Provide patient-specific reports to your oncologists in a fraction of the time and with greater confidence

1. Identify clinically significant variants with respect to potential treatments.
2. Highlight variants with evidence of prognostic and diagnostic value.
3. Include variants with potential clinical significance and associated therapies.
4. Ensure a consistent report format that clearly conveys the degree of importance with professional guideline levels of evidence for variant classification (NCCN, AMP/ASCO/CAP, etc).
5. Help minimize risk by identifying biomarkers with potential interactions, such as drug sensitivity, resistance, or other implications.

Patient ID: NSCLC - NRAS CDKN2A RB1 **Report ID:** NSCLC - NRAS CDKN2A RB1
Report Date: Dec 14, 2019 **Disease:** Non-small cell lung carcinoma (NSCLC)

1. Summary

CLINICALLY RELEVANT ALTERATIONS

TIER 1: VARIANTS OF STRONG CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
Tumor Mutational Burden	high	Nivolumab (B), Pembrolizumab (B/C), Atezolizumab (B/C), Durvalumab (B/C)	Avelumab (B/C)	None	Yes

Prognostic and Diagnostic Variants: None

TIER 2: VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
NRAS	Q61L	None	Binimetinib (C.2), Trametinib (C.2), Cobimetinib (D)	None	Yes
CDKN2A	V51fs*2	None	(Potential interaction: see note 1)	None	No
RB1	R445*	None	None	(Potential interaction: see note 2)	No

Note 1 (CDKN2A-V51fs*2): Cdk4/6 inhibitors require functional Rb1 for their mechanism of action. Therefore, due to the presence of an RB1 mutation, this tumor may not be sensitive to Cdk4/6 inhibitors such as palbociclib.
Note 2 (RB1-R445*): Cdk4/6 inhibitors
See interaction table.

Prognostic and Diagnostic Variants: None

GUIDELINES

Marker-Alteration	Summary
Tumor Mutational Burden	The NCCN Guidelines (v.7.2019) highlight nivolumab alone or in combination with ipilimumab for NSCLC patients with high tumor mutational burden (TMB), but note there is no consensus on measuring TMB.

INTERACTIONS

Marker-Alteration	Summary	Resistant Therapies	Synergistic Therapies	Diagnostic Level of Evidence	Prognostic Level of Evidence
CDKN2A-V51fs*2 RB1-R445*	Although therapies targeting Cdk4/6 might be relevant for one or several of the alterations contained in this report, loss of RB1, as reported here, has been associated with resistance to Cdk4/6 inhibitors in preclinical models (Fry et al., 2004; 15542782, Herrera-Abreu et al., 2016; 27020857, Young et al., 2014; 24495407, Taylor-Harding et al., 2015; 25557169, Wiedemeyer et al., 2010; 20534551,	Abemaciclib (D) Alvocidib (D) G1T38 (D) PF-06873600 (D) Palbociclib (D) Ribociclib (D)	None	None found	None found
	Michaud et al., 2010; 20354191, O'Leary et al., 2016; 27030077).	Ronicicliib (D)			

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

6. Provide detailed information on biomarker molecular function and incidence in disease for richer report context.
7. List molecularly targeted therapies specific to your country for each clinically significant biomarker with the type and level of evidence supporting the selection.
8. Simplify treatment selection by listing clinical trials by relevance and country.

2.1.2 BIOLOGICAL RELEVANCE of Tumor Mutational Burden-high

Tumor Mutational Burden alterations in Non-small cell lung carcinoma (NSCLC)	
Molecular function	A test result demonstrating high tumor mutational burden has been reported in this sample.
Incidence in disease	One analysis of 11205 NSCLC cases has reported an average tumor mutational burden of 10.7 mutations per megabase (Mb); increased tumor mutational burden was reported in NSCLC samples with MET amplification as compared with the absence of MET amplification (6.8 mutations per Mb versus 4.4 mutations per Mb, respectively) (Schrock et al., 2016; 27343443). Another study has reported an average tumor mutational burden of 6.3 mutations per Mb in 11855 lung adenocarcinoma and 9.0 mutations per Mb in 2102 lung squamous cell carcinoma cases (Chalmers et al., 2017; 28420421).

2.1.5 SAMPLE RELEVANT THERAPIES

Therapies targeting PDCD1

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
Nivolumab	Opdivo	B	Anti-PD-1, anti-tumor response stimulation.	FDA Approved (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Hepatocellular carcinoma (HCC), Hodgkin lymphoma (HL), Melanoma, Renal cell carcinoma, Head and neck squamous cell carcinoma (HNSCC), Small cell lung carcinoma (SCLC), and various other cancers)
Pembrolizumab	Keytruda	B/C	Anti-PD-1 receptor monoclonal antibody.	FDA Approved (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Gastric carcinoma, Hepatocellular carcinoma (HCC), Hodgkin lymphoma (HL), Melanoma, Merkel cell carcinoma, Head and neck squamous cell carcinoma (HNSCC), and various other cancers)

Therapies targeting CD274

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
Atezolizumab	Tecentriq	B/C	Anti-PD-L1 monoclonal antibody.	FDA Approved (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Urothelial carcinoma, Bladder carcinoma, Breast carcinoma (triple negative))
Durvalumab	Imfinzi	B/C	Anti-PD-L1 monoclonal antibody.	FDA Approved (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Urothelial carcinoma, Bladder carcinoma)

2.1.6 BIOMARKER-MATCHED CLINICAL TRIALS

Trials Prioritized By Clinical Specificity*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	Tumor Mutational Burden, NRAS	NCT03637491	A Study of Avelumab, Binimetinib and Talazoparib in Patients With Locally Advanced or Metastatic RAS-mutant Solid Tumors	Phase 2	CD274, MEK, PARP	•Overall contact: Pfizer CT.gov Call Center, ClinicalTrials.gov_Inquiries@pfizer.com, 1-800-718-1021 •AR (2), CA (2), CO (2), IN (1), PA (2), TX (1), UT (2), Singapore (5)
2	Tumor Mutational Burden	NCT03178552	A Study to Evaluate Efficacy and Safety of Multiple Targeted Therapies as Treatments for Participants With Non-Small Cell Lung Cancer (NSCLC)	Phase 2/Phase 3	ALK, CD274, NTRK1, NTRK2, NTRK3, RET, ROS1, RRM1	•Overall contact: Reference Study ID Number: BO29554 www.roche.com/about_roche/roche_worldwide.htm, global-roche-genentech-trials@gene.com, 888-662-6728 (U… •CA (1), CO (1… (1), KY (1), M… OR (1), TN (1… (4), Australia… Brazil (4), Ca… Costa Rica (1… Germany (8), … (6), Italy (9), … Republic of (… Zealand (1), … Poland (6), R… Serbia (4), Si… (16), Switzer… Thailand (4)

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Rick Lanman, MD
Chief Medical Officer, Guardant Health, Inc.