ONCOBOX ANALYSIS REPORT

Patient ID: ZZ

Age: ZZ

Gender: ZZ

Description: Glioblastoma ZZ

Normal tissue: Brain ZZ

We use normal tissue collected from healthy individuals to normalize gene expression values in patient's sample.

Clinical trial database: Glioblastoma, Glioma

We need information about the type of cancer to provide relevant links to current medical practice status of each drug.

Report completed: ZZ

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.

WHOLE EXOME SEQUENCING AND MUTATION ANALYSIS

The patient's tumor tissue sample was subjected to whole exome sequencing (WES). A total of 217.82 million reads were obtained, which resulted in mean ×147 average exon coverage. Whole exome sequencing analysis revealed status for the following clinically relevant mutations:

GENE	MUTATION	APPROVED THERAPY IN PATIENT'S CANCER TYPE	APPROVED THERAPY IN OTHER CANCER TYPES	COMMENTS
IDH1	NO			
IDH2	R132H	Not applicable	Not applicable	Is a favorable prognostic factor
BRAF	V600E	Not applicable	Vemurafenib, Encorafenib	Is associated with potential efficacy of BRAF inhibitors

Mutations in the following clinically relevant genes (in different tumor types) were not detected: KRAS, NRAS, EGFR, KIT, BRCA1, BRCA2.

Tumor Mutation Burden (TMB): 4 mutations/Mb (low level)*.

**Low TMB (<6 mutations/Mb) is associated with lower response rate to immunotherapy (anti-PD1, anti-PDL1, anti-CTLA4)*

ADDITIONAL MOLECULAR ANALYSES

- **MGMT methylation**

Method: methylation-specific real-time polymerase chain reaction (PCR)

Result: the analysis revealed methylation of MGMT promoter region

- **PDL1 expression (IHC)**

Method: immunohistochemical staining (IHC)

Result: membrane PDL1 expression in 3% of tumor cells

- **PDL1 expression (NGS)**

Method: NGS RNA-seq

Result: PDL1 expression is 2.59 times higher in patient's tumor than in normal tissue

ADJUSTMENT OF MEDICATIONS FOR INDIVIDUAL TUMOR

The patient's tumor tissue sample was subjected to transcriptomic profiling (RNA-seq). In total, 33.49 mln raw reads were obtained. 11.04 mln reads successfully mapped to exonic regions, indicating sufficient quality of the data. The patient's gene expression data (Patient ID: ZZ) were analyzed by our original innovative algorithm Oncobox™. Oncobox™ is a new method for the analysis of intracellular signaling pathway activation and predicting target drug efficacy in cancer using transcriptomic data from individual patient.

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 136 target drugs were analyzed, Drug-score index of which varied from -71.07 to 50.10 with the average value 3.23. 93 clinically used target cancer therapeutics with the highest values of the Drug-score index are shown below. The higher values of Drug-score index correspond to increased predicted efficacy of drugs. We also provide medical practice status for each drug from the list: FDA approval or phase of clinical trials, when available.

Summary

For Glioblastoma:

- The following target drugs with the highest values of the Drug-score index are FDA approved for indicated cancer types: Bevacizumab, Temozolomide.
- Phase III clinical trials were completed for Nimotuzumab. Phase III clinical trials are ongoing for 2 drugs.
- 27 drugs are on Phase II clinical trials (10 completed + 17 ongoing).
- 28 drugs are on Phase I clinical trials (0 completed + 28 ongoing).

For Glioma:

- The following target drugs with the highest values of the Drug-score index are FDA approved for indicated cancer types: Everolimus, Lomustine, Nimotuzumab, Temozolomide.
- Phase III clinical trials were completed for Vincristine. Phase III clinical trials are ongoing for 1 drug.

- 28 drugs are on Phase II clinical trials (7 completed + 21 ongoing).
- 28 drugs are on Phase I clinical trials (0 completed + 28 ongoing).

RANK	DRUG	SCORE
1	Aflibercept Glioma: Phase II completed - Gliomas link	50.10
2	Denileukin diftitox (Ontac)	46.90
3	Bevacizumab Glioblastoma: **Marketed http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125085s308lbl.pdf**	42.55
4	Idelalisib	37.01
5	Siltuximab	27.94
6	Flavopiridol (Alvociclib)	26.19
7	Thalidomide Glioma: Phase II link	22.56
8	Crizotinib Glioblastoma: Phase I Glioma: Phase II, brain tumors link	21.25
9	Tivantinib	20.81
10	Foretinib	19.22
11	Necitumumab	17.58
11	Cetuximab	17.58

RANK	DRUG	SCORE
11	Nimotuzumab Glioblastoma: Phase III completed link Glioma: **Marketed, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2715181/**	17.58
11	Panitumumab Glioma: Phase II link	17.58
15	Pomalidomide	14.61
16	CYT387 (Momelotinib)	12.90
16	Ruxolitinib	12.90
18	Cabozantinib Glioblastoma: Phase II completed link Glioma: Phase II completed - Astrocytoma link	12.44
19	Brigatinib	11.61
20	Perifosine Glioblastoma: Phase II link Glioma: Phase II link	11.41
21	Gefitinib Glioblastoma: Phase II completed link Glioma: Phase II completed link	11.17
21	Osimertinib	11.17

RANK	DRUG	SCORE
23	Napabucasin	11.13
24	Erlotinib Glioblastoma: Phase II completed link Glioma: Phase II link	10.99
25	Lapatinib Glioblastoma: Phase II link Glioma: Phase II completed link	10.79
26	Fulvestrant	10.33
26	Tamoxifen	10.33
28	Ibrutinib	9.92
29	Trebananib Glioblastoma: Phase II completed link Glioma: Phase II link	9.08
30	Palbociclib Glioblastoma: Phase II link Glioma: Phase II - Oligodendroglioma, Oligoastrocytoma link	7.57
30	Ribociclib Glioma: Phase II link	7.57

RANK	DRUG	SCORE
30	Abemaciclib (LY2835219) Glioblastoma: Phase II link	7.57
33	Vandetanib Glioblastoma: Phase II link Glioma: Phase II link	7.50
34	Vorinostat Glioblastoma: Phase II completed link Glioma: Phase III link	6.49
35	Romidepsin Glioblastoma: Phase II completed link Glioma: Phase II completed link	6.11
36	Belinostat Glioblastoma: Phase II link	6.09
37	Panobinostat Glioma: Phase II completed link	5.94
38	Dabrafenib	5.36

RANK	DRUG	SCORE
39	Arsenic trioxide Glioblastoma: phase II link Glioma: phase II link	5.20
40	Vindesine	4.46
40	Vincristine Glioma: Phase III completed link	4.46
40	Vinblastine	4.46
43	Apalutamide, ARN-509	4.32
43	Cyproterone acetate	4.32
43	Bicalutamide	4.32
43	Enzalutamide	4.32
43	Nilutamide	4.32
48	Toremifene	4.29
49	Ganetespib (STA-9090)	4.10
50	Everolimus Glioma: **Marketed - Subependymal giant cell astrocytoma** **https://www.fda.gov/Drugs/InformationOnDrugs/** **ApprovedDrugs/ucm488028.htm**	3.33
50	Temsirolimus Glioblastoma: Phase II completed link Glioma: Phase II link	3.33
52	Vinorelbine	3.09

RANK	DRUG	SCORE
53	Masitinib	2.49
54	Olaparib Glioblastoma: Phase II link	2.44
54	Rucaparib	2.44
56	Nilotinib Glioma: Phase II link	2.36
56	Ponatinib Glioblastoma: Phase II link	2.36
58	Rigosertib	2.31
59	Olaratumab Glioblastoma: Phase II completed link	2.27
60	Elotuzumab	2.26
61	Blinatumomab	1.91
62	Carfilzomib	1.88
63	Lenalidomide Glioblastoma: Inactive, No development reported	1.78
64	Afatinib Glioma: Phase II Completed link	1.57
65	Dasatinib Glioblastoma: Phase II completed link	1.39
66	Brentuximab vedotin	1.15

RANK	DRUG	SCORE
66	Claudiximab	1.15
68	Trametinib (Mekinst)	1.11
68	Selumetinib Glioma: Phase II link	1.11
68	Binimetinib (MEK162) Glioma: Phase II link	1.11
71	Veliparib Glioblastoma: Phase II completed link Glioma: Phase II link	0.96
72	Durvalumab Glioblastoma: Phase II link Glioma: Phase II link	0.93
73	Mogamulizumab	0.79
74	Temozolomide Glioblastoma: **Marketed - https://www.cancer.gov/about-cancer/treatment/drugs/fda-temozolomide** Glioma: **Marketed - https://www.cancer.gov/about-cancer/treatment/drugs/fda-temozolomide**	0.68
74	Lomustine Glioma: **Marketed (brain tumours) http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/017588s040lbl.pdf**	0.68

RANK	DRUG	SCORE
76	Niraparib	0.65
77	Homoharringtonine (Omacetaxine mepesuccinate)	0.64
78	Tecemotide (Emepepimut-S, L-BLP25)	0.63
79	Ixazomib (MLN9708)	0.61
80	Denosumab	0.55
81	Alectinib	0.45
81	Ceritinib (Zykadia, LDK378)	0.45
83	Bortezomib Glioblastoma: Phase II link Glioma: Phase II link	0.39
84	Alemtuzumab	0.37
85	Ipilimumab Glioblastoma: Phase III link	0.32
86	Pembrolizumab Glioblastoma: Phase II link Glioma: Phase II link	0.28
86	Nivolumab (BMS-936558) Glioblastoma: Phase III link	0.28
88	Letrozole	0.24
88	Exemestane	0.24

RANK	DRUG	SCORE
90	Atezolizumab Glioblastoma: Phase II link Glioma: Phase II link	0.21
90	Avelumab Glioblastoma: Phase II link	0.21
92	Degarelix	0.20
93	Megestrol	0.11

COMPLETE LIST OF DRUGS

RANK	DRUG	SCORE
1	Aflibercept	50.10
2	Denileukin diftitox (Ontac)	46.90
3	Bevacizumab	42.55
4	Idelalisib	37.01
5	Siltuximab	27.94
6	Flavopiridol (Alvociclib)	26.19
7	Thalidomide	22.56
8	Crizotinib	21.25
9	Tivantinib	20.81
10	Foretinib	19.22
11	Necitumumab	17.58
11	Cetuximab	17.58
11	Nimotuzumab	17.58
11	Panitumumab	17.58
15	Pomalidomide	14.61
16	CYT387 (Momelotinib)	12.90
16	Ruxolitinib	12.90
18	Cabozantinib	12.44
19	Brigatinib	11.61
20	Perifosine	11.41
21	Gefitinib	11.17
21	Osimertinib	11.17

RANK	DRUG	SCORE
23	Napabucasin	11.13
24	Erlotinib	10.99
25	Lapatinib	10.79
26	Fulvestrant	10.33
26	Tamoxifen	10.33
28	Ibrutinib	9.92
29	Trebananib	9.08
30	Palbociclib	7.57
30	Ribociclib	7.57
30	Abemaciclib (LY2835219)	7.57
33	Vandetanib	7.50
34	Vorinostat	6.49
35	Romidepsin	6.11
36	Belinostat	6.09
37	Panobinostat	5.94
38	Dabrafenib	5.36
39	Arsenic trioxide	5.20
40	Vindesine	4.46
40	Vincristine	4.46
40	Vinblastine	4.46
43	Apalutamide, ARN-509	4.32
43	Cyproterone acetate	4.32
43	Bicalutamide	4.32
43	Enzalutamide	4.32

RANK	DRUG	SCORE
43	Nilutamide	4.32
48	Toremifene	4.29
49	Ganetespib (STA-9090)	4.10
50	Everolimus	3.33
50	Temsirolimus	3.33
52	Vinorelbine	3.09
53	Masitinib	2.49
54	Olaparib	2.44
54	Rucaparib	2.44
56	Nilotinib	2.36
56	Ponatinib	2.36
58	Rigosertib	2.31
59	Olaratumab	2.27
60	Elotuzumab	2.26
61	Blinatumomab	1.91
62	Carfilzomib	1.88
63	Lenalidomide	1.78
64	Afatinib	1.57
65	Dasatinib	1.39
66	Brentuximab vedotin	1.15
66	Claudiximab	1.15
68	Trametinib (Mekinst)	1.11
68	Selumetinib	1.11
68	Binimetinib (MEK162)	1.11

RANK	DRUG	SCORE
71	Veliparib	0.96
72	Durvalumab	0.93
73	Mogamulizumab	0.79
74	Temozolomide	0.68
74	Lomustine	0.68
76	Niraparib	0.65
77	Homoharringtonine (Omacetaxine mepesuccinate)	0.64
78	Tecemotide (Emepepimut-S, L-BLP25)	0.63
79	Ixazomib (MLN9708)	0.61
80	Denosumab	0.55
81	Alectinib	0.45
81	Ceritinib (Zykadia, LDK378)	0.45
83	Bortezomib	0.39
84	Alemtuzumab	0.37
85	Ipilimumab	0.32
86	Pembrolizumab	0.28
86	Nivolumab (BMS-936558)	0.28
88	Letrozole	0.24
88	Exemestane	0.24
90	Atezolizumab	0.21
90	Avelumab	0.21
92	Degarelix	0.20
93	Megestrol	0.11
94	Vismodegib	0.05

RANK	DRUG	SCORE
94	Sonidegib (LDE225)	0.05
96	Cobimetinib	-0.15
97	Leuprolide	-0.20
98	Ofatumumab	-0.40
98	Ibritumomab tiuxetan	-0.40
98	Rituximab	-0.40
98	Obinutuzumab	-0.40
102	Venetoclax	-0.65
103	Axitinib	-0.80
104	Daratumumab	-0.87
105	Cabazitaxel	-1.47
105	Ixabepilone	-1.47
107	Buserelin	-1.60
107	Goserelin	-1.60
109	Vemurafenib	-2.64
109	Encorafenib	-2.64
111	Docetaxel	-2.83
111	Paclitaxel	-2.83
113	Tivozanib	-3.43
114	Trastuzumab	-3.47
114	Pertuzumab	-3.47
116	Inotuzumab ozogamicin	-3.61
116	Moxetumomab pasudotox	-3.61
118	Ethinylestradiol	-4.12

RANK	DRUG	SCORE
119	Dienogest	-4.21
120	Methyltestosterone	-4.32
121	Bosutinib	-4.46
122	Regorafenib	-4.61
123	Medroxyprogesterone acetate (MPA)	-4.79
124	Tretinoin	-4.95
125	Bexarotene	-5.03
126	Alitretinoin	-5.06
127	Sunitinib	-6.37
128	Pazopanib	-7.30
129	Ramucirumab (Cyramza)	-7.45
130	Estramustine	-8.98
131	Imatinib	-10.25
132	Sorafenib	-15.51
133	Nintedanib (BIBF 1120)	-18.27
134	Dovitinib	-25.29
135	Lenvatinib	-27.67
136	Midostaurin	-71.07

DIFFERENTIALLY EXPRESSED MOLECULAR TARGETS OF DRUGS

RANK	DRUG	UPREGULATED MOLECULAR TARGETS	DOWNREGULATED MOLECULAR TARGETS
1	Aflibercept	PGF, VEGFA	
2	Denileukin diftitox (Ontac)	IL2RA, IL2RB	
3	Bevacizumab	VEGFA	
4	Idelalisib	PIK3CG	
5	Siltuximab	IL6	
6	Flavopiridol (Alvociclib)	CDK1, CDK2, CDK4, CDK6	
7	Thalidomide	NFKB1, TNF	FGFR2
8	Crizotinib	MET	
9	Tivantinib	MET	
10	Foretinib	MET, MST1R	FLT4, KDR, TEK
11	Necitumumab	ZZ ZZ	ZZ ZZ
11	Cetuximab	ZZ ZZ	ZZ ZZ
11	Nimotuzumab	ZZ	ZZ
11	Panitumumab	ZZ	ZZ
15	Pomalidomide	ZZ	ZZ
16	CYT387 (Momelotinib)	ZZ	ZZ
16	Ruxolitinib	ZZ	ZZ
18	Cabozantinib	ZZ	ZZ

RANK	DRUG	UPREGULATED MOLECULAR TARGETS	DOWNREGULATED MOLECULAR TARGETS
19	Brigatinib	ZZ ZZ	ZZ ZZ
20	Perifosine	ZZ ZZ	ZZ ZZ
21	Gefitinib	ZZ	ZZ
21	Osimertinib	ZZ ZZ	ZZ ZZ
23	Napabucasin	ZZ ZZ	ZZ ZZ
24	Erlotinib	ZZ ZZ	ZZ ZZ
25	Lapatinib	ZZ ZZ	ZZ ZZ
26	Fulvestrant	ZZ ZZ	ZZ ZZ
26	Tamoxifen	ZZ ZZ	ZZ ZZ
28	Ibrutinib	ZZ ZZ	ZZ ZZ
29	Trebananib	ZZ	ZZ
30	Palbociclib	ZZ ZZ	ZZ ZZ
30	Ribociclib	ZZ	ZZ
30	Abemaciclib (LY2835219)	ZZ ZZ ZZ	ZZ ZZ ZZ
33	Vandetanib	ZZ	ZZ
34	Vorinostat	ZZ	ZZ
35	Romidepsin	ZZ ZZ	ZZ ZZ

RANK	DRUG	UPREGULATED MOLECULAR TARGETS	DOWNREGULATED MOLECULAR TARGETS
36	Belinostat	ZZ	ZZ
37	Panobinostat	ZZ	ZZ
38	Dabrafenib	ZZ	ZZ
39	Arsenic trioxide	ZZ	ZZ
40	Vindesine	ZZ	ZZ
40	Vincristine	ZZ	ZZ
40	Vinblastine	ZZ	ZZ
43	Apalutamide, ARN-509	ZZ ZZ ZZ	ZZ ZZ ZZ
43	Cyproterone acetate	ZZ ZZ	ZZ ZZ
43	Bicalutamide	ZZ ZZ	ZZ ZZ
43	Enzalutamide	ZZ ZZ	ZZ ZZ
43	Nilutamide	ZZ	ZZ

RANK	DRUG	UPREGULATED MOLECULAR TARGETS	DOWNREGULATED MOLECULAR TARGETS
48	Toremifene	ZZ	ZZ
49	Ganetespib (STA-9090)		
50	Everolimus	ZZ ZZ	ZZ ZZ
50	Temsirolimus	ZZ ZZ	ZZ ZZ
52	Vinorelbine	ZZ	ZZ
53	Masitinib	ZZ	ZZ
54	Olaparib	ZZ ZZ	ZZ ZZ
54	Rucaparib	ZZ ZZ	ZZ ZZ
56	Nilotinib	ZZ ZZ	ZZ ZZ
56	Ponatinib	ZZ ZZ	ZZ ZZ
58	Rigosertib	ZZ ZZ	ZZ ZZ
59	Olaratumab	ZZ ZZ	ZZ ZZ
60	Elotuzumab	ZZ ZZ	ZZ ZZ
61	Blinatumomab	ZZ ZZ	ZZ ZZ
62	Carfilzomib	ZZ	ZZ
63	Lenalidomide	ZZ ZZ	ZZ ZZ
64	Afatinib	ZZ ZZ	ZZ ZZ
65	Dasatinib	ZZ	ZZ

RANK	DRUG	UPREGULATED MOLECULAR TARGETS	DOWNREGULATED MOLECULAR TARGETS
66	Brentuximab vedotin	ZZ	
66	Claudiximab	ZZ	
68	Trametinib (Mekinst)		
68	Selumetinib		
68	Binimetinib (MEK162)		
71	Veliparib	ZZ ZZ	ZZ ZZ
72	Durvalumab	ZZ ZZ	ZZ ZZ
73	Mogamulizumab	ZZ ZZ	ZZ ZZ
74	Temozolomide	ZZ	ZZ
74	Lomustine	ZZ	ZZ
76	Niraparib	ZZ	ZZ
77	Homoharringtonine (Omacetaxine mepesuccinate)	ZZ ZZ ZZ ZZ	
78	Tecemotide (Emepepimut-S, L-BLP25)	ZZ ZZ ZZ	
79	Ixazomib (MLN9708)	ZZ	
80	Denosumab		
81	Alectinib		
81	Ceritinib (Zykadia, LDK378)		
83	Bortezomib	ZZ	
84	Alemtuzumab	ZZ	
85	Ipilimumab		

RANK	DRUG	UPREGULATED MOLECULAR TARGETS	DOWNREGULATED MOLECULAR TARGETS
86	Pembrolizumab	ZZ	ZZ
86	Nivolumab (BMS-936558)	ZZ ZZ	ZZ ZZ
88	Letrozole	ZZ ZZ	ZZ ZZ
88	Exemestane	ZZ ZZ	ZZ ZZ
90	Atezolizumab	ZZ ZZ	ZZ ZZ
90	Avelumab	ZZ ZZ	ZZ ZZ
92	Degarelix	ZZ ZZ	ZZ ZZ
93	Megestrol	ZZ	ZZ
94	Vismodegib		
94	Sonidegib (LDE225)		
96	Cobimetinib		
97	Leuprolide	ZZ ZZ	ZZ ZZ
98	Ofatumumab	ZZ ZZ	ZZ ZZ
98	Ibritumomab tiuxetan	ZZ ZZ	ZZ ZZ
98	Rituximab	ZZ ZZ	ZZ ZZ
98	Obinutuzumab	ZZ	ZZ
102	Venetoclax	ZZ	ZZ
103	Axitinib	ZZ	ZZ
104	Daratumumab	ZZ	ZZ
105	Cabazitaxel	ZZ	ZZ
105	Ixabepilone	ZZ	ZZ

RANK	DRUG	UPREGULATED MOLECULAR TARGETS	DOWNREGULATED MOLECULAR TARGETS
107	Buserelin	ZZ	ZZ
107	Goserelin	ZZ	ZZ
109	Vemurafenib	ZZ ZZ	ZZ ZZ
109	Encorafenib	ZZ ZZ	ZZ ZZ
111	Docetaxel	ZZ ZZ ZZ	ZZ ZZ ZZ
111	Paclitaxel	ZZ ZZ ZZ	ZZ ZZ ZZ
113	Tivozanib	ZZ	ZZ
114	Trastuzumab		
114	Pertuzumab		
116	Inotuzumab ozogamicin	ZZ ZZ ZZ	ZZ ZZ ZZ
116	Moxetumomab pasudotox	ZZ ZZ ZZ	ZZ ZZ ZZ
118	Ethinylestradiol	ZZ	ZZ
119	Dienogest	ZZ ZZ	ZZ ZZ
120	Methyltestosterone	ZZ ZZ	ZZ ZZ
121	Bosutinib	ZZ ZZ	ZZ ZZ
122	Regorafenib	ZZ	ZZ
123	Medroxyprogesterone acetate (MPA)	ZZ ZZ ZZ	ZZ ZZ ZZ
124	Tretinoin	ZZ	ZZ

RANK	DRUG	UPREGULATED MOLECULAR TARGETS	DOWNREGULATED MOLECULAR TARGETS
125	Bexarotene	ZZ	ZZ ZZ
126	Alitretinoin	ZZ ZZ	ZZ ZZ
127	Sunitinib	ZZ ZZ ZZ	ZZ ZZ ZZ
128	Pazopanib	ZZ ZZ	ZZ ZZ
129	Ramucirumab (Cyramza)	ZZ ZZ ZZ	ZZ ZZ ZZ
130	Estramustine	ZZ	ZZ
131	Imatinib	ZZ ZZ	ZZ ZZ
132	Sorafenib	ZZ ZZ ZZ	ZZ ZZ
133	Nintedanib (BIBF 1120)	ZZ ZZ ZZ	ZZ ZZ ZZ
134	Dovitinib	ZZ ZZ ZZ	ZZ ZZ ZZ
135	Lenvatinib	ZZ	ZZ
136	Midostaurin	ZZ	ZZ

APPENDIX A: VERSIONS

Oncobox: 1.5.1
Pathway databases: Oncobox 826 1.2.1
Drug databases: Oncobox 2.1