Study Report: Patient #627

Identification Number: 130. 6. 627

Disclaimer

The information provided in this report is intended solely for the use by the certified specialists in the fields of oncology, genetics and molecular medicine. This report may not be used for drug prescription and appointing therapy regimen, except when interpreted by a medical doctor. Do not hesitate to contact our research and production team in case of any doubts or uncertainties, as well as for report interpretation (upon request).

CONCLUSIONS AFTER THE PATIENTS' GENOME AND TRANSCROPTOME ANALYSIS

DIAGNOSIS: Lung cancer, sex: male, born on 1951.

Based on single patient surgery biosample (FFPE block) corresponding to lung cancer pathological tissue and containing >85% non-necrotic lung cancer cells, a single RNA specimen was isolated using two 300 μm-wide slices. The DNA and RNA was profiled. Differential gene expression was profiled against total RNAs isolated from normal human lungs (four age and sex – matching normal controls), which were used as healthy tissue controls for normalization of gene expression.

Using bioinformatic platform OncoBox we profiled activation of molecular targets, differentially active in the patients' biosamples compared to the norms. The data allowed an analysis of potential activities of target cancer drugs, and of a number of non-target drugs approved by the regulatory authorities in the US, Canada, and EU.

Top target drugs showing the best score and predicted to be the most efficient for the treatment of the individual patient's tumor were selected. Totally 148 target drugs were analyzed. The higher values of Drug Score index correspond to increased predicted efficiency of drugs. According to the obtained results representing Drug Scores for the pharmacological components (Exhibit 1), several currently marketed respective drugs may be potentially effective for treatment of the current patient (given in the order of decreasing efficiency from higher to lower levels).

The selected top drugs list is the following:

Regorafenib, *Pazopanib*, Sunitinib, Imatinib, *Dasatinib,* **Crizotinib**, Axitinib, Thalidomide, *Trametinib*, *Ruxolitinib.*

Molecular targets of the respective drugs, differentially expressed in the patient's tumor are shown on Exhibit 2.

According to current clinical standards, the following drug from the above list is routinely used for the treatment of the metastatic non-small cell lung cancer:

Crizotinib
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202570s013lbl.pdf

In addition, the multi tyrosine kinase inhibitor drug *Regorafenib* is under the 1st phase clinical trials for the non-small cell lung cancer, *Pazopanib* – under the 2nd phase, *Dasatinib* – under the 1st phase, *Trametinib* и *Ruxolitinib* - under the 2st phase clinical trials for the non-small cell lung cancer.

The drugs Sunitinib, Imatinib and Axitinib were used for the treatment non-small cell lung cancer in the past, but actually are standardly discontinued for this cancer type.

Date of completion of the current report:

Jan 19 2016

Performed stages:

-IGH analysis of biomaterial samples

-isolation of nucleic acids from biomaterials

-genome-wide profiling of mutations

-transcriptome-wide profiling of gene expression

-analysis of differential gene expression

-analysis of differentially regulated intracellular signaling pathways

-analysis of cancer target chemotherapeutics

I HEREBY CONFIRM RELEVANCE OF THE DATA PRESENTED IN THIS REPORT TO THE PATIENT CASE #627

/ Anton Buzdin, Chief Scientific Officer /

APPENDIX

Exhibit 1

Full list of Drug Score indexes calculated for the patient #627

Drug Score value reflects potential benefit for the patient from administration of a respective drug in terms of degradation of tumor cells and repression of tumor growth. DS index reflects calculated potential usefulness of a drug according to intracellular signaling pathway activation signature and based on the concentrations of gene products for molecular targets for a given type of anticancer therapy. The highest Drug Score values correspond to drugs which may have a largest potential for treatment of the individual patient. "Database" means what type of molecular targets database was used to calculate a Drug Score for the individual biosample. The information obtained using the knowledgebase DRUGBANK is thought to be the most accurate. Numbers indicate top 10 positions of drugs rated as being of high potential benefit to the patient.

№	Drug	Database	Drug Score	Type
	Nintedanib (BIBF 1120)	primary	16,9	inhibitor
	Foretinib	primary	16,2	inhibitor
1	**Regorafenib**	drugbank	15,2	inhibitor
2	**Pazopanib**	drugbank	12,6	inhibitor
3	**Sunitinib**	drugbank	12,2	inhibitor
	Nilotinib	primary	11,4	inhibitor
	Masitinib	primary	11,1	inhibitor
	Dovitinib	primary	10,9	inhibitor
	Dasatinib	primary	5,9	inhibitor
4	**Imatinib**	drugbank	5,9	inhibitor
5	**Dasatinib**	drugbank	5,0	inhibitor
6	**Crizotinib**	drugbank	4,6	inhibitor
	Tivozanib	primary	4,5	inhibitor
7	**Axitinib**	drugbank	4,5	inhibitor
	Vandetanib	primary	4,4	inhibitor
	Tivantinib	primary	4,3	inhibitor
8	**Thalidomide**	drugbank	4,1	inhibitor
	Thalidomide	primary	4,1	inhibitor
	Binimetinib (MEK162)	primary	3,5	inhibitor
	Selumetinib	primary	3,5	inhibitor

9	**Trametinib (Mekinst)**	drugbank	3,5	inhibitor
10	**Ruxolitinib**	drugbank	3,2	inhibitor
	Full list of drugs is unavailable in the demo.	drugbank	3,2	inhibitor
		drugbank	3,0	inhibitor
		drugbank	2,5	inhibitor
		primary	2,3	inhibitor
		drugbank	2,3	inhibitor
		primary	1,4	inhibitor
		drugbank	1,1	inhibitor
		primary	1,1	inhibitor
		primary	1,0	inhibitor
		primary	0,8	inhibitor
		drugbank	0,7	inhibitor
		drugbank	0,7	inhibitor
		primary	0,6	inhibitor
		primary	0,5	multivalent
		primary	0,5	inhibitor
		drugbank	0,5	inhibitor
		primary	0,4	multivalent
		drugbank	0,4	inhibitor
		drugbank	0,4	inhibitor
		primary	0,4	inhibitor
		drugbank	0,4	inhibitor
		drugbank	0,4	inhibitor
		drugbank	0,4	inhibitor
		drugbank	0,4	inhibitor
		primary	0,4	inhibitor
		primary	0,3	inhibitor
		drugbank	0,3	inhibitor
		drugbank	0,3	inhibitor
		drugbank	0,3	inhibitor
		primary	0,3	inhibitor
		drugbank	0,3	inhibitor
		primary	0,3	inhibitor
		drugbank	0,3	inhibitor
		primary	0,2	inhibitor
		drugbank	0,2	inhibitor
		primary	0,2	inhibitor
		drugbank	0,2	inhibitor
		drugbank	0,2	inhibitor
		drugbank	0,2	inhibitor
		drugbank	0,2	inhibitor
		primary	0,2	inhibitor
		drugbank	0,2	inhibitor

		primary	0,1	inhibitor
		primary	0,1	multivalent
		drugbank	0,1	inhibitor
		primary	0,1	inhibitor
		primary	0,1	inhibitor
		primary	0,1	inhibitor
		primary	0,1	inhibitor
		drugbank	0,1	activator
		primary	0,1	activator
		drugbank	0,1	activator
		drugbank	0,1	activator
		primary	0,1	activator
		primary	0,1	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	inhibitor
		primary	0,0	multivalent
		drugbank	0,0	inhibitor
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	mab
		drugbank	0,0	multivalent
		drugbank	0,0	inhibitor
		drugbank	0,0	mab
		drugbank	0,0	mab
		drugbank	0,0	killermab
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	multivalent
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	inhibitor
		drugbank	0,0	mab
		drugbank	0,0	mab
		drugbank	0,0	mab
		primary	0,0	inhibitor

		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	inhibitor
		primary	0,0	inhibitor
		primary	0,0	inhibitor
		drugbank	0,0	mab
		primary	0,0	multivalent
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	mab
		drugbank	0,0	multivalent
		drugbank	0,0	killermab
		primary	0,0	inhibitor
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	inhibitor
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	inhibitor
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	multivalent
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	killermab
		primary	0,0	mab
		drugbank	0,0	inhibitor
		primary	0,0	mab
		drugbank	0,0	activator
		drugbank	0,0	inhibitor
		drugbank	0,0	killermab
		primary	0,0	inhibitor
		drugbank	0,0	mab
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	activator
		drugbank	0,0	activator
		drugbank	0,0	inhibitor
		drugbank	0,0	mab
		drugbank	0,0	killermab

		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	0,0	inhibitor
		primary	0,0	mab
		drugbank	0,0	mab
		drugbank	0,0	mab
		drugbank	0,0	activator
		primary	0,0	mab
		drugbank	0,0	activator
		primary	0,0	multivalent
		drugbank	0,0	activator
		primary	0,0	mab
		primary	0,0	mab
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		drugbank	0,0	mab
		drugbank	0,0	mab
		drugbank	0,0	inhibitor
		drugbank	0,0	activator
		drugbank	0,0	activator
		drugbank	0,0	activator
		drugbank	0,0	activator
		drugbank	0,0	activator
		drugbank	0,0	activator
		primary	0,0	activator
		drugbank	0,0	inhibitor
		drugbank	0,0	multivalent
		primary	0,0	inhibitor
		drugbank	0,0	inhibitor
		primary	-0,1	inhibitor
		primary	-0,1	inhibitor
		primary	-0,2	inhibitor
		drugbank	-0,3	activator
		drugbank	-0,4	inhibitor
		primary	-0,4	activator
		drugbank	-0,4	inhibitor
		primary	-0,5	inhibitor
		primary	-0,9	inhibitor
		primary	-1,1	inhibitor
		drugbank	-1,2	inhibitor
		drugbank	-1,2	inhibitor
		primary	-1,8	inhibitor

		primary	-2,4	mab
		drugbank	-2,8	multivalent
		drugbank	-4,3	mab

Exhibit 2

Differentially expressed molecular targets of drugs

Drug	Up-regulated molecular targets	Down-regulated molecular targets
Abemaciclib		
Afatinib		
Aflibercept	VEGFB	VEGFA
Full list of drugs is unavailable in the demo.		
		RXRG
		RXRG
		CCND1
		PML
	FLT1 KDR FLT4	
		VEGFA
		RXRG
	MAP2K1	
	PSMD2 PSMB5 PSMA1 PSMA5 PSMB6	PSMD1 PSMB7
	PSMA1 PSMA5 PSMB5 PSMB6 CTSG	PSMB7
	SRC	
	SRC	
	TUBA1B TUBA3E TUBB6	TUBB2B
	ABCG2 TUBA1B TUBA3E TUBB6	TUBB2B
	MET KDR	RET
	PSMB5	
	PSMB5	
		FCGR3A
	TUBA1B TUBA3E TUBB6 GABRB2 GLRA2 GLRA3	TUBB2B GLRA1

	TUBA1B TUBA3E TUBB6	TUBB2B
	MET	
	JAK2	
	BTK SRC FYN YES1	FGFR1 CSF1R MAP2K5
	SRC YES1 FYN	
		BCL2
		MAP2
	FLT1 PDGFRA KDR FLT4 YES1 TOP1	FGFR1 FGFR3
	MUC1	
	CYP3A5	
		MAP2 MAP1A
		MAP2 MAP1A
	TOP2B	
	CDK7	
	CDK5 CDK7	
		ADORA3
	FLT1 KDR FLT4 MET PDGFRA	FGFR1
	TFPI	
	IL1B NFE2L2	BGLAP
		HSP90AA1
	RPL3	

	BTK	
	TOP2B	
	PDGFRA ABCG2	RET
	TLR8	
	TOP1	ACHE
	TOP1 TOP1MT	
	TUBA1B TUBA3E TUBB6	TUBB2B
	PSMB5	
	CYP3A5	ERBB3
	ACTA1	
		AHR
	CYP19A1	
	TOP1 TOP2B	
	TOP1 TOP2B	
		ADAM17
	MMP21 MMP27 MMP28	
	SRC CYP2C9 FYN PDGFRA PIM1 YES1	DDR1 EPHA3 FGFR3 FRK CSF1R
	CYP2C9	
	GABRA2 GABRA3 GABRA5 GABRB2	GABRE GABRQ
	TOP2B ABCC1	
	TOP2B	

	NQO2 PDGFRA EPHB4	
	FGFR2 PDGFRA FLT1 KDR FLT4 SRC	FGFR1 FGFR3
	PARP2	
	ABHD12	LPL FASN DAGLA
		FASN
	CYP17A1	
	TUBA1B TUBA3E TUBB6 BCL2L1	BCL2 TUBB2B MAP2
	FLT1 KDR FLT4 PDGFRA	
	GART	
	GART	
		FCGR1A
	FLT1 KDR FLT4 PDGFRA FGFR2 MAPK11	RET RET FGFR1 NTRK1
	PLK1	
		HGF
		FCGR1A FCGR3A
	HDAC5 HDAC8	HDAC9 HDAC1 HDAC2
	JAK2	
	PTGS1	
	PTGS1	
	MAP2K1	
	SMO	
	KDR FLT4 FLT1	RET FGFR1
	FLT1 KDR FLT4 PDGFRA	CSF1R

	FGFR2	
	FGFR2	
	MET CAMK2D PIM1 FLT4	PAK3
	FLT1 KDR FLT4	
	TOP1 TOP1MT	ACHE HIF1A
	TOP1 TOP1MT	
	MAP2K1	
		RXRG
		RXRG
	TOP2B	
	KDR SRC FLT1 RIPK2	RET
	KDR	
	PARP4	
	ABCG2	
	TUBA1B TUBA3E TUBB6	TUBB2B
	TUBA1B TUBA3E TUBB6	TUBB2B
	TUBA1B TUBA3E TUBB6	TUBB2B
	CALM1 CALM2 TUBA1B TUBA3E TUBB6	CALM3 TUBB2B
	TUBA1B TUBA3E TUBB6	TUBB2B
	SMO	
	HDAC8 HDAC5	HDAC1 HDAC2 HDAC9
	VEGFB	VEGFA