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Understanding the Report Com|PI|i|t DX®

On the first page of the report
on the results section

You will find all the genes
that were analyzed and the genomic alterations,
identified on the patient's tumor.


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MOLECULAR ANALYSIS REPORT
Laboratory Director: George Nasioulas PhD.
Sample Information
Name.
Patient's ID.
Date Of Birth.
Material.
Sample ID.
Report No.
Date Received.
Com|PI|i|t DX
Comprehensive Panel for Individualized Treatment
Results
Tumor Type: Melanoma
Genomic Alterations Identified
BRAF c.1799TA (p.V6OOE)
KIT c.19OOCT (p.R634W)
P53 c.38OCT (p.S127F), c.568 CT (p.P19OS), c625AG (p.R2O9G)
Genomic Alterations Identified
ABL1, EZH2, JAK3, PTEN, AKT1, FBXW7, IDH2, PTPN11,ALK, FGFR1, KDR, RB1, APC, FGFR2, KIT, RET,ATM, FGFR3, KRAS, SMAD4, BRAF, FLT3, MET, SMARCB1, CDH1, GNA11, ML1, SMO, CDKN2A, GNAS, MPL, SRC, CSF1R, GNAQ, NOTCH1, STK11, CTNNB1, HNF1, NPM1, TP53, EGFR, HRAS, NRAS, VHL, ERBB2, IDH1, PDGFRA, ERBB4, JAK2, PIK3CA, ALK fusions, ROS1 fusions, RET fusions, NTKR1 fusions.
Scientific Director
George Nasioulas, Ph.D.
Molecular biologist
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Results

Tumor Type: Melanoma

Genomic Alterations Identified
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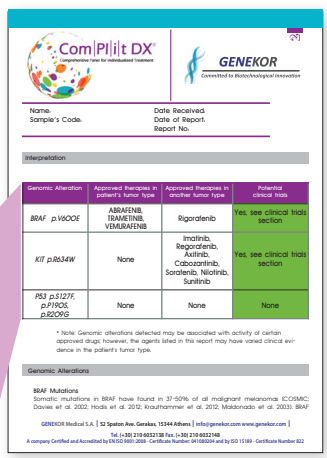
On the second page of the report
on the interpretation section

You will find the genomic alterations
with the respective on-and off-label approved therapies,
and the respective Clinical trials, where available.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Interpretation
Genomic Alteration | Approved therapies in patient's tumor type | Approved therapies in another tumor type | Potential clinical trials
BRAF p.V6OOE | ABRAFENIB, TRAMETINIB, VEMURAFENIB | Rigorafenib | Yes, see clinical trials section
KIT p.R634W | None | Imatinib, Regorafenib, Axitinib, Cabozantinib, Sorafenib, Nilotinib, Sunitinib | Yes, see clinical trials section
P53 p.S127F, p.P19OS, p.R2O9G | None | None | None
* Note: Genomic alterations detected may be associated with activity of certain approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type.
Genomic Alterations
BRAF Mutations
Somatic mutations in BRAF have found in 37-50% of all malignant melanomas (COSMIC; Davies et al. 2002; Hodis et al. 2012; Krauthammer et al. 2012; Maldonado et al. 2003). BRAF
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Genomic Alteration	Approved therapies in patient's tumor type	Approved therapies in another tumor type	Potential clinical trials
BRAF p.V6OOE	ABRAFENIB, TRAMETINIB, VEMURAFENIB	Rigorafenib	Yes, see clinical trials section
KIT p.R634W	None	Imatinib, Regorafenib, Axitinib, Cabozantinib, Sorafenib, Nilotinib, Sunitinib	Yes, see clinical trials section
P53 p.S127F, p.P19OS, p.R2O9G	None	None	None

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Genomic Alterations
BRAF Mutations
Somatic mutations in BRAF have been found in 37-50% of all malignant melanomas (COSMIC, Davies et al. 2002, Hodis et al. 2012, Krauthammer et al. 2012, Maldonado et al. 2003). BRAF mutations are found in all melanoma subtypes but are the most common in melanomas derived from skin without chronic sun-induced damage [Curtin et al. 2005, Maldonado et al.2003]. In this category of melanoma, BRAF mutations are found in ~ 59% of samples [Curtin et al. 2005].
The most prevalent BRAF mutations detected in melanoma are missense mutations that introduce an amino acid substitution at valine 600. Approximately 80-90% of V600 BRAF mutations are V600E (valine to glutamic acid, COSMIC, Lovly et al. 2012, Rubinstein et al. 2010). BRAF V600E mutations are associated with increased sensitivity to BRAF inhibitors (Chapman et al. 2011, Falchook et al. 2012a, Flaherty et al. 2010, Flaherty et al. 2012a, Hauschild et al. 2012, Sosman et al. 2012). Patients whose tumors harbored V600E and V600K mutations showed better responses th the MEK inhibitor, trametinib, than to chemotherapy (dacarbazine or paclitaxel, Flaherty et al. 2012b), patients with V600E or V600K-mutated tumors also showed better responses to trametinib than patients with BRAF wild type tumors [Falchook et al. 2012b].
The FDA has approved use of the combination therapy dabrafenib and trametinib for melanoma patients with V600E or V600K mutations based on an interim analysis of a phase III trial showing improved response rates and response duration compared to dabrafenib alone (FDA 2014, Long et al. 2014). Improved progression-free survival and response rates compared to dabrafenib monotherapy were observed in an earlier phase I/II trial, as well (Flaherty et al. 2012a). Patients with V600-mutated tumors and no prior BRAF inhibitors treated with combination vemurafenib and cobimetinib experienced improved response rate and progression-free survival compared to patients with V600-mutated tumors and recent progression on vemurafenib (Ribas et al. 2014). This study included patients with V600E and V600K mutations (Ribas et al. 2014).
BRAF Mutations
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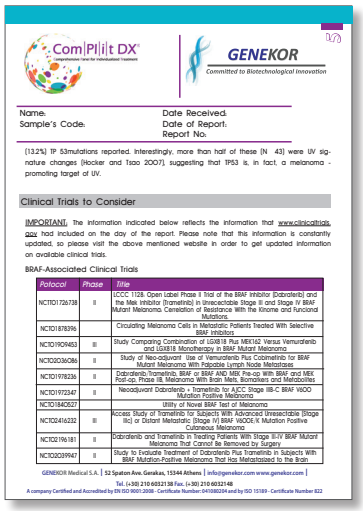
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(13.2%) TP 53mutations reported. Interestingly, more than half of these (N 43) were UV signature changes (Hocker and Tsao 2007), suggesting that TP53 is, in fact, a melanoma - promoting target of UV.
Clinical Trials to Consider
IMPORTANT. The information indicated below reflects the information that www.clinicaltrials.gov had included on the day of the report. Please note that this information is constantly updated, so please visit the above mentioned website in order to get updated information on available clinical trials.
BRAF-Associated Clinical Trials

Protocol	Phase	Title
NCT01072738	II	CCCC 1128. Open Label Phase II Trial of the BRAF Inhibitor (Dabrafenib) and the Mek Inhibitor (Trametinib) in Unresectable Stage III and Stage IV BRAF Mutant Melanoma. Correlation of Resistance With the Kinome and Functional Mutations.
NCT01878396		Circulating Melanoma Cells in Metastatic Patients Treated With Selective BRAF Inhibitors
NCT01909453	III	Study Comparing Combination of LGX818 Plus MEK162 Versus Vemurafenib and LGX818 Monotherapy in BRAF Mutant Melanoma
NCT02036086	II	Study of Neo-adjuvant Use of Vemurafenib Plus Cobimetinib for BRAF Mutant Melanoma With Palpable Lymph Node Metastases
NCT01978236	II	Dabrafenib-Trametinib, BRAF or BRAF AND MEK Pre-op With BRAF and MEK Post-op, Phase IB, Melanoma With Brain Mets, Biomarkers and Metabolites
NCT01972347	II	Neoadjuvant Dabrafenib + Trametinib for AJCC Stage IIIB-C BRAF V600 Mutation Positive Melanoma
NCT01840527		Utility of Novel BRAF Test of Melanoma
NCT02416232	III	Access Study of Trametinib for Subjects With Advanced Unresectable (Stage IIIc) or Distant Metastatic (Stage IV) BRAF V600E K Mutation Positive Cutaneous Melanoma
NCT02196181	II	Dabrafenib and Trametinib in Treating Patients With Stage IIIUV BRAF Mutant Melanoma That Cannot Be Removed by Surgery
NCT02039947	II	Study to Evaluate Treatment of Dabrafenib Plus Trametinib in Subjects With BRAF Mutation-Positive Melanoma That Has Metastasized to the Brain

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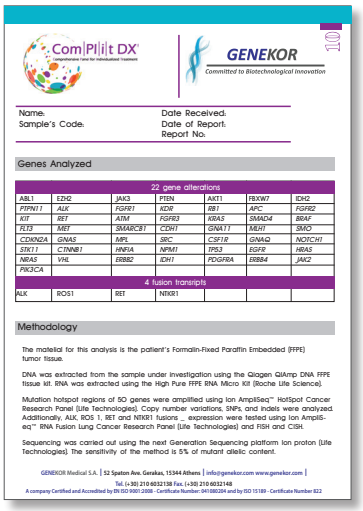
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Genes Analyzed

22 gene alterations						
ABL1	EZH2	JAK3	PTEN	AKT1	FBXW7	IDH2
PTPN11	ALK	FGFR1	KDR	RB1	APC	FGFR2
KIT	RET	ATM	FGFR3	KRAS	SMAD4	BRAF
FLT3	MET	SMARCB1	CDH1	GNA11	MEN1	SMO
CDKN2A	GNAS	NPS	SRC	CSF1R	GNAQ	NOTCH1
STK11	CTNNB1	HNF1A	NPM1	TP53	EGFR	HRAS
NRAS	VHL	ERBB2	IDH1	PDGFRA	ERBB4	JAK2
PIK3CA						
4 fusion transripts						
ALK	ROS1	RET	NTKR3			

Methodology
The material for this analysis is the patient's Formalin-Fixed Paraffin Embedded (FFPE) tumor tissue.
DNA was extracted from the sample under investigation using the Qiagen QIAmp DNA FFPE tissue kit. RNA was extracted using the High Pure FFPE RNA Micro Kit (Roche Life Science).
Mutation hotspot regions of 50 genes were amplified using Ion AmpliSeq™ HotSpot Cancer Research Panel (Life Technologies). Copy number variations, SNPs, and indels were analyzed. Additionally, ALK, ROS 1, RET and NTKR1 fusions _ expression were tested using Ion AmpliSeq™ RNA Fusion Lung Cancer Research Panel (Life Technologies) and FISH and CISH.
Sequencing was carried out using the next Generation Sequencing platform Ion proton (Life Technologies). The sensitivity of the method is 5% of mutant allelic content.
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On the Genomic Alterations Section a more detailed interpretation about the Genomic Alterations identified is contained, including frequencing ratios, biological impact and related tergeted therapies.

On the Clinical Trials Section all the currently available clinical trials are reported according to the molecular profile of the patient's tumor.

Furthermore, details about the methodology of the assay are reported on the Methodology Section.