REPORTING

Report Date:	MAY-09-2024
Receipt Date:	MAY-06-2024
Collection Date:	MAY-03-2024
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Tien-Hua Chen
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Additional Recipient: N/A

Complete Tumor Response Map on page 2

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

KEY ✓ Approved in indication ~ Approved in other indication ⊗ Lack of response

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 3)	% cfDNA or Amplification
BRAF V600E	✓ Atezolizumab+vemurafenib+cobimetinib, Dabrafenib, Dabrafenib+trametinib, Encorafenib+binimetinib, Trametinib, Vemurafenib, Vemurafenib+cobimetinib	Yes	1.7%

Variants of Uncertain Clinical Significance
PDGFRA R500Q (0.5%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Comments

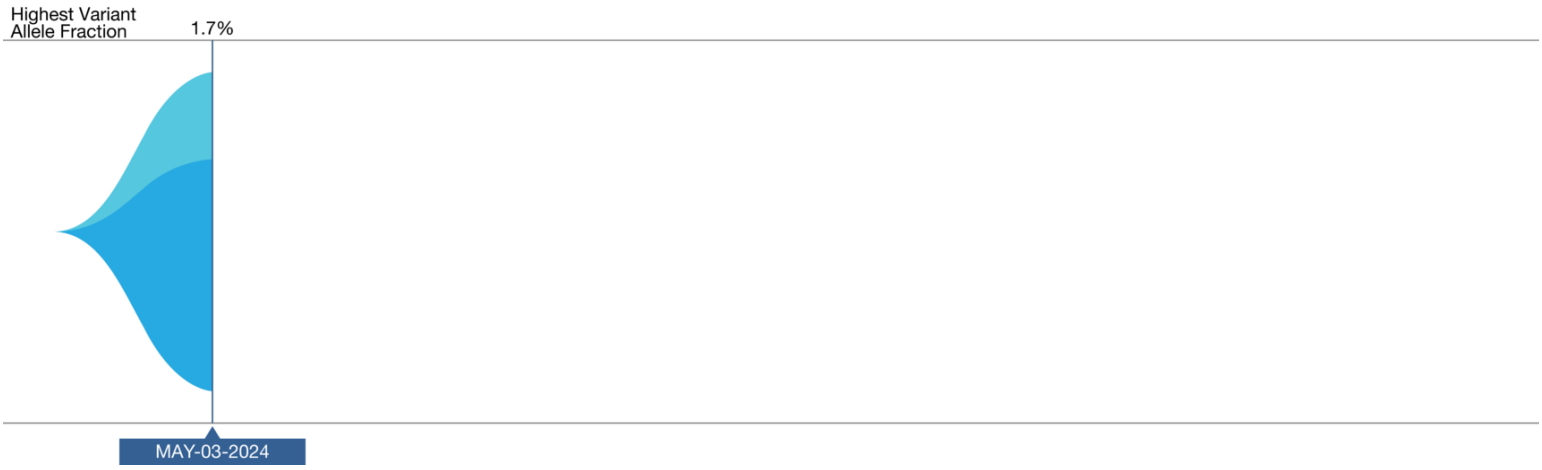
Reported by: VL

Additional Biomarkers

Biomarker	Additional Details
MSI-High	NOT DETECTED

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (portal.guardanthealth.com) for the Tumor Response Map with all test dates.



Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	
BRAF V600E	1.7%	
PDGFRA R500Q	0.5%	Variants of Uncertain Clinical Significance §

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.
§ See definitions section for more detail

Available Clinical Trials (within the same state as the ordering physician)

There may be additional trials not listed here. Visit: **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A1036310 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
BRAF V600E	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			

More clinical trial options available at **portal.guardanthealth.com**

Definitions

Variants of Uncertain Clinical Significance: The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Interpretation

Somatic alterations were detected in the circulating cell-free DNA isolated from this patient's blood specimen. These genomic alterations are cancer-associated somatic variants, some of which have been associated with either increased or reduced clinical response to specific treatments. The percentage of altered cell-free DNA circulating (% cfDNA) in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn over, size, heterogeneity, vascularization, disease progression, and treatment.

Method and Limitations

Guardant360 sequences 74 cancer-associated genes to identify somatic alterations. Cell-free DNA (cfDNA) is extracted from plasma, enriched for targeted regions, and sequenced using the Illumina platform and hg19 as the reference genome. All exons are sequenced in some genes; only clinically significant exons are sequenced in other genes. The types of genomic alterations detected by Guardant360 include single nucleotide variants, gene amplifications, fusions, short insertions/deletions (longest detected, 70 base pairs), and splice site disrupting events (see Table 1). Microsatellite Instability (MSI) is assessed for all cancer types by evaluating somatic changes in the length of repetitive sequences on the Guardant360 panel. A "Not Detected" result in samples where the highest % cfDNA is < 0.2% is an inconclusive result because it does not preclude MSI-High status in tissue. MSI status is currently not reported for earlier panel versions. This version of the Guardant360 test is not validated for the detection of other types of genomic alterations, such as complex rearrangements or gene deletions. Certain sample or variant characteristics, such as low cfDNA concentration, may result in reduced analytic sensitivity. Guardant360 cannot discern the source of circulating cfDNA, and for some variants in the range of ~40 to 60% cfDNA, the test cannot easily distinguish germline variants from somatic alterations. Guardant360 is not validated for the detection of germline or de novo variants that are associated with hereditary cancer risk. Tissue genotyping should be considered when plasma genotyping is negative, if clinically appropriate.

Table 1: Genes on the Guardant360 Panel

Guardant360 reports single nucleotide variants, splice site mutations, and insertion and deletion variants (indels) in all clinically relevant exons in 74 genes and reports other variant types in select genes as indicated below.

AKT1	*ALK* #	*APC*	*AR* †	*ARAF*	*ARID1A*	*ATM*	*BRAF* †	*BRCA1*
BRCA2	*CCND1* †	*CCND2* †	*CCNE1* †	*CDH1*	*CDK12*	*CDK4* †	*CDK6* †	*CDKN2A*
CTNNB1	*DDR2*	*EGFR* †	*ERBB2* †	*ESR1*	*EZH2*	*FBXW7*	*FGFR1* †	*FGFR2* † #
FGFR3 #	*GATA3*	*GNA11*	*GNAQ*	*GNAS*	*HNF1A*	*HRAS*	*IDH1*	*IDH2*
JAK2	*JAK3*	*KIT* †	*KRAS* †	*MAP2K1*	*MAP2K2*	*MAPK1*	*MAPK3*	*MET* †
MLH1	*MPL*	*MTOR*	*MYC* †	*NF1*	*NFE2L2*	*NOTCH1*	*NPM1*	*NRAS*
NTRK1 #	*NTRK3*	*PDGFRA* †	*PIK3CA* †	*PTEN*	*PTPN11*	*RAF1* †	*RB1*	*RET* #
RHEB	*RHOA*	*RIT1*	*ROS1* #	*SMAD4*	*SMO*	*STK11*	*TERT* ‡	*TP53*
TSC1	*VHL*							

‡ Guardant360 reports alterations in the promoter region of this gene.

† Guardant360 reports amplifications of this gene.

Guardant360 reports fusion events involving this gene.

About the Test

The Guardant360 assay was developed and its performance characteristics were determined by Guardant Health, Inc. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test may be used for clinical purposes and should not be regarded as investigational or for research only. Guardant Health's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing. The laboratory report should be interpreted in the context of other clinical information and laboratory, pathology, and imaging studies by a qualified medical professional prior to initiating or changing a patient's treatment plan. The selection of any, all, or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) is entirely at the discretion of the treating medical professional. Drug and trial information are based on the diagnosis written on the submitted test request form; this information is not based on any supplemental information provided by the requesting medical professional, including pathology reports or other molecular studies. Some drugs listed in this report may not be approved or cleared by the FDA for the indicated use. Guardant Health makes no endorsement, express or implied, of any product, physician, or procedure contained in this report. This report makes no promises or guarantees that a particular medication will affect (or not affect) the clinical outcome of any patient.

Testing Performed at: Guardant Health

Laboratory Director: Martina Lefterova, MD PhD | CLIA ID: 05D2070300 | CAP #: 8765297 | 505 Penobscot Drive, Redwood City, CA, 94063, USA

Additional information is available

Any therapeutic annotations are based on publicly available information. This information is described in the "Detailed Therapy Results" and "Relevance of Detected Alterations" sections.

Visit **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A1036310 in the subject line of the email for:

- Additional clinical trials
- Detailed Therapy Results
- Relevance of Detected Alterations
- References

If you would like to receive this additional information with every Guardant360 report, please call client services at **855.698.8887** to opt-in.

Additional information begins on the next page.

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
BRAF V600E	NCT04249843 MapKure,clinicaltrials@mapkure.com,1-877-828-5568	Study of Safety, Pharmacokinetics, and Antitumor Activity of BGB-3245 in Participants With Advanced or Refractory Tumors	Phase 1	Houston, TX; Baton Rouge, LA; Boston, MA; New York, NY; Beverly Hills, CA; Charlottesville, VA; Australia (4)
	NCT04511013 Catrina Mireles,cmireles@swog.org, 2106148808 x1014	A Study to Compare the Administration of Encorafenib + Binimetinib + Nivolumab Versus Ipilimumab + Nivolumab in BRAF-V600 Mutant Melanoma With Brain Metastases	Phase 2	Orlando, FL; Paducah, KY; Sheridan, WY; Richmond, IN; Fort Smith, AR; Mobile, AL; Cody, WY; Great Bend, KS; Pittsburgh, PA; Garden City, KS; Birmingham, AL; Cheyenne, WY; Fairhope, AL; Salt Lake City, UT; Oklahoma City, OK (2); Lincoln, NE (2); Tampa, FL (3); WA (18); WI (14); IA (13); OH (59); ID (13); MI (18); CA (12); MN (24); MO (22); OR (11); IL (36); MT (8); AK (9); CO (18); NC (7)
	NCT04557956 See https://clinicaltrials.gov/ct2/show /NCT04557956	Testing the Addition of the Anti-cancer Drug, Tazemetostat, to the Usual Treatment (Dabrafenib and Trametinib) for Metastatic Melanoma That Has Progressed on the Usual Treatment	Phase 1 /Phase 2	Madison, WI; Atlanta, GA; Winston-Salem, NC; Pittsburgh, PA; Chicago, IL; Salt Lake City, UT; MO (5); FL (5)
	NCT04678648 Bonnie Wettersten, MS, clinicaltrials@rascaltherapeutics.com, (847) 644-9818	A Trial of RSC-1255 for Treatment of Patients With Advanced Malignancies	Phase 1	Los Angeles, CA; Denver, CO; Philadelphia, PA; Sacramento, CA; Aurora, CO; Nashville, TN
	NCT04913285 Kinnate Clinical Operations, clinicaltrials@kinnate.com,858.252.2723	A Study to Evaluate KIN-2787 in Participants With BRAF and/or NRAS Mutation Positive Solid Tumors	Phase 1	Los Angeles, CA; Cleveland, OH; Stanford, CA; La Jolla, CA; Nashville, TN; Tampa, FL; Fairfax, VA; Orlando, FL (2); New York, NY (2); France (5); Australia (2); Spain (5)
	NCT04985604 Day One Biopharmaceuticals, clinicaltrials@dayonebio.com,650-484-0899	Tovorafenib (DAY101) Monotherapy or in Combination With Other Therapies for Patients With Melanoma and Other Solid Tumors	Phase 1 /Phase 2	Los Angeles, CA; Newport Beach, CA; Indianapolis, IN; Pittsburgh, PA; Portland, OR; Jacksonville, FL; Nashville, TN; Canada (2)
	NCT05538130 Pfizer CT.gov Call Center,ClinicalTrials.gov_Inquiries@pfizer.com,1-800-718-1021	A Study to Learn About the Study Medicine Called PF-07799544 in People With Advanced Solid Tumors	Phase 1	Houston, TX; Seattle, WA (2); Detroit, MI (2); Cleveland, OH (2); New York, NY (2); Portland, OR (2); Tampa, FL (4); AR (7); Canada (7)
	NCT06194929 Rachel Kingsford,rachel.kingsford@hci.utah.edu,801-585-0115	Defactinib and Avutometinib, With or Without Encorafenib, for the Treatment of Patients With Brain Metastases From Cutaneous Melanoma	Phase 1 /Phase 2	Salt Lake City, UT

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status	
BRAF V600E	ABM-1310			Braf (V600E) kinase inhibitor.	Phase 1 (Solid Tumor)
	ASN007			ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	ASTX029			ERK1/2 kinase inhibitor.	Phase 2 (Solid Tumor)
	Atezolizumab		Tecentriq	Anti-PD-L1 monoclonal antibody.	Phase 3 (Melanoma) FDA Approved in other indications (Non-small cell lung carcinoma (NSCLC), Small cell lung carcinoma (SCLC), Alveolar soft part sarcoma)
	Atezolizumab+vemurafenib+cobimetinib		Tecentriq+Zelboraf+Cotellic	Anti-PD-L1 monoclonal antibody + Braf (V600E) kinase inhibitor + MEK1,2 inhibitor combination.	Phase 3 (Melanoma) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation)
	Avutometinib			Dual Raf/MEK kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Non-small cell lung carcinoma (NSCLC), Uveal melanoma, Ovarian carcinoma)
	BDTX-4933			Braf class 1, 2, and 3 inhibitor.	Phase 1 (Solid Tumor)
	Belvarafenib			Pan-Raf kinase inhibitor.	Phase 1 (Melanoma) Phase 1 (Solid Tumor)
	BI 3011441			MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Binimetinib		Mektovi	MEK1,2 inhibitor.	Phase 3 (Cutaneous melanoma) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation)
	Brimarafenib			Braf class 1, 2, and 3 inhibitor.	Phase 2 (Solid Tumor) Phase 1 (Pancreatic ductal adenocarcinoma, Colorectal carcinoma (CRC))
	CFT1946			Braf class 1 inhibitor and degrader.	Phase 2 (Melanoma) Phase 2 (Non-small cell lung carcinoma (NSCLC))
	CMAB009			Anti-Egfr monoclonal antibody.	Phase 3 (Colorectal carcinoma (CRC))
	Cobimetinib		Cotellic	MEK1,2 inhibitor.	Phase 3 (Melanoma) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation, Histiocytic and dendritic cell neoplasms)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status	
	Dabrafenib	Tafinlar		Braf (V600E) kinase inhibitor.	Phase 3 (Melanoma) FDA Approved in other indications (Melanoma with BRAF V600E)
	Dabrafenib+trametinib	Tafinlar+Mekinist		Braf (V600E) kinase inhibitor + MEK1,2 inhibitor combination.	Phase 3 (Melanoma) FDA Approved in other indications (Anaplastic thyroid carcinoma with BRAF V600E, Melanoma with BRAF V600E/K mutation, Solid tumor with BRAF V600E, Low-grade glioma with BRAF V600E, NSCLC with BRAF V600E)
	Defactinib			Focal adhesion kinase (FAK) inhibitor, upstream of MAPK pathway.	Phase 2 (Solid Tumor) Phase 2 (Lymphoma, Multiple myeloma (MM))
	E6201			MEK1,2, Mekk1, and Flt3 inhibitor.	Phase 1 (Melanoma) Phase 1 (Solid Tumor, Acute myeloid leukemia (AML))
	Encorafenib	Braftovi		Braf (V600E/K) kinase inhibitor.	Phase 3 (Melanoma) Phase 3 (Colorectal carcinoma (CRC))
	Encorafenib+binimetinib	Braftovi+Mektovi		Braf (V600E/K) kinase inhibitor + MEK1,2 inhibitor combination.	Phase 3 (Melanoma) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation, NSCLC with BRAF V600E)
	HLX208			Braf (V600E) inhibitor.	Phase 2 (Melanoma) Phase 2 (Erdheim Chester Disease (ECD), Anaplastic thyroid carcinoma, Langerhans cell histiocytosis (LCH), Solid Tumor, Brain and Central Nervous System Tumors)
	HMPL-295			ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	IMM-1-104			MEK1,2 inhibitor.	Phase 2 (Melanoma) Phase 2 (Non-small cell lung carcinoma (NSCLC), Pancreatic ductal adenocarcinoma)
	JZP815			pan-Raf kinase inhibitor.	Phase 1 (Solid Tumor)
	KIN-2787			Pan-Raf kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	KL-140			Anti-Egfr monoclonal antibody.	Phase 3 (Colorectal carcinoma (CRC))
	Lifirafenib			Dual Braf/Egfr inhibitor.	Phase 1 (Melanoma) Phase 1 (Solid Tumor, Brain and Central Nervous System

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status	
					Tumors)
	LTT462			ERK1/2 kinase inhibitor.	Phase 1 (Melanoma) Phase 1 (Solid Tumor)
	Mirdametinib			MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioma, Non-small cell lung carcinoma (NSCLC), Neurofibroma, Breast carcinoma, Glioneuronal tumor, Neurofibromatosis type 1, Lung cancer, Colorectal carcinoma (CRC))
	MK-8353			ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	Naporafenib			Pan-Raf kinase inhibitor.	Phase 1 (Melanoma) Phase 1 (Solid Tumor)
	PF-07799544			MEK Brain Penetrant Inhibitor.	Phase 1 (Melanoma) Phase 1 (Glioma, Non-small cell lung carcinoma (NSCLC), Thyroid carcinoma, Colorectal carcinoma (CRC))
	Pimasertib			MEK1,2 inhibitor.	Phase 2 (Melanoma) Phase 2 (Pancreatic ductal adenocarcinoma, Ovarian carcinoma, Hematologic malignancies, Colorectal carcinoma (CRC))
	Plixorafenib			Braf mutant kinase inhibitor.	Phase 2 (Melanoma) Phase 2 (Glioma, Solid Tumor, Hairy cell leukemia)
	QLH11906			pan-Raf kinase inhibitor.	Phase 1 (Solid Tumor)
	RSC-1255			Ras inhibitor.	Phase 1 (Solid Tumor)
	Selumetinib		Koselugo	MEK1,2 inhibitor.	Phase 3 (Melanoma) FDA Approved in other indications (NF1-related plexiform neurofibroma)
	SHR7390			MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Temuterkib			ERK1/2 kinase inhibitor.	Phase 1 (Melanoma) Phase 1 (Pancreatic ductal adenocarcinoma, Solid Tumor)
	Tizaterkib			ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Hematologic malignancies)
	Tovorafenib		Ojemda	Pan-Raf kinase inhibitor.	Phase 1 (Melanoma) FDA Approved in other indications (Low-grade glioma with BRAF V600 mutation or BRAF fusion /rearrangement)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status	
	Trametinib		Mekinist	MEK1,2 inhibitor.	Phase 3 (Melanoma) FDA Approved in other indications (Melanoma with BRAF V600 mutation)
	Ulixertinib			ERK1/2 kinase inhibitor.	Phase 2 (Melanoma) Phase 2 (Gastric carcinoma, Histiocytic and dendritic cell neoplasms, Langerhans cell histiocytosis (LCH), Uveal melanoma, Acute myeloid leukemia (AML), Gastrointestinal carcinoma, Non-Hodgkin lymphoma (NHL), Myelodysplastic Syndrome (MDS))
	Vemurafenib		Zelboraf	Braf (V600E) kinase inhibitor.	Phase 3 (Melanoma) FDA Approved in other indications (Erdheim Chester Disease (ECD), Melanoma with BRAF V600E)
	Vemurafenib+cobimetinib		Zelboraf+Cotellic	Braf (V600E) kinase inhibitor + MEK1,2 inhibitor combination.	Phase 3 (Melanoma) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation)
	XP-102			pan-Raf kinase inhibitor.	Phase 2 (Melanoma) Phase 2 (Non-small cell lung carcinoma (NSCLC), Thyroid carcinoma, Colorectal carcinoma (CRC))

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
BRAF V600E	BRAF activating mutations or amplification have been reported to result in uncontrolled cell growth and tumorigenesis. [1,2]. Activating BRAF mutations have been detected frequently in benign nevi, primary melanoma cases, and melanoma metastases, although several studies have reported that BRAF mutations alone are insufficient for primary melanoma development and tumorigenesis; additional activation of the PI3K and MAPK pathways, through loss of Pten function or other mutations, has been shown to play a critical role in melanoma development and progression. [2-8]. BRAF mutations in melanoma have been associated with the superficial spreading subtype and non-chronically sun damaged skin. [9-13].	Braf signals upstream of the MAPK pathway, and BRAF amplification or activating mutations may confer sensitivity to inhibitors of Braf and/or components of the MAPK pathway, including MEK. [14]. The BRAF V600-specific inhibitors vemurafenib and dabrafenib have been approved for the treatment of BRAF V600E-positive melanoma. [15,16]. In addition, the MEK inhibitors trametinib and cobimetinib (in combination with vemurafenib) have been FDA-approved for BRAF V600E- and V600K-positive melanoma as has the encorafenib-binimetinib combination. [17-19]. Vemurafenib has additionally been approved for BRAF V600-positive Erdheim-Chester disease. [20]. Encorafenib in combination with cetuximab has been FDA-approved for the treatment of pretreated adult colorectal cancer patients with metastatic disease and harboring a BRAF V600E mutation, as detected by an FDA-approved test. [21-23]. BRAF encodes the signaling protein Braf, which is downstream of Ras and activates the MAPK pathway. [2]. Encorafenib in combination with binimetinib has been approved by the FDA for adult patients with metastatic non–small cell lung carcinoma with a BRAF V600E mutation. [24]. The combination of dabrafenib and trametinib has been FDA-approved for V600E/K-positive melanoma as well as V600E-positive solid tumor (excluding CRC), non-small cell lung carcinoma, anaplastic thyroid carcinoma, and pediatric low-grade glioma. [16,25-31]. The triple combination of atezolizumab plus cobimetinib and vemurafenib has also been FDA-approved for the treatment of V600E/K-positive melanoma. [32]. The pan-Raf inhibitor tovorafenib has been approved by the FDA for the treatment of pediatric patients 6 months of age and older with relapsed or refractory low-grade glioma harboring a BRAF fusion or rearrangement, or a BRAF V600 mutation. [33].	

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