkers
 - Secondary germline
 - Drugs and trials
 - Coverage and sequence summary
 - Citations

- バイオマーカーについては、最大で以下の7セクションごとの臨床的解釈を、レポートに記載することが可能
 - Gene Summary
 - Outcomes & Frequency
 - Biomarker Summary
 - Clinical Evidence
 - Drug Sensitivity
 - Drug Resistance
 - Prognostic
 - Diagnostic



Patient Name: NSCLC Sample
Report Date: (DRAFT)
Tumor Type: NSCLC

Patient Information		Reference Information		Sample Information	
Patient Name	NSCLC Sample	Ordering Physician		Specimen Site	
DOB		Order Date		Collection Date	
Sex	Unknown	Contact/Recipient		Received Date	
MRN		Additional		Accession #	

ABOUT THE TEST

Golden Labs utilizes a Next Generation Sequencing (NGS) based assay of 50 cancer related genes to detect relevant genomic alterations that provide therapeutic guidance, disease diagnostic evidence or prognostic indication. See Method & Limitations.

RESULTS SUMMARY

BIOMARKERS WITH FDA APPROVED DRUGS

GENOMIC FINDING	FDA-APPROVED THERAPIES IN PATIENT'S TUMOR TYPE	FDA-APPROVED THERAPIES IN ANOTHER TUMOR TYPE	POTENTIAL CLINICAL TRIALS
<i>EGFR</i> T790M	Osimertinib	None	Yes, see clinical trials section
<i>MET</i> Activating Mutation	Capmatinib, Tepotinib, Crizotinib	None	Yes, see clinical trials section
<i>ALK</i> Fusion	Crizotinib, Alectinib, Ceritinib, Brigatinib, Lorlatinib	None	None

GERMLINE ALTERATIONS DETECTED

GENE	TYPE	DESCRIPTION	GENOTYPE	DISEASERISK	CLASSIFICATION
<i>TP53</i>	missense variant	Arg273His	Homozygous	Autosomal Dominant	Likely pathogenic

EGFR

T790M

Tier I - Level A

Drug Sensitivity

Drug Resistance

Sensitivity to Drugs:

Osimertinib

Resistance to Drugs:

Erlotinib

Gefitinib

Afatinib

Dacomitinib

EGFR T790M Biomarker Summary:

EGFR p.T790M is an exon 20 missense mutation that is associated with acquired resistance to EGFR tyrosine kinase inhibitor (TKI) therapy in non-small cell lung cancer (NSCLC). EGFR p.T790M has been reported as an acquired mutation in approximately 60% of NSCLC patients with disease progression after initial response to first- or second-generation EGFR TKIs (PMID: 25979928, 23470965, 25271963, 24101047, 15737014, 17020982, 19589612). Within the EGFR ATP binding pocket, codon Thr790 represents a "gatekeeper" residue that regulates TKI binding. The precise mechanisms of EGFR p.T790M resistance remain unclear, although preclinical studies suggest that this mutation confers TKI resistance by increasing EGFR affinity for ATP and/or sterically hindering TKI binding to EGFR (PMID: 18227510, 15728811, 15897464, 17020982). The EGFR p.T790M mutation is generally detected together with EGFR sensitizing mutations such as exon 19 deletions (Ex19del) or p.L858R (PMID: 31562956, 30108370). In very rare cases (~0.5% of never-smokers with NSCLC), EGFR p.T790M has been identified in treatment-naïve NSCLC patients; in this context, EGFR p.T790M may be a germline mutation that is associated with predisposition to familial lung cancer (PMID: 16258541, 22588155, 24736066).

✓ バイオマーカー情報

Osimertinib

FDA Approved Therapy
Within Indication

FDA Approved

Drug Sensitivity

Approved For:

Metastatic Non-Small Cell
Lung Cancer

Relevant Biomarker:

EGFR T790M

Commercial Labels:

Tagrisso

Indication for Use: Osimertinib is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR-TKI therapy.

Osimertinib Description:

Osimertinib is an oral, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) drug developed by AstraZeneca Pharmaceuticals. Its use is indicated for the treatment of metastatic non-small cell lung cancer (NSCLC) in cases where tumour EGFR expression is positive for the T790M mutation as detected by FDA-approved testing and which has progressed following therapy with a first-generation EGFR tyrosine kinase inhibitor. Approximately 10% of patients with NSCLC have a rapid and clinically effective response to EGFR-TKIs due to the presence of specific activating EGFR mutations within the tumour cells. More specifically, deletions around the LREA motif in exon 19 and exon 21 L858R point mutations are correlated with response to therapy.

Development of third-generation EGFR-TKIs, such as osimertinib, has been in response to altered tumour resistance patterns following treatment and toxic side effects that impact patient quality of life. Treatment with first-generation EGFR-TKIs (gefitinib and erlotinib) has been associated with the development of resistance through activating mutations in the EGFR gene. Second-generation EGFR-TKIs (afatinib and dacomitinib) were then developed to be more potent inhibitors, although their use is associated with increased toxicity through nonspecific targeting of wild-type EGFR. In contrast, third-generation inhibitors are specific for the gate-keeper T790M mutations which increases ATP binding activity to EGFR and result in poor prognosis for late-stage disease. Furthermore, osimertinib has been shown to spare wild-type EGFR during therapy, thereby reducing non-specific binding and limiting toxicity.

✓ 薬剤情報

TP53

Homozygous p.R273H
NM_000546.6:c.818G>A

Likely pathogenic

Interpretation Disorder: Unspecified / All Highly Penetrant Disorders

ACMG Classification: Likely pathogenic

Interpretation: The missense variant NM_000546.6(TP53):c.818G>A (p.Arg273His) causes the same amino acid change as a previously established pathogenic variant. The variant is observed in one or more well-documented healthy adults. There is a small physicochemical difference between arginine and histidine, which is not likely to impact secondary protein structure as these residues share similar properties. 29 variants within 6 amino acid positions of the variant Arg273His have been shown to be pathogenic, while none have been shown to be benign. The Arg273His missense variant is predicted to be damaging by both SIFT and PolyPhen2. The arginine residue at codon 273 of TP53 is conserved in all mammalian species. The nucleotide c.818 in TP53 is predicted conserved by GERP++ and PhyloP across 100 vertebrates. For these reasons, this variant has been classified as Likely Pathogenic.

Technical Data for TP53 Arg273His:

Transcript and Coding Change	NM_000546.6:c.818G>A (p.Arg273His)
Location	17:7577120
Human Genome (GRCh37)	NC_000017.10: g.7577120C>T
Human Genome (GRCh38)	NC_000017.11: g.7673802C>T
dbSNP Identifier	rs28934576
ClinVar Variant ID	12366
Ashkenazi Jewish Allele Frequency	1/10072 (0.01%)
NGS Reads Supporting Change	100.00%

✓ 生殖細胞系列バリエーション情報

NCT03940703

Started: 2019-09-19
Ends: 2023-03-30

Phase 2

Relevant Therapy:

Osimertinib
Tepotinib

Relevant Biomarker:

MET Activating Mutation

Nearby Sites:

Nagoya-shi
Nagoya University Hospital -
Dept of Respiratory Medicine

A Study of Tepotinib Plus Osimertinib in Osimertinib Relapsed MET Amplified NSCLC (INSIGHT 2)

This study will assess the antitumor activity, safety, tolerability, and pharmacokinetics (PK) of the Mesenchymal-epithelial Transition Factor (MET) inhibitor tepotinib combined with the 3rd generation EGFR inhibitor osimertinib in participants with advanced or metastatic non-small cell lung cancer (NSCLC).

Eligibility: Age 18 Years+, Male or Female

✓ 臨床試験情報

お問い合わせ先：フィルジエン株式会社

TEL: 052-624-4388 (9:00～18 : 00)

FAX: 052-624-4389

E-mail: biosupport@filgen.jp