QCI Interpret One

Deliver oncologist-ready reports in minutes with clinically actionable evidence and recommendations

1. Provide a panel description and include summary comments of test results.
2. Identify clinically significant variants with respect to potential treatments, variants with potential clinical significance and associated therapies, and variants with biological significance.
3. Notify oncologists of potential interactions.
4. Guide oncologists to the summary of relevant guidelines for patient management.
5. Provide a Table of Contents to orient oncologists for fast review.

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Consulting physician		Patient		Sample	
Provider	General Hospital	Name	Michelle Doe	Accession Number	7-SP17-9111-B1-RNA_HighConfidenceVariants.zip
Physician	Dr. E Smith	Age	58		
Pathologist	Dr. R Jones	Gender	Female		
Report Date	May 20, 2020	Diagnosis	Breast carcinoma	Collection site	Breast
		Stage	IV	Type	Biopsy
				Collection date	May 11, 2020

1 Panel Analysis: Somatic cancer

Description of panel, purpose and what ever we need to tell the patient / oncologist in order to introduce the scope and relevance of the report. Somatic Cancer Panel is a comprehensive genomic profiling test designed to identify somatic mutations, copy numbers, fusions across 456 genes in tumor samples.

Overall comment

Patient specific comment to be added. Please note the interactions of mutations on clinical outcome.

2 Analysis results: Positive

1 Biomarker	Approved treatments	Other findings
Tumor Mutation Burden: TMB-low (5.7 Mutations/Megabase)	-	-
2 Variants of strong clinical significance, Tier 1	**Approved treatments**	**Other findings**
ERBB2: amplification, Pathogenic	DS-8201a Lapatinib Neratinib Pertuzumab Trastuzumab Trastuzumab emtansine	**Resistance: cetuximab, erlotinib, osimertinib** Trials: 3 Phase 3 6 Phase 2 1 Early Phase 1
PIK3CA: p.H1047R, Pathogenic	Alpelisib/fulvestrant	**Resistance: vemurafenib** Trials: 1 Expanded Access 2 Phase 2 1 Phase 1/Phase 2 6 Phase 1
2 Variants of potential clinical significance, Tier 2	**Approved treatments**	**Other findings**
CCND1: amplification, Pathogenic	-	Trials: 3 Phase 2
TP53 †: p.L348*, Pathogenic	-	-
2 Variants of biological significance, Tier 3	**11 Variants of uncertain significance, Tier 3**	
FGF10: amplification, Likely Pathogenic		
MYCN: amplification, Pathogenic		

† Allele Fraction (AF) >40%. AF suggests that it may be germline and pathogenic or likely pathogenic. Recommend obtaining confirmatory germline testing.

3 Interactions

Clinically relevant co-occurring variants are reported in the "interactions" section starting on page 2.

4 Guidelines

Potentially relevant guidelines are reported in the "guidelines" section starting on page 2.

Approval

Electronically signed on: May 20, 2020 by Dr. Jones

5 Report content

*This is a sample report that has been edited to illustrate key components. To view a full report, contact bioinformaticssales@qiagen.com

6 GUIDELINES

The NCCN Guidelines (v.2.2020) note that Her2-positive breast carcinoma patients may consider adjuvant chemotherapy plus trastuzumab, regardless of hormone receptor status, depending on the physician's evaluation of the individual patient; in certain situations, regimens including pertuzumab, ado-trastuzumab emtansine, or lapatinib may also be considered. The NCCN Guidelines (v.3.2020) list fulvestrant plus alpelisib as a preferred second-line therapy (category 1) for hormone receptor-positive, Her2-negative breast cancer patients with tumors harboring a PIK3CA mutation.

7 INTERACTIONS

PI3K pathway activation, as evidenced by the presence of activating PIK3CA mutations or decreased expression of Pten, has been associated with resistance to Her2-targeted therapies in some clinical studies, though in other studies no association was found (Guarneri et al., 2015; 26245675, Cescon and Bedard, 2015; 25559805, Majewski et al., 2015; 25559818, Pogue-Geile et al., 2015; 25559813, Chandarlapaty et al., 2012; 23092874, Sueta et al., 2014; 25542038) [PMID:26245675, PMID:25559805, PMID:25559818, PMID:25559813, PMID:23092874, PMID:25542038].

8 TREATMENT OPTIONS

Therapies with potential clinical benefit (7)

DS-8201A

Fam-trastuzumab deruxtecan-nxki, a HER2-directed antibody and topoisomerase inhibitor conjugate, is FDA-approved for treating adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

Phase 3 clinical trials (3)

TRASTUZUMAB EMTANSINE, TUCATINIB

Randomized, Double-blind, Phase 3 Study of Tucatinib or Placebo in Combination With Ado-trastuzumab Emtansine (T-DM1) for Subjects With Unresectable Locally-advanced or Metastatic HER2+ Breast Cancer (HER2CLIMB-02)
NCT03975647

Qualifying variant

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

Contact
United States: AZ, CA, CO, DE, FL, GA, IL, MD, MI, MO, NE, NJ, OR, TN, TX, VA
Seattle Genetics Trial Information Support; clinicaltrials@seagen.com; 866-333-7436;

9 VARIANT DETAILS

PIK3CA H1047R

Gene: PIK3CA
Exon: 21
Nucleotide: NM_006218.4: g.178952085A>G c.3140A>G
Amino Acid: p.H1047R
Allelic Fraction: 32.0% (of 2977 reads)
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
1 Sensitive
10 Trials

Biomarker summary: PIK3CA-H1047R is an activating mutation.

Clinical relevance: PIK3CA encodes the protein p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival [189, 56]. Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which are currently being tested in clinical trials [99, 143]. In addition, the p110-alpha inhibitor alpelisib has been approved by the FDA for the treatment of postmenopausal women, and men, with PIK3CA-mutated, hormone receptorpositive, Her2-negative advanced or metastatic breast cancer who experience disease progression on or following an endocrine-based therapy [10].

Disease summary: A study of 1394 early stage breast cancer samples reported that positive p110-alpha expression was associated with higher tumor grade, larger tumor size, nodal involvement, and vascular invasion. Higher p110-alpha expression was associated with basal-like breast cancer, Her2-positive breast cancer, and triple negative non-basal tumors [5]. Additional studies have reported that p110-alpha-positivity is associated with lower grade disease in breast cancer samples [113, 166, 184]. A pooled analysis of 10319 breast cancer patients from 19 studies has reported that PIK3CA mutation was associated with ER positivity, lower tumor grade, and smaller tumor size [251]. PIK3CA mutations and activation of the PI3K pathway may play a role in resistance to hormonal therapy in ER-positive breast cancers, as well as to Her2-targeted therapies in Her2-positive breast cancers, although some studies have reported no association between activation of the PI3K pathway and resistance to Her2-targeted therapies [62, 103, 155, 172, 236, 19, 122].

Molecular function: PIK3CA H1047R is a missense alteration that occurs in the kinase domain of the p110-alpha protein (UniProt). H1047R is a commonly reported hotspot mutation in the PIK3CA gene, and has been reported to result in increased lipid binding, elevated kinase activity, and oncogenic transformation in preclinical studies [111, 88, 14, 96, 162].

Incidence: PIK3CA mutations have been reported in 27% (4981/18180) of Breast carcinoma samples analyzed in COSMIC (Jan 2019). PIK3CA mutations have been reported in 27-48% of Breast carcinoma samples (cBioPortal for Cancer Genomics, Jan 2019). Literature studies have reported PIK3CA mutations in 26-40% of breast carcinoma samples overall [163, 61, 249, 153, 146]. In addition, PIK3CA mutations have been reported in 29-38% of hormone receptor-positive breast cancer samples and in 9-14% of triple negative breast cancer (TNBC) samples [61, 55, 21, 2].

6. Clearly convey the professional guideline evidence for each variant.
7. Inform on co-occurring variants with prognostic and diagnostic relevance and drug sensitivity and resistance.
8. List molecularly targeted therapies specific to your country for each clinically significant biomarker with the type and level of evidence supporting the selection.
9. Use oncologist-reviewed interpretive comments in three levels of detail (concise, intermediate, and complete) with variant-and disease-specific information, including molecular function, and diagnostic, prognostic, and therapeutic relevance.