TruSight™ Oncology 500 Solid Tumor

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601 Genome Way
Huntsville, AL
35806

HUDSONALPHA DISCOVERY
SEQUENCING + BIOINFORMATICS™

STUDY	DISEASE	PARTICIPANT	REPORT DATE	REPORT STATUS
haib20SL6185	Carcinoma of colon	6185-SL-0008		Final

CLINICALLY RELEVANT RESULTS

Tier I - Strong Clinical Significance

VARIANT	CLINICAL IMPACT
KRAS p.G12V c.35G>T A NM_033360.2 VAF % 15.7 DEPTH 319	**Not likely to benefit from** — Panitumumab or Cetuximab *in Malignant tumor of colon* INTERPRETATION (1) LIMITATIONS OF USE: ERBITUX is not indicated for treatment of Ras mutant colorectal cancer or when the results of the Ras mutation tests are unknown. ERBITUX is not indicated for the treatment of patients with CRC that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-Ras or N-Ras and hereafter is referred to as "Ras" or when the Ras status is unknown. (2) CLINICAL STUDIES: Retrospective subset analyses of Ras-mutant and wild-type populations across several randomized clinical trials, including CRYSTAL, were conducted to investigate the role of Ras mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment related toxicity.

Tier II - Potential Clinical Significance

VARIANT	CLINICAL IMPACT
PIK3CA p.H1047R c.3140A>G C	**May benefit from** — Alpelisib *in Human epidermal growth factor 2 negative carcinoma of breast, Malignant tumor of breast, Infiltrating duct carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Hormone receptor*

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VARIANT	CLINICAL IMPACT
NM_006218.2 VAF % 16.1 DEPTH 335	*positive malignant neoplasm of breast, Infiltrating carcinoma with ductal and lobular features, or Infiltrating lobular carcinoma of breast*

INTERPRETATION

(1) Alpelisib is recommended for treatment of recurrent or stage IV (M1) hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative disease with no visceral crisis in postmenopausal women or premenopausal women treated with ovarian ablation/suppression, as second-line therapy or beyond in combination with fulvestrant if PIK3CA mutation positive (preferred regimen). (2) Men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis.

CDK12

p.E398Nfs*38
c.1192delG

C

NM_016507.2
VAF % 19.4
DEPTH 278

May benefit from

— Olaparib *in Malignant tumor of prostate or Adenocarcinoma of prostate*

INTERPRETATION

(1) INDICATIONS AND USAGE: Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (2) CLINICAL STUDIES: HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer: The efficacy of Lynparza was evaluated in PROfound (NCT02987543), randomized, open-label, multicenter trial that evaluated the efficacy of Lynparza versus a comparator arm of investigators choice of enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer (mCRPC). Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either BRCA1, BRCA2, or ATM were randomized in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L) were randomized in Cohort B; patients with comutations (BRCA1, BRCA2, or ATM plus a Cohort B gene) were assigned to Cohort A. No patients were enrolled who had mutations in two of the 15 pre-specified HRR genes: FANCL and RAD51C.

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VARIANT	CLINICAL IMPACT

INTERPRETATION

Determination of deleterious or suspected deleterious somatic or germline HRR mutation status in line with the FDA approved mutation classification and testing criteria for the Foundation Medicine F1CDx tissue-based assay and assessment of the germline-BRCA status using the Myriad BRACAnalysis CDx blood-based assay was performed retrospectively. The major efficacy outcome of the study was radiological progression free survival (rPFS) (Cohort A) as determined by BICR using RECIST version 1.1 and Prostate Cancer Clinical Trials Working Group 3 (PCWG3) (bone) criteria. Additional efficacy outcomes included confirmed objective response rate (ORR) (Cohort A), rPFS (combined Cohorts A+B) as assessed by BICR, and overall survival (OS) (Cohort A). PROfound demonstrated a statistically significant improvement in BICR-assessed rPFS for Lynparza compared to investigators choice of enzalutamide or abiraterone acetate in Cohort A and Cohort A+B. In an exploratory analysis for patients in Cohort B, the median rPFS was 4.8 months for Lynparza vs 3.3 months for comparator with a HR of 0.88 (95% CI 0.58, 1.36). The major efficacy outcome was supported by a statistically significant improvement in ORR by BICR for patients with measurable disease at baseline in Cohort A. In Cohort B, ORR by BICR was 3.7% (95% CI 0.5, 12.7) in Lynparza treated patients and 8.3% (95% CI 1.0, 27.0) in patients treated with enzalutamide or abiraterone acetate. The final analysis of overall survival (OS) demonstrated a statistically significant improvement in OS in patients randomized to Lynparza compared to patients in the enzalutamide or abiraterone acetate arm in Cohort A. Consistent results were observed in exploratory analyses of rPFS for patients who received or did not receive prior taxane therapy and for those with germline-BRCA mutations identified using the Myriad BRACAnalysis CDx assay compared with those with BRCA mutations identified using the Foundation Medicine F1CDx assay.

Other Biomarkers

BIOMARKER	CLINICAL IMPACT
TMB	

INTERPRETATION

8.7
muts/Mb

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BIOMARKER	CLINICAL IMPACT
MSI	

INTERPRETATION

2.3%
Unstable Sites

POTENTIAL CLINICAL TRIALS

Clinical Trials associated with this patient's genomic profile and tumor type are displayed below.

TITLE	TRIAL IDENTIFIER	PHASE	VARIANT
Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial)	**NCT02465060** https://clinicaltrials.gov/show/NCT02465060	II	***PIK3CA*** p.H1047R c.3140A>G
M6620 (VX-970) in Selected Solid Tumors	**NCT03718091** https://clinicaltrials.gov/show/NCT03718091	II	***CDK12*** p.E398Nfs*38 c.1192delG
Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors	**NCT02079740** https://clinicaltrials.gov/show/NCT02079740	I/II	***KRAS*** p.G12V c.35G>T
Onvansertib in Combination With FOLFIRI and Bevacizumab for Second Line Treatment of Metastatic Colorectal Cancer Patients With a Kras Mutation	**NCT03829410** https://clinicaltrials.gov/show/NCT03829410	I/II	***KRAS*** p.G12V c.35G>T
Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors	**NCT03284502** https://clinicaltrials.gov/show/NCT03284502	I	***PIK3CA*** p.H1047R c.3140A>G
Rucaparib and Irinotecan in Cancers With Mutations in DNA Repair	**NCT03318445** https://clinicaltrials.gov/show/NCT03318445	I	***CDK12*** p.E398Nfs*38 c.1192delG

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CLASSIFICATION AND LEVELS OF EVIDENCE

The variant classification system used in this report is based on joint consensus recommendations of the Association for Molecular Pathology, American Society of Clinical Oncology, and the College of American Pathologists (J Mol Diagn 2017, 19:4-23). Tiers IA, IB, IIC, IID, III and IV describe variant categories of descending clinical significance in the patient. Variants in Tier IV are not reported in accordance with the consensus recommendations.

IA	IB	IIC	IID
Variant of strong clinical significance, Level A evidence (FDA approved therapy or practice guideline in patient's tumor type)	Variant of strong clinical significance, Level B Evidence (consensus in the field based on well-powered studies in patient's tumor type)	Variant of potential clinical significance, Level C evidence (FDA approved therapy or practice guideline in other tumor type(s), evidence from multiple small published studies, or based on availability of investigational therapies)	Variant of potential clinical significance, Level D evidence (case reports or preclinical studies)

III	Variant of uncertain clinical significance
IV	Benign or likely benign variant

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TEST DETAILS

REPORTED GENES

A total of 523 genes were subjected to targeted next generation sequencing analysis. Details available upon request.

CGW VERSION

CGW_v6.13.1

DATABASE DETAILS

The versions, releases, builds, dates of the following databases were used to generate this report.

- Genomic Build: GRCh37.p13
- Genomic Annotation Sources: NCBI RefSeq v105
- COSMIC: v91
- NHLBI ESP: v.0.0.30
- dbNSFP: 3.5c
- gnomAD: r2.1
- ExAC: v1.0
- ClinVar: 20190603
- dbSNP: 149

METHODOLOGY

Assay Methods: The test was performed using the Illumina TruSight ™ Oncology 500 (TSO500) targeted hybrid-capture based next generation sequencing assay. It employs Unique molecular identifiers (UMI) to enable detection of variants, present in solid tumor, formalin-fixed paraffin-embedded (FFPE) tumor, and cfDNA samples, at low VAFs with a high degree of sensitivity and specificity. TSO500 is designed to detect multiple classes of mutations including single-nucleotide variants (SNVs), multi-nucleotide variants (<3bp), small Insertions (1-18bp)/Deletions (1-27bp) and Copy Number Variants (CNVs). The assay also detects, quantitatively, microsatellite instability (MSI) and tumor mutational burden (TMB). Fusions are detected in RNA (TSO500 Solid Tumor reports only). DNA and RNA (TSO500 Solid Tumor reports) or cfDNA (cfDNA reports) extractions are performed and RNA is then reverse transcribed to cDNA. The genomic DNA and cDNA (TSO500 Solid Tumor reports) or cfDNA (TSO500 cfDNA reports) are sheared to prepare sequencing libraries. The regions of interest are hybridized to biotinylated probes, magnetically pulled down with streptavidin-coated beads, and eluted to enrich the library pool. Finally, libraries are normalized, then pooled and sequenced on an Illumina NextSeq or NovaSeq instrument.

Secondary Analysis Methods: The DNA and RNA data is analyzed using the Illumina Software TSO500 v2.1 Local App or the cfDNA data is analyzed using the Illumina Software TSO500 v3 Dragen Server pipeline at Discovery Life Sciences. Further processing of data for interpretation and annotation using a customized analysis pipeline within the Clinical Genomics Workspace software platform from PierianDx is then performed.

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Variant Calling: Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen) and classified as per the AMP classification system into tiers IA, IB, IIC, IID, III and IV. These tiers are stratified by clinical utility ('actionability' for clinical decision-making as to diagnosis, prognosis, treatment options, and carrier status) and previously reported data in the medical literature. Variations found in gnomAD (https://gnomad.broadinstitute.org/) that have ≥1% minor allele frequency (except those that are also in ClinVar denoted as clinically relevant, used in a clinical diagnostic assay, or reported as a mutation in a publication) are classified as known polymorphisms. Small variant calls in the HLA-A, KMT2B, KMT2C, and KMT2D genes are filtered out due to potential mis-mapping as a result of sequence homology with other genomic regions.

Notes:

- This assay does not detect complex structural alterations or large indels, with the exception of a subset of clinically relevant complex EGFR exon 19 indels that are specifically targeted. Variants located outside of targeted capture regions will not be detected.

- It is possible that pathogenic variants may not be reported by one or more of the tools because of the parameters used. However, tool parameters were optimized to maximize specificity and sensitivity.

DISCLAIMER

The results provided in this report are for Research Use Only (RUO) and informational in nature. The information contained in this report cannot be used for patient treatment and/or prognostic decisions. All interpretations are made by the PierianDx Clinical Knowledgebase. No interpretations of variants have been made by Discovery Life Sciences.

The RUO assay was performed using tumor tissue; it is therefore not possible to determine whether variants detected are somatic or germline in origin unless a matched germline normal sample was analyzed using the same RUO assay and a tumor/normal pair VCF was generated prior to PierianDx interpretation or, in cases where tumor-only sample was analyzed, a tumor-only informed bioinformatics pipeline was used to generate the VCF prior to PierianDx interpretation.

High confidence Variant Allele Fraction (VAF) cutoffs for the results provided in this report were set at 5% based on RUO verification studies performed at Discovery Life Sciences.

PATIENT AND ORDER DETAILS

PATIENT

SEX

ETHNICITY

RACE

SPECIMEN

SPECIMEN TYPE

Formalin-fixed paraffin-embedded tissue specimen

EXT. SPECIMEN ID

% TUMOR IN SELECTED AREA

CASE

REVIEW STATUS

Final

DATE ACCESSIONED

12/04/2020 16:44

DATE REPORTED

ACCESSION NUMBER

6185-SL-0008_rerun

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