QIAGEN

QCI® Interpret One

Oncology variant interpretation just got more precise

Sample to Insight

Deliver oncologist-ready variant interpretation reports

Competing to offer an in-house comprehensive genomic profiling service for tumor samples is challenging, especially as panels increase in size and complexity. Today's clinical labs are under mounting pressure to interpret next-generation sequencing (NGS) tests faster and with greater precision than ever before. That's why we created QCI Interpret One.

With QCI Interpret One, lab directors can prepare, prioritize and report on clinically relevant variants associated with solid tumors and hematological malignancies without the time-consuming step of researching and writing variant- and disease-specific evidence summaries. Users get access to an "expert second opinion" for variant classification, and they can deliver professional reports directly to physicians and oncologists to better inform clinical decision making.

By combining flexible and automatable QIAGEN Clinical Insights software, powered by superior structured content in the QIAGEN Clinical Knowledge Base, with the trusted services of N-of-One, a QIAGEN company and world-leading provider of somatic variant interpretation, QCI Interpret One helps clinical labs advance their complex genomic profiling services to enable personalized cancer care.

Confidently interpret variants

In addition to expertly curated sources, such as professional guidelines, FDA therapies, clinical trials, and published literature, QCI Interpret One provides access to decision-ready oncologist-reviewed variant interpretive comments for confident decision-making.

Accelerate test turn-around-time

Speed up variant interpretation with dynamically computed disease-specific variant classification, immediate access to interpretive comments, and automatable workflows to help you scale for higher test volumes.

Deliver oncologist-ready reports

Generate customizable and standardized clinical reports with variant- and disease-specific information, including molecular function, and diagnostic, prognostic, and therapeutic relevance, available treatments, and open and recruiting clinical trials.

Confident classifications for every variant, for every disease, for every patient

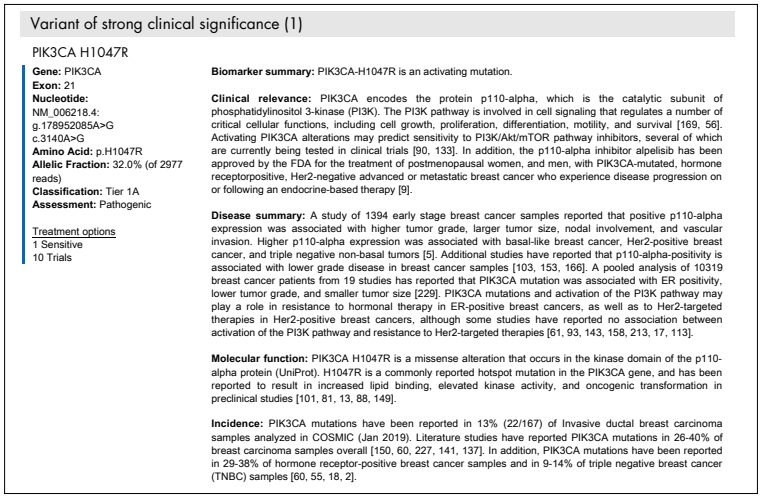
The content core of QCI Interpret One, the QIAGEN Clinical Knowledge Base transforms unstructured data into actionable insight. By aggregating, manually curating, and modeling scientific literature and professional guidelines with semantic consistency, the QIAGEN Clinical Knowledge Base captures biological, phenotypic, therapeutic, and outcomes information that enables QCI Interpret One to compute variant- and disease-specific classifications for every alteration in every disease for every patient case.

Over 200,000 tumors interpreted

New to QIAGEN Clinical Insights is the inclusion of oncologist-reviewed interpretative comments from N-of-One. With over a decade of experience in clinical genomics interpretation for oncology, N-of-One's team has interpreted more than 200,000 tumor samples for pathologists and lab directors. Variant scientists and oncologists translate molecular data specific to each patient into state-of-the-art clinical insights within minutes, giving you immediate access to variant-and disease-specific expert summaries. Aggregated knowledge from N-of-One experts and the QIAGEN Clinical Knowledge Base allows you to confidently classify variants and better determine their clinical significance.

Superior structured content

The QIAGEN Clinical Knowledge Base delivers superior structured content directly to your variant interpretation pipeline allowing you to instantly prioritize variants and dynamically review the clinical relevance based on the phenotype. For every variant in over 31,000 cancer types, you receive a computed ACMG and AMP classification, computed molecular function, the alteration's incidence in disease, structured interpretative comments, information on hereditary clinical cases, treatment information, including alteration-specific drug sensitivity and resistance, and a list of open and recruiting clinical trials. All the information you need is in one location, saving you time and money.



Variant of strong clinical significance (1)

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 [169, 56]. Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which are currently being tested in clinical trials [90, 133]. 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 [9].

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 [103, 153, 166]. 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 [229]. 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 [61, 93, 143, 158, 213, 17, 113].

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 [101, 81, 13, 88, 149].

Incidence: PIK3CA mutations have been reported in 13% (22/167) of Invasive ductal breast carcinoma samples analyzed in COSMIC (Jan 2019). Literature studies have reported PIK3CA mutations in 26-40% of breast carcinoma samples overall [150, 60, 227, 141, 137]. 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 [60, 55, 18, 2].

Sample of an oncology interpretation summary customizable with additional ready-to-use in-depth information on the diagnostic, prognostic, therapeutic significance and supporting study outcomes of relevant Phase 1-3 clinical studies and preclinical studies.

Through QCI Interpret One, you access:

- Oncologist-reviewed variant- and disease-specific interpretation summaries
- > 170,000 variant-specific expert molecular impact summaries
- FDA approved therapeutics
- Worldwide open and recruiting clinical trials
- Professional guidelines (NCCN, ACMG, AMP/ASCO/CAP, WHO)
- Curated bibliography of >300,000 variant-specific articles with hyperlinked citations for quick confirmation
- >25 databases, including COSMIC, ClinVar, and population frequency database, such gnomAD and QIAGEN's Allele Frequency Community (AFC)
- Weekly updated therapeutic, prognostic, and diagnostic evidence, including drug labels, recruiting clinical trials, practice guidelines, and clinical/functional studies

Accelerate test turnaround time

QCI Interpret One enables clinical labs to speed up variant interpretation through automatable workflows and integrated curation and interpretation services.

Decision-ready interpretations at your fingertips

QCI Interpret One instantly delivers concise oncologist-reviewed evidence for each biomarker in the context of the cancer sub-type, listing information on the mutation's molecular characteristics, roles in disease, and therapeutic, prognostic, and diagnostic implications. Saving you significant time by eliminating the need for manual curation and providing you with over 170,000 decision-ready interpretive comments for your reports, QCI Interpret One helps you accelerate test turnaround time and increase caseload volume.

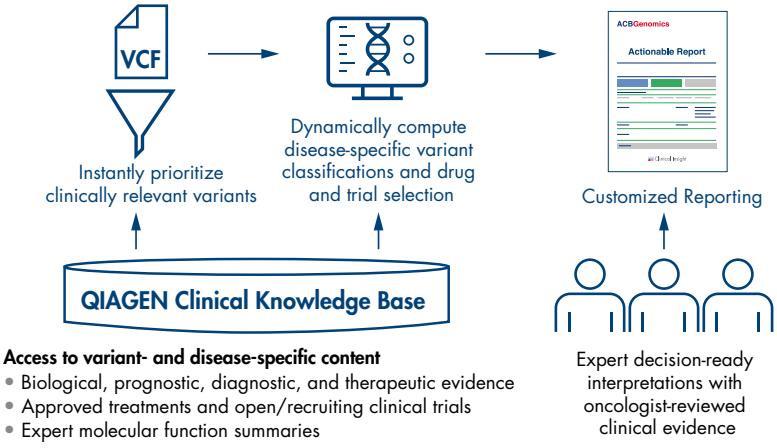
Configurable and automatable workflows

With QCI Interpret One, you can reduce hands-on time with configurable and automatable NGS interpretation workflows. Plus, you can access preconfigured, ready-to-use workflows for QIAGEN and commercial panels. The software also lets you customize your lab's specific reporting policies to automate variant reporting and drug and trial selection, and you can leverage a feature-rich API to integration with your LIMS to scale-up your case processing.

On-demand clinical curation and interpretation services

Leave the heavy-lifting to QIAGEN. On top of accessing over 170,000 decision-ready interpretive comments, you can submit your variants to QIAGEN to receive customized, oncologist-reviewed interpretations and summary comments for every clinically relevant variant detected. An ideal solution for labs working with rare or novel variants, QCI Interpret One's on-demand clinical curation and interpretation services does the research, curation, and interpretation for you, replacing labor intensive processes with automated simplicity. Any somatic NGS panel can be submitted, and depending on size and complexity, results can be returned within hours.

VCF to report in three simple steps with QCI Interpret One



Need a secondary NGS analysis solution? QIAGEN Clinical Analysis and Interpretation Services provide managed secondary NGS analysis services.

Learn more at **https://digitalinsights.qiagen.com/services-overview/clinical-analysis-and-interpretation-services/**

Deliver oncologist-ready reports

The content, transparency, and delivery of clinical oncology NGS test reports are critical for timely and effective patient care. QCI Interpret One supports customizable and standardized reporting to ensure adherence with industry guidelines, while also making reports easy to understand and act upon by oncologists and clinicians.

QCI Interpret One is designed to augment in-house expertise. By providing you with all of the content necessary to generate a comprehensive, patient-specific report, yet giving you full control over final classifications, comments, and recommendations, the software and service enhance decision-making in the clinical workflow. With over 170,000 oncologist-reviewed variant- and disease-specific interpretive comments, AMP/ASCO/CAP and ACMG/AMP-based classifications, and customizable report components to support your unique panel, reporting policies, and customer need, QCI Interpret One enables professional, up-to-date clinical oncology reporting.

"QIAGEN's new QCI Interpret One is impressive. It combines the former N-of-One interpretation summaries with QIAGEN's QCI Interpret structured variant interpretation database. No one is better than QIAGEN for Variant Interpretation."

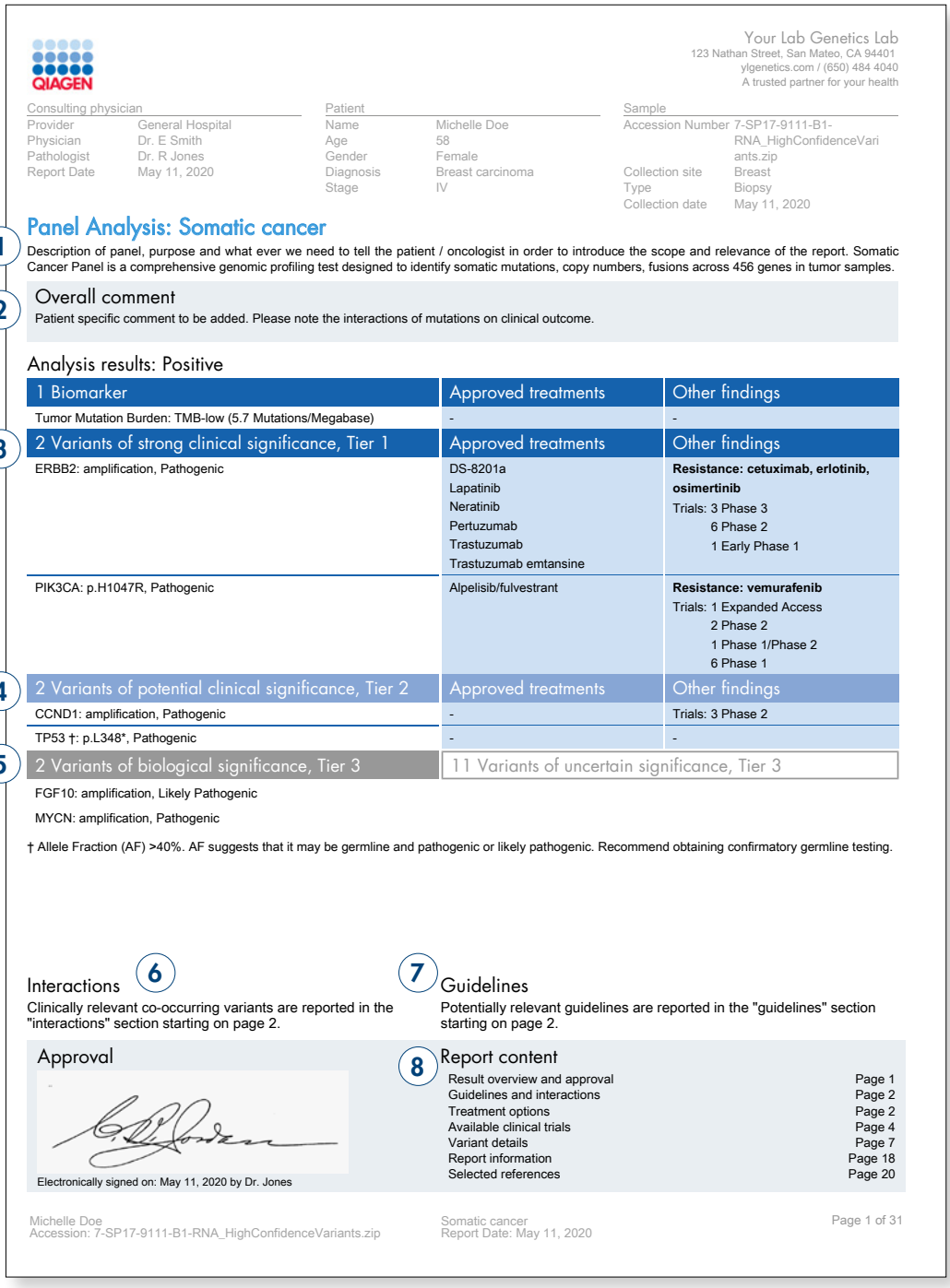
Ravindra Kolhe, MD, PhD
Chief, Section of Molecular and Genetic Pathology, Augusta University

QCI Interpret One reports include:

- Oncologist-reviewed variant- and disease-specific interpretation summaries offering concise, intermediate, or comprehensive information on:
  - Molecular function
  - Therapeutic, prognostic, and diagnostic relevance
  - Variant interactions, such as effect of co-occurring variants on therapies, drug resistance and sensitivities
- Clinical practice guideline recommendations
- Relevant local recruiting clinical trials
- FDA-approved drug therapies
- Primary literature references

Deliver oncologist-ready reports in minutes with clinic

1. Provide a panel description.
2. Include summary comments of test results.
3. Identify clinically significant variants with respect to potential treatments.
4. Include variants with potential clinical significance and associated therapies.
5. Include variants with biological significance.
6. Notify your oncologist of potential interactions.
7. Guide oncologists to the summary of relevant guidelines for patient management.
8. Provide a Table of Contents to orient oncologist 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 11, 2020	Diagnosis	Breast carcinoma	Collection site	Breast
		Stage	IV	Type	Biopsy
				Collection date	May 11, 2020

Panel Analysis: Somatic cancer

1 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.

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

Analysis results: Positive

1 Biomarker	Approved treatments	Other findings
Tumor Mutation Burden: TMB-low (5.7 Mutations/Megabase)	-	-

3

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

4

2 Variants of potential clinical significance, Tier 2	Approved treatments	Other findings
CCND1: amplification, Pathogenic	-	Trials: 3 Phase 2
TP53 †: p.L348*, Pathogenic	-	-

5

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.

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

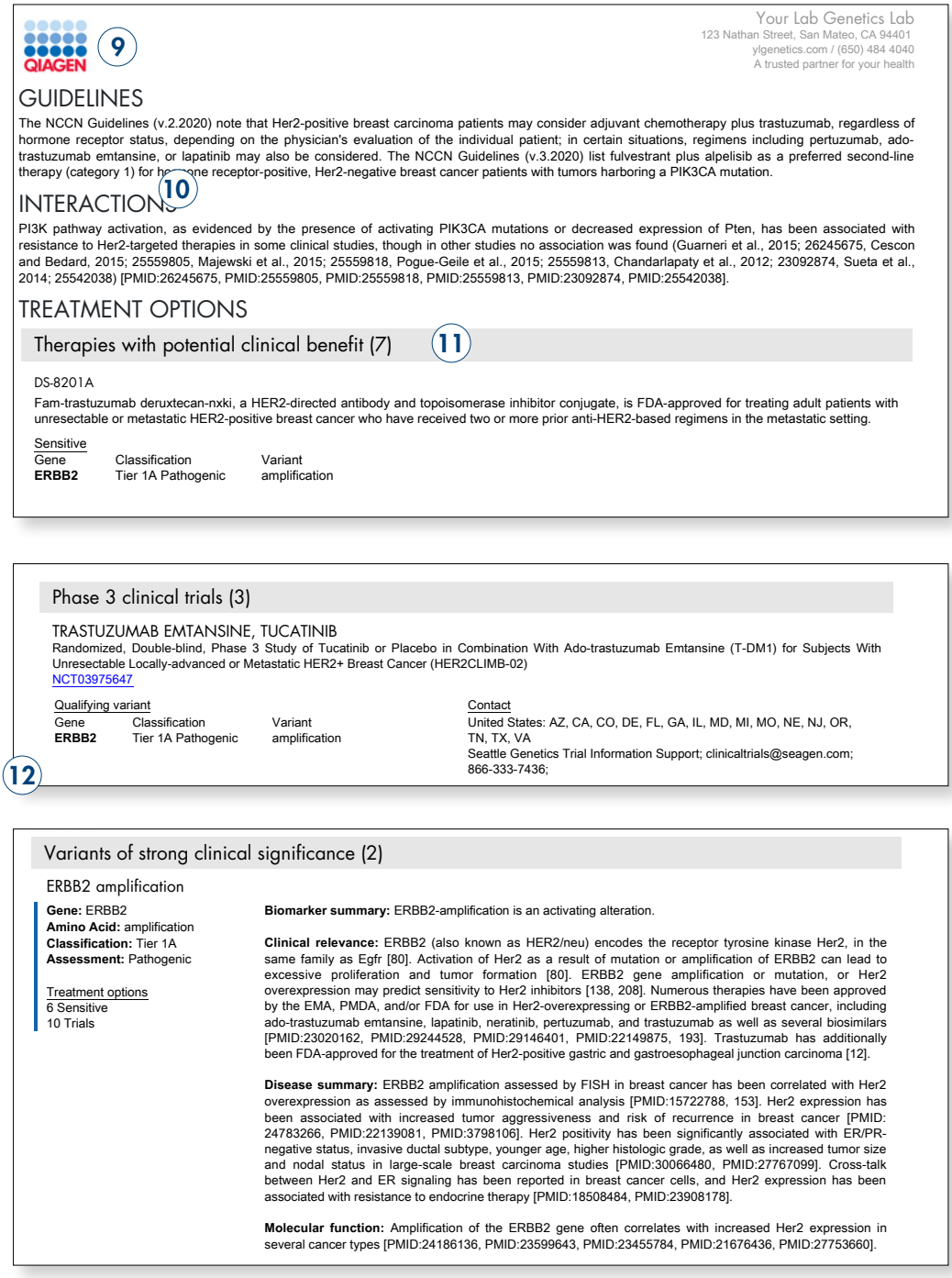
7 **Guidelines**
Potentially relevant guidelines are reported in the "guidelines" section starting on page 2.

Approval

Electronically signed on: May 11, 2020 by Dr. Jones

8 **Report content**

ally actionable evidence and recommendations



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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.

INTERACTIONS 10

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].

TREATMENT OPTIONS

Therapies with potential clinical benefit (7) 11

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;

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Variants of strong clinical significance (2)

ERBB2 amplification

Gene: ERBB2
Amino Acid: amplification
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
6 Sensitive
10 Trials

Biomarker summary: ERBB2-amplification is an activating alteration.

Clinical relevance: ERBB2 (also known as HER2/neu) encodes the receptor tyrosine kinase Her2, in the same family as Egfr [80]. Activation of Her2 as a result of mutation or amplification of ERBB2 can lead to excessive proliferation and tumor formation [80]. ERBB2 gene amplification or mutation, or Her2 overexpression may predict sensitivity to Her2 inhibitors [138, 208]. Numerous therapies have been approved by the EMA, PMDA, and/or FDA for use in Her2-overexpressing or ERBB2-amplified breast cancer, including ado-trastuzumab emtansine, lapatinib, neratinib, pertuzumab, and trastuzumab as well as several biosimilars [PMID:23020162, PMID:29244528, PMID:29146401, PMID:22149875, 193]. Trastuzumab has additionally been FDA-approved for the treatment of Her2-positive gastric and gastroesophageal junction carcinoma [12].

Disease summary: ERBB2 amplification assessed by FISH in breast cancer has been correlated with Her2 overexpression as assessed by immunohistochemical analysis [PMID:15722788, 153]. Her2 expression has been associated with increased tumor aggressiveness and risk of recurrence in breast cancer [PMID: 24783266, PMID:22139081, PMID:3798106]. Her2 positivity has been significantly associated with ER/PR-negative status, invasive ductal subtype, younger age, higher histologic grade, as well as increased tumor size and nodal status in large-scale breast carcinoma studies [PMID:30066480, PMID:27767099]. Cross-talk between Her2 and ER signaling has been reported in breast cancer cells, and Her2 expression has been associated with resistance to endocrine therapy [PMID:18508484, PMID:23908178].

Molecular function: Amplification of the ERBB2 gene often correlates with increased Her2 expression in several cancer types [PMID:24186136, PMID:23599643, PMID:23455784, PMID:21676436, PMID:27753660].

9 Clearly convey the professional guideline evidence for each variant in the context of disease.

10 Inform on co-occurring variants with prognostic and diagnostic relevance and drug sensitivity and resistance.

11 List molecularly targeted therapies specific to your country for each clinically significant biomarker with the type and level of evidence supporting the selection.

12 Use oncologist-reviewed interpretive comments in three levels of detail with variant- and disease-specific information, including molecular function, and diagnostic, prognostic, and therapeutic relevance.

Choose the clinical oncology NGS test interpretation solution that best fits your needs

QIAGEN Clinical Insights (QCI)

A clinical genomics interpretation portfolio offering expert-curated knowledge, software and services, QCI supports clinical NGS testing for any indication, on your platform, with unlimited scalability.

		QCI Interpret Clinical decision support software	QCI Interpret One Clinical decision support software with on-demand interpretation service	QCI Precision Insights Professional interpretation service
Integration Need	LIMS integration	●	●	●
	API upload of VCF, metadata, annotated files	●	●	●
Interpretation Need	Germline interpretation	●		
	Somatic interpretation		●	●
	Multi-omics interpretation			●
Resources/Expertise	Report-ready evidence summaries	Gene level	Variant and disease level	Variant and disease level
	Oncologist-reviewed clinical evidence		●	●
	Up -to-date and structured content	●	●	●
Variant Filtering/ Bioinformatics	VCF/variant filtering	●	●	
	Report-ready evidence summaries		●	●
Reporting	Flexible report pdf generation	●	●	
	Flexibility to build your own report using XML with external report generators	●	●	●

Learn more about QCI Interpret One and the QCI portfolio at
www.digitalinsights.qiagen.com/qci-interpret-one

QCI Interpret One is an evidence-based decision support software and service intended as an aid in the interpretation of variants observed in genomic next-generation sequencing data. The software and service evaluates genomic variants in the context of published biomedical literature, professional association guidelines, publicly available databases, annotations, drug labels, and clinical trials. Based on this evaluation, the software proposes a classification and bibliographic references to aid in the interpretation of observed variants. The software and service is NOT intended as a primary diagnostic tool by physicians or to be used as a substitute for professional healthcare advice. Each laboratory is responsible for ensuring compliance with applicable international, national, and local clinical laboratory regulations and other specific accreditations requirements.

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